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Responsible Party:	Laboratorios Silanes S.A. de C.V. (Jorge González Canudas)
ClinicalTrials.gov Identifier:	NCT00941382 History of Changes
Other Study ID Numbers:	OB Sil-02
Study First Received:	July 14, 2009
Last Updated:	July 15, 2009
Health Authority:	Mexico: Federal Commission for Sanitary Risks Protection

Keywords provided by Laboratorios Silanes S.A. de C.V.:
- sibutramine
- metformin
- obesity

Additional relevant MeSH terms:

- Obesity
- Overnutrition
- Nutrition Disorders
- Overweight
- Body Weight
- Signs and Symptoms
- Metformin
- Sibutramine
- Hypoglycemic Agents
- Physiological Effects of Drugs
- Pharmacologic Actions
- Appetite Depressants
- Anti-Obesity Agents
- Central Nervous System Agents
- Therapeutic Uses
- Antidepressive Agents
- Psychotropic Drugs

ClinicalTrials.gov processed this record on September 09, 2010


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Study Of Comparative Effects Of Oral Clonidine Vs Oral Diazepam Pre-Medication On The Extent And Duration Of Sensory Blockade In Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia.

Internet Journal of Anesthesiology, 2009 by Namrata Toshniwal, Alka Halbe, Hemlatha Iyyer

Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre which decreases sympathetic outflow. Decreased sympathetic nervous system activity is manifested as decreases in systemic blood pressure, heart rate and cardiac output. Our results show that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbhej singh, George, Y .Gaines and Paul .F.White, in which they concluded that oral Clonidine shortened the onset time of tetracaine's sensory block & prolonged the duration of sensory & motor block. There are more studies, which also show that oral clonidine premedication prolong the sensory as well as motor blockade from Lignocaine & Tetracaine spinal anaesthesia. The antinociceptive effect produced by the orally administered 2- adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.

Keywords: Spinal anesthesia; Clonidine; Analgesia

Introduction

Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre which decreases sympathetic outflow. Decreased sympathetic nervous system activity is manifested as decreases in systemic blood pressure, heart rate and cardiac output. Our results show that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbhej singh, George, Y .Gaines and Paul .F.White, in which they concluded that oral Clonidine shortened the onset time of tetracaine's sensory block & prolonged the duration of sensory & motor block. There are more studies, which also show that oral clonidine premedication prolong the sensory as well as motor blockade from Lignocaine & Tetracaine spinal anaesthesia. The antinociceptive effect produced by the orally administered 2- adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.

METHODS

After obtaining approval from institutional ethics committee and written informed consent from all patients, this prospective and randomized study was carried out in 60 ASA grade I and II patients scheduled for vaginal hysterectomy in Dept of Anesthesiology, TNMC and Nair Hospital, Mumbai

All Patients were assessed on the previous day of the surgery and patient satisfying the inclusion criteria were included in the study.

Procedure, its complications and alternative methods were explained to the patient in his own language and patients consent was taken.

Criteria for inclusion:

1. Age : 18-60 yrs

2. Weight : 40-70kg

3. ASA : Grade I & II

4. Concious Co — operative patient

Criteria for exclusion:

1. Consent not available

2. Age <18 or >60 yrs

3. Weight < 40 or >70 kg

4. ASA grade III, IV, & V

5. Any contra — indication to spinal anaesthesia (Absolute or relative)

6. Non — co operative patient

7. Patients who are on antihypertensive or any sedative or on any antipsychotic drugs.

Base line record of pulse rate (by cardio scope), Blood pressure (by sphygmomanometer and NIBP)), Spo[sub 2] (by pulse oximetry) and respiratory rate were taken as Tbase.

In our study groups age and also physical parameters like weight and height were comparable among the two groups. There was no significant difference in preoperative parameters like pulse rate, respiratory rate and mean arterial pressure between the two groups.

The patients were randomly divided in two groups- Group C & Group D of 30 each. Patient in Group C received Clonidine 4 -5mcg/kg oral premedication and patients in Group D received Diazepam 0.20-0.25mg/kg oral premedication 90 minutes before spinal anaesthesia.

Blinding was done by packing the three tablets of 100mcg each of clonidine and three tablets of 5mg each of Diazepam in silver foil, subsequently the packets were placed in small plastic pouches and were numbered randomly as per computer generated number. Person dispensed the drug and person observed did not know the content of the packet. Decoding of packets was done at the end of the study.

After preloading, under all aseptic precautions with patient in sitting position, spinal anaesthesia was given with 23 G Quincke needle in L3-4 interspace with 2.5 cc of 0.5 % Bupivacaine and 25mcg Fentanyl. Patient was made to sit for 2 minutes after subarachnoid block and then made supine. Onset, duration, height of sensory block, time taken to reach highest level, and the time taken for two segment regression, time taken for four segment regression and the time when patient asks for analgesia were monitored and noted sensory blocked were evaluated by pinprick sensation.

Onset of anaesthesia was considered as appearance of analgesia at L1.

Duration of analgesia was considered as the time between onset and the time when patient asked for analgesia.

After operation patient were observed till sensory level weaned upto L1 and patient remained in the Gynaec recovery till patient received first dose of analgesia and that time was noted.

Results

The mean age in Group C was 50.93 years with standard deviation of 5.343 years and that in Group D was 50.93 years with standard deviation of 4.877 years. The groups were comparable according to age, weight and height.

Mean arterial pressure (MAP) was significantly lower in Group C as compared to Group D. Similar trends in falling Mean and Diastolic blood pressure are seen as with systolic blood pressure and the results were significant with lower blood pressure with Clonidine as compared to Diazepam.

According to above Table no 3, there was significant difference in time for onset of anaesthesia for Groups C and D. The mean time for onset of anaesthesia for Group C was 6.73 min with standard deviation of 2.392min and that for Group D was 8.50 min with standard deviation of 2.432 min. (p value 0.006). Our results demonstrate that there was significant difference in time for onset of anaesthesia for Groups C & D.

There was also a significant difference in time taken to reach highest sensory level in Group C and D. The mean time taken to reach highest level for Group C was 18.97min with standard deviation of 6.239min and that for Group D was 24.40 min with standard deviation of 6.026min. (p value 0.001).

The mean time taken for two segment regressions in Group C was 103.87 min with standard deviation of 12.754 min and that with Group D was 90.53 mins with standard deviation of 17.419 min. (p value 0.001)

The mean time taken for four segment regressions in Group C was 140.67 min with standard deviation of 27.753 min and that with Group D was 122.83 min with standard deviation of 24.589 min. (p value 0.001)

The mean time when patient asks for analgesia in Group C was 286.67 with standard deviation of 79.017min and that with Group D was 114.30 min with standard deviation of 15.234 min.The difference was significant. (p value 0.001)

The time for surgery with Group C was95.00 with standard deviation of 6.823 min and that for Group D was 96.17 min with standard deviation of 7.391. The difference was non-significicant. (p value 0.528)

Discussion

Clonidine is rapidly absorbed after oral administration. Peak plasma concentration is rapidly achieved in 60-90 mins is highly lipid soluble, easily crosses blood -brain barrier and therefore may interact with alpha -adrenergic receptors at spinal and supraspinal sites within the central nervous system.In addition previous studies suggest that clonidine may also affect peripheral sensory nerves as a sole agent or in combination with local anaesthetics.

Clonidine has been demonstrated to inhibit neurotransmission in both A-delta and C nerve fiber which are theorized to mediate pin-prick, surgical pain. Finally Clonidine has been demonstrated to potentiate inhibitory effects of local anaesthetics on C fiber activity. Therefore Clonidine may exert its effects within the central nervous system at peripheral nerve roots by potentiation of effects of local anaesthetics.

We have compared our results with previous study which also showed the same results.[1][2][3][4][5][6]. The primary mechanism of Clonidine analgesia is via a non -opoid spinal action on central alpha 2 adrenergic receptor in the dorsal horn of spinal cord.

The analgesic an effect of clonidine is mediated by the same central alpha2 adrenoreceptors that mediated its hypotensive effects. Clonidine added to local anaesthetics enhances the effects of local anaesthetics on C fiber action potentials.

We have also studies showing that prolongation of sensory anaesthesia when clonidine and fentanyl was combined was solely due to clonidine[1].

Our results showed that premedication with 4-5gm/ kg oral clonidine premedication prolongs the duration of sensory blockade by Bupivacaine and Fentanyl spinal anaesthesia as compared to that of 0.20-0.25mg/kg Diazepam oral premedication, and this results agree with the study done in 1992, by Kouechi Ota, Akiyoshi Namiki, Yoshihito Ujike & Ikuko Takahashi 3 . They concluded that prolongation of tetracaine sensory analgesia may be produced by premedication with oral clonidine premedication may have a distinct advantage because of its capacity to prolong sensory blockade & its potent sedating properties.

We added fentanyl to bupivacaine to determine its effect on anesthesia quality, and sensory block. The administration of intrathecal opioids may provide benefits in augmenting sensory level, but also carries a risk of respiratory depression but we had taken care of it by watching respiratory rate and saturation.

Our results showed that there was significant difference in the time of onset of anaesthesia, which coincides with the study done by Herbhej singh, George, Y .Gaines and Paul .F. White[1], in which they concluded that oral clonidine shortened the onset time of tetracaine's sensory block & prolonged the duration of sensory & motor block.

There are more studies, which also show that oral clonidine premedication prolong the sensory as well as motor blockade from Lignocaine & Tetracaine spinal anaesthesia. The antinociceptive effect produced by the orally administered 2-adrenergic agonist is mainly caused by direct spinal activation due to spread of the drug via the systemic circulation into the spinal cord. Neuraxial Clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimuli. Clonidine modifies function of K channels in the CNS causing cell membrane hyperpolarization which decreases anaesthetic requirements.

The dose of clonidine (4-5gm/ kg) & time Interval (90min before spinal anaesthesia) were decided according to previous studies regarding safety of clonidine premedication in elderly & dose response studies of oral clonidine for tetracaine spinal anaesthesia.

Thus in the end as per results from our comparative study of effect of oral clonidine versus oral diazepam premedication on sensory blockade by intrathecal bupivacaine 0.5%(2.5ml) and fentanyl 25mcg, showed that clonidine hastens the onset of action, and reduces the time taken to reach highest sensory level.Clonidine also prolongs the total duration of sensory block by increasing the time for 2 and 4 segment sensory regression, also there was significant extension of analgesia.

Although few incidences of hypotension, bradycardia, nausea, vomiting and pruritus (Diazepam) were noted with both the groups, the difference was not statistically significant.

Endnotes

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2. Gaumann ,Brunet Jirounek, Clonidine enhances the effects of lidocaine on C fibre action potential.Anesth Analg 1992;719-25 (s)

3. Ota K,Namiki A,Ujike Y,et al,Prolongation of tetracaine spinal anesthesia by oral clonidine Anesth Analg 1992;75 ;262-4 (s)

4. Belzarena SD ,Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section.Anesth Analg 1992;74;653-7 (s)

5. Filos KS ,Goudas LC,Patoroni O,Polyzou V .Intrathecal clonidine as a sole analgesic for pain relief after cesarean section.Anesthesiology 1992;77;267-74 (s)

6. Koichi OTA,Akiyoshi Namiki ,Yoshihito Ujike,and Ikuko Takahashi,Prolongation of tetracaine spinal anesthesia by oral clonidine.Anesth Analg 1992;75;262-4 (s)

PHOTO (BLACK & WHITE): Table 1: Comparison of Mean Age, W eight and Height

PHOTO (BLACK & WHITE): Table 2: Comparison of various pre-operative variables

PHOTO (BLACK & WHITE): Table 3: Comparison of various sensory block related parameters

Citation:

N. Toshniwal, A. Halbe & H. Iyyer : Study Of Comparative Effects Of Oral Clonidine Vs Oral Diazepam Pre-Medication On The Extent And Duration Of Sensory Blockade In Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia . The Internet Journal of Anesthesiology. 2009 Volume 19 Number 2

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Lexile Reading Level: 1620
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Pazopanib Plus Lapatinib Compared To Lapatinib Alone In Subjects With Inflammatory Breast Cancer

This study is currently recruiting participants.
Verified by GlaxoSmithKline, July 2010

First Received: November 9, 2007 Last Updated: July 8, 2010 History of Changes

Sponsor:	GlaxoSmithKline
Information provided by:	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT00558103

Purpose

The double blind part of the study is being conducted to compare the efficacy and safety of pazopanib in combination with lapatinib with that of lapatinib alone in subjects with inflammatory breast cancer whose tumors overexpress the ErbB2 protein. There is also an Open-label pazopanib arm to this study designed to test whether pazopanib given alone and lapatinib given alone would be safe and effective to treat patients with inflammatory breast cancer.

Condition	Intervention	Phase
Inflammatory Breast Cancer	Drug: lapatinib (Tykerb) Drug: pazopanib (GW786034) Drug: Pazopanib	Phase III

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Official Title: A Randomized, Multicenter, Phase III Study Comparing the Combination of Pazopanib and Lapatinib Versus Lapatinib Monotherapy in Patients With ErbB2 Over-expressing Inflammatory Breast Cancer

Resource links provided by NLM:

Genetics Home Reference related topics: breast cancer

MedlinePlus related topics: Breast Cancer Cancer

Drug Information available for: Lapatinib Lapatinib Ditosylate Pazopanib

U.S. FDA Resources

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measures:

- Progression-free survival at anytime. [Time Frame: on going]

Secondary Outcome Measures:

- Overall Response Rate (ORR)Overall survival (OS)Safety and tolerabilityHealth Status Assessments [Time Frame: on going]

Estimated Enrollment:	360
Study Start Date:	December 2007
Estimated Study Completion Date:	June 2012
Estimated Primary Completion Date:	June 2012 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
arm 1: Active Comparator	Drug: lapatinib (Tykerb) comparator Drug: pazopanib (GW786034) comparator
Pazopanib Open-label: Active Comparator Pazopanib alone arm incorporated into study VEG108838 (lapatinib + pazopanib vs. lapatinib monotherapy in patients with recurrent Her2+ IBC).	Drug: Pazopanib Pazopanib monotherapy

Eligibility

Ages Eligible for Study:	18 Years and older
Genders Eligible for Study:	Female
Accepts Healthy Volunteers:	No

Criteria

Inclusion criteria:

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product that may impact patient eligibility is provided in the pazopanib IB and lapatinib prescribing information (or the lapatinib IB).

For Cohort 1 of this study, eligible patients met inclusion criteria outlined in the original version of the protocol and protocol amendment 1.

For Cohort 2 of this study, eligible patients must meet all of the following criteria:

- Patients must have evaluable Inflammatory Breast Cancer (IBC) substantiated by all of the following prior to randomization:
- History of invasive breast cancer documented by a biopsy and accompanying pathology report
- Current photographs* (global view and close-up views of all skin lesions) submitted at screening demonstrating unequivocal evidence of IBC as determined by either the medical monitor alone or in consulation with one or more of the study Principal Investigators.
- All patients must have photography at screening. Canfield Scientific Inc. will provide centralized monitoring, tracking, and collection of patients' photographs throughout the study. Screening photographs must be uploaded to the Canfield Scientific Inc website and approved by Canfield Scientific Inc, as the central photography vendor. The photographs, along with the completed Inflammatory Breast Cancer Skin Assessment Tool (IBSAT), must be reviewed and approved by GSK before a patient can be randomized. Sites should allow a

minimum of 3 business days for this process. Sites submitting quality photographs and IBSATs on a regular basis will receive an exemption from this requirement for future patients.

- Patients with secondary IBC are eligible.
- Measurable lesions (cutaneous or radiographic) may be in the field of prior standard or palliative radiation therapy; however, there must be at least a 4 week period between the last radiation treatment and the baseline scan documenting disease status for the lesion to be measurable. If the irradiated lesion is the only site of disease, documented progression of the irradiated lesion is required.
- Disease progression or relapse following treatment for invasive breast cancer, which must have included a chemotherapy regimen. In regions where trastuzumab is available with no barriers to access*, patients must have received prior trastuzumab in addition to chemotherapy in order to be eligible. * (Barriers to access may include financial considerations.)
- Unequivocal ErbB2 overexpressing breast cancer, defined as 3+ staining by immunohistochemistry (IHC), or 2+ staining by IHC in conjunction with ErbB2 gene amplification by FISH/CISH, or ErbB2 gene amplification by FISH/CISH alone (in subjects whose tumor blocks were not assessed by IHC). ErbB2 gene amplification is defined by: > six (6) ErbB2 gene copies/nucleus for test systems without an internal control probe or an ErbB2/CEP 17 ratio of more than 2.2.

Sites must submit a copy of the laboratory report demonstrating unequivocal ErbB2 overexpression, if testing performed at a local laboratory, with the screening worksheet. Archived tumor must be provided for all patients for ErbB2 FISH testing by the central laboratory. Patients will remain on study based on local ErbB2 expression results. If archived tumor is not available, a biopsy must be obtained at screening and sent to TMD Laboratoraties for ErbB2 FISH testing.

- Patients must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow up. Procedures conducted as part of the patient's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol.

Note: Informed consent may be obtained prior to the protocol-specified screening window (i.e. Day -14 to Day -1).

- Females age ≥ 18 years, except in Tunisia. In Tunisia, patients must be ≥ 20 years to be eligible for this study.
- Adequate organ function as defined below:
- System (Laboratory Values)
- Hematologic:Absolute neutrophil count (ANC)(≥ 1.5 X 10^9/L)Hemoglobin1(≥9 g/dL)Platelets (≥100 X 10^9/L)International normalized ratio (INR)(≤ 1.2 X upper limit of normal (ULN)) Partial thromboplastin time (PTT)(≤1.2 X ULN)
- Hepatic:Total bilirubin2 (≤ 1.5 X upper limit of normal (ULN))AST and ALT(≤ 2.5 X ULN)
- Renal:Serum Creatinine (≤ 1.5 mg/dL)Or, if serum creatinine >1.5 mg/dL,
- Calculated creatinine clearance(≥50 mL/min)
- Urine Protein to Creatinine Ratio(<1)
- Patients may not have had a transfusion within 7 days of screening assessment.
- Exception: Patients with elevated bilirubin levels due to Gilberts syndrome are eligible.
- Cardiac ejection fraction within the institutional range of normal as measured by echocardiogram. MUGA scans will be accepted in cases where an echocardiogram cannot be performed or is inconclusive or where MUGA scans are the accepted standard. Patients with known history of uncontrolled or symptomatic angina, arrhythmias, or congestive heart failure are not eligible.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
- A female is eligible to enter and participate in this study if she is of:

Non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who has had:

- A hysterectomy
- A bilateral oophorectomy (ovariectomy)

- A bilateral tubal ligation
- Is post-menopausal
- Patients not using hormone replacement therapy (HRT) must have experienced total cessation of menses for ≥ 1 year and be greater than 45 years in age, OR, in questionable cases, have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

Patients must discontinue HRT prior to study enrollment due to the potential for inhibition of CYP enzymes that metabolize estrogens and progestins (See Section 8). For most forms of HRT, at least 2-4 weeks must elapse between the cessation of HRT and determination of menopausal status; length of this interval depends on the type and dosage of HRT. If a female patient is determined not to be post-menopausal, they must use adequate contraception, as defined immediately below.

Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, has used adequate contraception since the pregnancy test and agrees to use adequate contraception as described below. GSK acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female patient's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception (condom with spermicidal jelly, foam suppository, or film; diaphragm with spermicide; or male condom and diaphragm with spermicide).

Note: Oral contraceptives are not reliable due to potential drug drug interactions.

Female patients who are lactating should discontinue nursing prior to the first dose of investigational product and should refrain from nursing throughout the treatment period and for 14 days following the last dose of investigational product.

- French patients: In France, a patient will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

Exclusion Criteria:

- Patients meeting any of the following criteria must not be enrolled in the study:
- Treatment in the 14 days prior to randomization with any cancer therapy (tumor embolization, chemotherapy, immunotherapy, biological therapy, or hormonal therapy) or treatment with mitomycin within 6 weeks prior to randomization. Such treatment may not be resumed or begun after study entry. Note: Patients receiving LH-RH analogue therapy prior to the study may continue to receive LH-RH analogues for the duration of study participation. Bisphosphonates are permitted if started prior to Day 1.
- Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity (with the exception of alopecia).
- Prior lapatinib therapy or other Her2/ErbB2 targeted therapy (except trastuzumab).
- Prior therapy with an anti-VEGF antibody or other VEGF/VEGF-R targeted therapy.
- Use of an investigational agent, including an investigational anti-cancer agent, within 28 days or 5 half-lives, whichever is longer, prior to the first dose of investigational product.
- Use of any prohibited medication within the timeframes listed in Section 8.1.3
- History of another malignancy.
- Note: Subjects who have had another malignancy and have been disease-free for 5 years, or subjects with a history of completely resected non-melanomatous skin carcinoma or successfully treated in situ carcinoma are eligible. If subject previously had breast cancer, it must have been HER2+ with either 3+ overexpression by IHC or unequivocal HER2 gene amplification by FISH or CISH.
- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 2

months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

- Clinically significant gastrointestinal abnormalities that may increase the risk for GI bleeding including, but not limited to:
- Active peptic ulcer disease
- Known intraluminal metastatic lesion/s with suspected bleeding
- Inflammatory bowel disease
- Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning study treatment.
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but limited to:
- Malabsorption syndrome
- Major resection of the stomach or small bowel.
- Presence of uncontrolled infection.
- Prolongation of corrected QT interval (QTc) > 480 msecs.
- History of any one or more of the following cardiovascular conditions within the past 6 months:
- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Arterial thrombosis
- Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (see Section 15.9 Appendix 9 for description).
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].

Note: Initiation or adjustment of antihypertensive medication(s) is permitted during the screening period, in order to control a patient's BP prior to randomization. Blood pressure must be re-assessed on two occasions that are separated by a minimum of 1 hour. The mean SBP / DBP values from each blood pressure assessment must be < 140/90mmHg in order for a patient to be eligible for the study. See Section 6.2 and Section 6.4.2 for details on blood pressure control and reassessment prior to study enrollment.

- History of cerebrovascular accident, including TIA, pulmonary embolism or deep venous thrombosis (DVT).
- Prior major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (other than ulcers due to inflammatory breast cancer).
- Evidence of active bleeding or bleeding diathesis.
- Hemoptysis within 6 weeks prior to first dose of investigational product.
- Known endobronchial lesions or involvement of large pulmonary vessels by tumor.
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures.
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to pazopanib or lapatinib.
- Have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment).

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT00558103

Contacts

Contact: US GSK Clinical Trials Call Center 877-379-3718

Show 132 Study Locations

Sponsors and Collaborators

GlaxoSmithKline

Investigators

Study Director: GSK Clinical Trials GlaxoSmithKline

More Information

No publications provided

Responsible Party:	GSK (Study Director)
ClinicalTrials.gov Identifier:	NCT00558103 History of Changes
Other Study ID Numbers:	VEG108838
Study First Received:	November 9, 2007
Last Updated:	July 8, 2010
Health Authority:	United States: Food and Drug Administration

Keywords provided by GlaxoSmithKline:

- Tykerb
- Her2
- ErbB2
- GW786034
- GW572016
- Skin
- Cutaneous Disease
- RECIST
- Inflammatory
- Breast Cancer
- Pazopanib
- Lapatinib

Additional relevant MeSH terms:

- Breast Neoplasms
- Neoplasms by Site
- Neoplasms
- Breast Diseases
- Skin Diseases
- Lapatinib
- Protein Kinase Inhibitors
- Enzyme Inhibitors
- Molecular Mechanisms of Pharmacological Action
- Pharmacologic Actions
- Antineoplastic Agents
- Therapeutic Uses

ClinicalTrials.gov processed this record on September 09, 2010

Dronedarone is less effective, but safer than amiodarone in atrial fibrillation

On the Horizon Rapid Review

NHS NPC National Prescribing Centre

27 October 2009,

An indirect comparison meta-analysis found that dronedarone was significantly less effective than amiodarone in preventing recurrence of AF, but was associated with fewer side effects requiring discontinuation. It was predicted that for every 100 people treated for one year for AF with dronedarone rather than amiodarone, there would be 23 more recurrences of AF and 6 fewer adverse events requiring discontinuation.

Level of evidence
Level 2 (limited quality, patient-orientated evidence) according to the SORT criteria

Action
Dronedarone may be launched in the UK by the end of 2009. It is likely to be indicated in clinically stable adult patients with history of, or current non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate. Contraindications, special warnings, and monitoring requirements (as will be described in the summary of product characteristics [SPC]) are not yet published.

The exact place in therapy of dronedarone is uncertain. Until NICE guidance on dronedarone is published (due June 2010) prescribers should continue to follow the existing NICE guideline for the management of AF. Dronedarone could be considered as an option, **within its licensed indications, by specialists** for those patients for whom amiodarone is indicated, but not appropriate, e.g. if there are intolerable adverse effects. Clinicians will need to balance whether the use of dronedarone — a less efficacious but possibly safer antiarrhythmic drug than amiodarone — is justified for their patients with AF. For patients who are already receiving and tolerating amiodarone and have not developed unacceptable side effects, there would appear to be no good reason to switch to dronedarone.

Dronedarone is likely to be significantly more expensive than currently used anti-arrhythmic drugs, which are mainly available generically. Local decision making bodies on medicines are advised to

engage with stakeholders and agree a protocol for use when dronedarone is launched. This includes identifying those patients for whom the drug may be appropriate and planning for possible NICE guidance. It is important that steps are taken to inform prescribers of any contraindications and precautions, to ensure that dronedarone is used appropriately.

What is the background to this?
On 24 September 2009, the EMEA Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for dronedarone (Multaq®). It recommended granting a marketing authorisation for adult clinically stable patients with history of, or current non-permanent AF, to prevent recurrence of AF or to lower ventricular rate. A key study considered in providing this opinion was the ATHENA trial, which we have reviewed in a previous blog. In the ATHENA trial of 4,628 patients with AF or flutter, dronedarone was more effective than placebo (mean follow-up of 21 months) in reducing cardiovascular (CV) hospital admissions or death from any cause (31.9% vs. 39.4%; hazard ratio 0.76, 95% confidence interval (CI) 0.69 to 0.84, P<0.001), as well as other trials.

Because of the limited information available from studies that directly compare the efficacy and safety of dronedarone with amiodarone, Piccini and colleagues carried out a systematic review and indirect comparison meta-analysis using data from placebo-controlled trials of the two drugs in over 6000 people with AF.

Further information about AF can be found on the cardiovascular floor of NPCi. Dronedarone has been reviewed in an On the Horizon bulletin. Dronedarone is part of the 19th wave of technology appraisals from NICE, but a NICE clinical guideline on the management of AF is already available.

What does this study claim?
The study claims that dronedarone is less effective than amiodarone for the maintenance of sinus rhythm, but has fewer side effects.

The meta-analysis identified a statistically significant estimated reduction in recurrent AF with amiodarone versus placebo (odds ratio [OR] 0.12; 95%CI 0.08 to 0.19) but not for dronedarone versus placebo (OR 0.79; 95% CI 0.33 to 1.87). Using a logistic regression model incorporating all trial evidence, amiodarone was found to be superior to dronedarone (OR 0.49; 95% CI 0.37 to 0.63; P<0.001) for the prevention of recurrent AF, but was more likely to result in adverse events requiring drug discontinuation (OR 1.81; 95% CI 1.33 to 2.46; P<0.001).

The authors also suggest a 'trend' for reduced mortality in favour of dronedarone, although no statistically significant difference between treatments was identified (P=0.066).

How does this relate to other studies?
These results are consistent with the results of the DIONYSOS trial that directly compared dronedarone with amiodarone for the maintenance of sinus rhythm. However, results of DIONYSOS are only reported in a press release and are yet to be published in a peer-reviewed journal. DIONYSOS was a study of 504 patients with AF (mean follow-up 7 months). Dronedarone was less effective than amiodarone in preventing AF recurrence, or withdrawal due to intolerance or lack of efficacy (74% vs. 55%, P<0.001). Fewer thyroid and neurological events were reported in the dronedarone patients, but there were more reports of diarrhoea, vomiting and nausea. Amiodarone caused more bradycardia and QT prolongation. No cases of Torsade de Pointes were reported.

So what?
The present study found that dronedarone was significantly less effective in preventing recurrence of AF, but was associated with fewer side effects leading to discontinuation than with amiodarone. The indirect meta-analytical approach used in this study has many limitations (see accompanying

Editorial) and the findings of this study can only be considered hypothesis generating and require confirmation from direct comparisons in adequately powered trials. Nevertheless, the reduction in efficacy and reduction in adverse effects seen in this study are consistent with the preliminary results from DIONYSOS.

Although the ATHENA study identified a significant benefit for preventing hospitalisation for CV events or death for dronedarone over placebo, no benefit over amiodarone has yet been demonstrated in this regard. Whether or not dronedarone offers any particular advantage over amiodarone for an individual with AF will require a value judgement of whether likely benefits from reduced side effects outweigh the disadvantage of a shorter time to recurrence of AF. At present there is no good quality clinical evidence from comparative studies measuring important patient-oriented outcomes (e.g. quality of life) demonstrating whether or not dronedarone offers any net clinical benefit over amiodarone at a population level.

NICE guidelines on the management of atrial fibrillation detail those situations where amiodarone might be considered. However, there are many other approaches that should be considered before, or as alternatives to, the use of amiodarone.

Full prescribing details (including dosage, contraindications, drug and food interactions, and monitoring requirements) for dronedarone have yet to be published. As discussed in a previous blog of the ATHENA trial, it may be advisable not to initiate therapy with dronedarone in patients with severe heart failure and left ventricular dysfunction.

Dronedarone is already licensed for use in the US. Contraindications in the US include patients with severe heart failure or those with NYHA 2 or 3 heart failure with a recent decompensation requiring hospitalisation or referral to a specialised heart failure clinic. Increases in serum creatinine have occurred in clinical trials with dronedarone, and there are potentially important drug interactions to consider (e.g. with strong CYP3A inhibitors such as voriconazole, and with drugs that prolong the QT interval, which might increase the risk of Torsade de Pointes). It is important that steps are taken to inform prescribers of any contraindications and precautions, to ensure that dronedarone is used and monitored appropriately.

Study details

Piccini JP, Hasselblad V, Peterson ED, et al. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. J Am Coll Cardiol 2009;54:1089–95

Design: Systematic review and indirect comparison meta-analysis of RCTs of amiodarone (4 studies) and dronedarone (4 studies) versus placebo for the prevention of AF.

Patients: The dronedarone and amiodarone trials included 5,967 and 669 patients respectively. The mean age across all trials was 65 years. Studies of subjects age <18 years and subjects with acute cardioversion, catheter ablation, and post-operative AF were excluded. In all 4 dronedarone trials, patients with permanent AF were excluded. Additional exclusion criteria included advanced symptomatic heart failure, a corrected QT interval >500ms, and bradycardia with a heart rate <50 beats/min. In contrast to the dronedarone trials, the amiodarone trials predominantly included patients with persistent and permanent AF.

Interventions: Dronedarone or amiodarone versus placebo. All trials had a follow up of at least 6 months (means of 13 and 16 months, respectively).

Comparison: The effect of amiodarone versus dronedarone was summarised by the use of indirect comparison meta-analysis and normal logistic meta-regression models.

Outcomes and Results:
There was a significant estimated reduction in recurrent AF with amiodarone versus placebo (OR 0.12; 95%CI 0.08 to 0.19) but not dronedarone versus placebo (OR 0.79; 95%CI 0.33 to 1.87). A normal logistic regression model incorporating all trial evidence found amiodarone superior to dronedarone (OR 0.49; 95%CI 0.37 to 0.63; P<0.001) for the prevention of recurrent AF. There was no statistically significant difference between amiodarone and dronedarone identified with regard to all-cause mortality (OR 1.61; 95% CI 0.97 to 2.68; P=0.066). More patients discontinued treatment because of adverse effects with amiodarone than with dronedarone (OR 1.81; 95%CI 1.33 to 2.46; P<0.001). For every 1,000 patients treated with dronedarone instead of amiodarone, it was estimated that there would be approximately 228 more recurrences of AF in exchange for 62 fewer adverse events requiring discontinuation of drug.

Sponsorship: The lead author is supported by an American College of Cardiology Foundation/Merck award.

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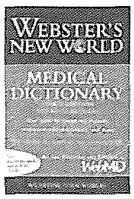

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Definition of Contraindication

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Contraindication: A condition which makes a particular treatment or procedure inadvisable. A contraindication may be absolute or relative.

- An absolute contraindication is a situation which makes a particular treatment or procedure absolutely inadvisable. In a baby, for example, aspirin is absolutely contraindicated because of the danger that aspirin will cause Reye syndrome.
- A relative contraindication is a condition which makes a particular treatment or procedure somewhat inadvisable but does not rule it out. For example, X-rays in pregnancy are relatively contraindicated (because of concern for the developing fetus) unless the X-rays are absolutely necessary.

A contraindication is literally contra- (against) an indication, against something that is indicated as advisable or necessary.

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233 HEART FAILURE

Eugene Braunwald

Heart failure is the pathophysiologic state in which an abnormality of *cardiac* function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues *and/or* can do so only from an abnormally elevated diastolic volume. Heart failure is frequently, but not always, caused by a defect in myocardial contraction, and then the term *myocardial failure* is appropriate. The latter may result from a primary abnormality in heart muscle, as occurs in the cardiomyopathies and in viral myocarditis (Chap. 239). Myocardial failure also may result from extramyocardial abnormalities, such as coronary atherosclerosis which leads to myocardial ischemia and infarction, as well as from abnormalities of the heart valves in which the heart muscle is damaged by the long-standing excessive hemodynamic burden imposed by the valvular abnormality, and/or by the rheumatic process (Chap. 236).

In other patients with heart failure, however, a similar clinical syndrome is present but without any detectable abnormality of *myocardial* function. In some of these patients the normal heart is suddenly presented with a mechanical load that exceeds its capacity, such as an acute hypertensive crisis, rupture of an aortic valve cusp, or massive pulmonary embolism. Heart failure, in the presence of normal myocardial function, also occurs in chronic conditions in which there is impairment of filling of the ventricles due to a mechanical abnormality such as tricuspid and/or mitral stenosis, constrictive pericarditis without myocardial involvement, endocardial fibrosis, and some forms of hypertrophic cardiomyopathy. In many patients with heart failure, particularly those with valvular or congenital heart disease, a combination of impaired myocardial function and mechanical abnormality exists.

Heart failure should be distinguished from (1) conditions in which there is circulatory congestion consequent to abnormal salt and water retention but in which there is no disturbance of cardiac function per se (the latter syndrome, termed the *congested state*, may result from the abnormal salt and water retention of renal failure or from excess parenteral administration of fluids and electrolytes) and (2) noncardiac causes of inadequate cardiac output, including shock due to hypovolemia and redistribution of blood volume (Chap. 38).

The ventricles respond to a chronically increased hemodynamic burden with the development of hypertrophy. With volume overload when the ventricle is called on to deliver an elevated cardiac output for prolonged periods, as in valvular regurgitation, it develops *eccentric hypertrophy*, i.e., cavity dilatation, with an increase in muscle mass so that the ratio between wall thickness and ventricular cavity size remains relatively constant. With chronic pressure overload, as in valvular aortic stenosis or untreated hypertension, it develops *concentric hypertrophy*, in which the ratio between wall thickness and ventricular cavity size increases. In both conditions, a stable hyperfunctioning state may exist for many years, but myocardial function may ultimately deteriorate, leading to heart failure. Heart failure represents a major public health problem in industrialized nations. It appears to be the only common cardiovascular condition that is increasing in prevalence and incidence. In the United States, heart failure is responsible for almost 1 million hospital admissions and 40,000 deaths annually. Since heart failure is more common in the elderly, its prevalence is likely to continue to increase as the population ages.

CAUSES OF HEART FAILURE

In evaluating patients with heart failure, it is important to identify not only the *underlying cause* of the heart disease but also the *precipitating cause* of heart failure. The cardiac abnormality produced by a congenital or acquired lesion such as valvular aortic stenosis may exist for many years and produce no clinical disability. Frequently, however, clinical manifestations of heart failure appear for the first time in the course of some acute disturbance that places an additional load on a myocardium that chronically is excessively burdened. The heart may be compensated but have little additional reserve, and the additional load imposed by a precipitating cause results in further deterioration of cardiac function. Identification of such precipitating causes is of critical importance because their prompt alleviation may be lifesaving. In the absence of underlying heart disease, these acute disturbances do not usually, by themselves, lead to heart failure.

PRECIPITATING CAUSES

1. *Infection.* Patients with pulmonary vascular congestion are also more susceptible to pulmonary infections; any infection may precipitate heart failure. The resulting fever, tachycardia, and hypoxemia and the increased metabolic demands may place a further burden on the overloaded, but compensated myocardium of a patient with chronic heart disease.

2. *Anemia.* In the presence of anemia, the oxygen needs of the metabolizing tissues can be met only by an increase in the cardiac output (Chap. 59). Although such an increase in cardiac output can be sustained by a normal heart, a diseased, overloaded, but otherwise compensated heart may be unable to augment sufficiently the volume of blood that it delivers to the periphery. In this manner, the combination of anemia and previously compensated heart disease can lead to inadequate oxygen delivery to the periphery and precipitate heart failure.

3. *Thyrotoxicosis and pregnancy.* As in anemia and fever, in thyrotoxicosis and pregnancy, adequate tissue perfusion requires an increased cardiac output. The development or intensification of heart failure may actually be one of the first clinical manifestations of hyperthyroidism in a patient with underlying heart disease that was previously compensated (Chap. 331). Similarly, heart failure not infrequently occurs for the first time during pregnancy in women with rheumatic valvular disease, in whom cardiac compensation may return following delivery.

4. *Arrhythmias.* In patients with compensated heart disease, arrhythmias are among the most frequent precipitating causes of heart failure. They exert a deleterious effect for a variety of reasons: (a) Tachyarrhythmias reduce the time period available for ventricular filling. In patients with ischemic heart disease, tachyarrhythmias also may cause ischemic myocardial dysfunction. (b) The dissociation between atrial and ventricular contractions characteristic of many arrhythmias results in the loss of the atrial booster pump mechanism, thereby raising atrial pressures. (c) In any arrhythmia associated with abnormal intraventricular conduction, myocardial performance may become further impaired because of the loss of normal synchronicity of ventricular contraction. (d) Marked bradycardia associated with complete atrioventricular block or other severe bradyarrhythmias reduces cardiac output unless stroke volume rises reciprocally; this compensatory response cannot occur with serious myocardial dysfunction even in the absence of heart failure.

5. *Rheumatic and other forms of myocarditis.* Acute rheumatic fever and a variety of other inflammatory or infectious processes affecting the myocardium may impair myocardial function in patients with or without preexisting heart disease (Chaps. 236 and 239).

6. *Infective endocarditis.* The additional valvular damage, anemia, fever, and myocarditis that often occur as a consequence of infective endocarditis may, singly or in concert, precipitate heart failure (Chap. 126).

7. *Physical, dietary, fluid, environmental, and emotional excesses.* The augmentation of sodium intake, the inappropriate discontinuation of medications to treat heart failure, blood transfusions, physical overexertion, excessive environmental heat or humidity, and emotional crises all may precipitate heart failure in patients with heart disease who were previously compensated.

8. *Systemic hypertension.* Rapid elevation of arterial pressure, as may occur in some instances of hypertension of renal origin or upon discontinuation of antihypertensive medication, may result in cardiac decompensation (Chap. 246).

9. *Myocardial infarction.* In patients with chronic but compensated ischemic heart disease, a fresh infarct, sometimes otherwise silent clinically, may further impair ventricular function and precipitate heart failure (Chap. 243).

10. *Pulmonary embolism.* Physically inactive patients with low cardiac output are at increased risk of developing thrombi in the veins of the lower extremities or the pelvis. Pulmonary emboli may result in further elevation of pulmonary arterial pressure, which in turn may produce or intensify ventricular failure. In the presence of pulmonary vascular congestion, such emboli also may cause pulmonary infarction (Chap. 261).

A systematic search for these precipitating causes should be made in every patient with the new development or recent intensification of heart failure, especially if it is refractory to the usual methods of therapy. If properly recognized, the precipitating cause of heart failure usually can be treated more effectively than the underlying cause. Therefore, the prognosis in patients with heart failure in whom a precipitating cause can be identified, treated, and eliminated is more favorable than it is in patients in whom the underlying disease process has advanced to the point of producing heart failure.

FORMS OF HEART FAILURE

Heart failure may be described as *systolic* or *diastolic*, *high-output* or *low-output*, *acute* or *chronic*, *right-sided* or *left-sided*, and *forward* or *backward*. These descriptors are often useful in a clinical setting, particularly early in the patient's course, but late in the course of chronic heart failure the differences between them often become blurred.

SYSTOLIC VERSUS DIASTOLIC FAILURE The distinction between these two forms of heart failure, described on p. 1284 and in Fig. 232-8, relates to whether the principal abnormality is the inability to contract normally and expel sufficient blood (systolic failure) or to relax and fill normally (diastolic failure). The major clinical manifestations of systolic failure relate to an inadequate cardiac output with weakness, fatigue, reduced exercise tolerance, and other symptoms of hypoperfusion, while in diastolic failure they relate principally to an elevation of filling pressures. In many patients, particularly those who have both ventricular hypertrophy *and* dilatation, abnormalities both of contraction and relaxation coexist.

Diastolic heart failure may be caused by increased resistance to ventricular inflow and reduced ventricular diastolic capacity (constrictive pericarditis and restrictive, hypertensive, and hypertrophic cardiomyopathy), impaired ventricular relaxation (acute myocardial ischemia, hypertrophic cardiomyopathy), and myocardial fibrosis and infiltration (dilated, chronic ischemic, and restrictive cardiomyopathy).

HIGH-OUTPUT VERSUS LOW-OUTPUT HEART FAILURE It is useful to classify patients with heart failure into those with a low cardiac output, i.e., *low-output heart failure*, and those with an elevated cardiac output, i.e., *high-output heart failure*. The former occurs secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease, while the latter is seen in patients with heart failure and hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease. In clinical practice, however, low-output and high-output heart failure cannot always be readily distinguished. The normal range of cardiac output is wide [2.2 to 3.5 (L/min)/m^2], and in many patients with so-called low-output heart failure the cardiac output may actually be just within the normal range at rest (although it is lower than it had been previously), but it fails to rise normally during exertion. On the other hand, in patients with so-called high-output heart failure the output may not exceed the upper limits of normal (although it would have been elevated had it been measured before heart failure supervened), but rather it may have fallen to the upper limit of normal. Regardless of the *absolute* level of the cardiac output, however, cardiac failure may be said to be present when the characteristic clinical manifestations described below are accompanied by a depression of the curve relating ventricular end-diastolic volume to cardiac performance (see Fig. 232-6).

An integral physiologic component of *systolic* heart failure (p. 1284) is the delivery of an inadequate quantity of oxygen required by the metabolizing tissues. In the absence of peripheral shunting of blood, this is reflected in an abnormal widening of the normal arterial–mixed venous oxygen difference (35 to 50 mL/L in the basal state). In mild cases, such an abnormality may not be present at rest but becomes evident only during exertion or other hypermetabolic states. In patients with high cardiac output states, such as those associated with arteriovenous fistula or thyrotoxicosis, the arterial–mixed venous oxygen difference is normal or low. The mixed venous oxygen saturation is raised by the admixture of blood that has been diverted from the metabolizing tissues, and it may be presumed that even in these patients the delivery of oxygen to the latter is reduced despite the normal or even elevated mixed venous oxygen saturation. When heart failure occurs in such patients, the arterial–mixed venous oxygen difference, regardless of the absolute value, still exceeds the level that existed prior to the development of heart failure. Therefore, the cardiac output, though normal or even elevated, is lower than before heart failure supervened.

The mechanisms responsible for the development of heart failure in patients whose cardiac outputs are initially high are complex and depend on the underlying disease process. In most of these conditions the heart is called on to pump abnormally large quantities of blood in order to deliver the normal quota of oxygen to the metabolizing tissues. The burden placed on the myocardium by the increased flow load resembles that produced by chronic regurgitant valvular lesions. In addition, thyrotoxicosis and beriberi also may impair myocardial metabolism directly, while severe anemia may interfere with myocardial function by producing myocardial anoxia, especially in the presence of underlying obstructive artery disease.

ACUTE VERSUS CHRONIC HEART FAILURE The prototype of acute heart failure is the patient who is entirely well but who suddenly develops a large myocardial infarction or rupture of a cardiac valve. Chronic heart failure is typically observed in patients with dilated cardiomyopathy or multivalvular heart disease that develops or progresses slowly. Acute heart failure is usually largely systolic, and the sudden reduction in cardiac output often results in systemic hypotension without peripheral edema. In chronic heart failure, arterial pressure tends to be well maintained until very late in the course, but there is often accumulation of edema. Despite these obvious differences in clinical presentation, there is no fundamental distinction between acute and chronic heart failure. For example, intensive efforts to prevent expansion of blood volume by means of dietary sodium restriction and the administration of diuretics will frequently delay the development of exertional dyspnea and edema in patients with chronic valvular heart disease (i.e., it will mask the clinical manifestations of chronic heart failure) until an acute episode, such as an arrhythmia or infection, precipitates acute heart failure. Without intensive efforts to restrict blood volume, the same patients would have been considered to have been suffering from chronic heart failure, even though their underlying myocardial disease was no further advanced.

RIGHT-SIDED VERSUS LEFT-SIDED HEART FAILURE Many of the clinical manifestations of heart failure result from the accumulation of excess fluid behind either one or both ventricles (Chaps. 32 and 37). This fluid usually localizes upstream to (behind) the specific cardiac chamber that is initially affected. For example, patients in whom the left ventricle is mechanically overloaded (e.g., aortic stenosis) or weakened (e.g., postmyocardial infarction) develop dyspnea and orthopnea as a result of pulmonary congestion, a condition referred to as *left-sided heart failure*. In contrast, when the underlying abnormality affects the right ventricle primarily (e.g., valvular pulmonic stenosis or pulmonary hypertension secondary to pulmonary thromboembolism), symptoms resulting from pulmonary congestion such as orthopnea or paroxysmal nocturnal dyspnea are less common and edema, congestive hepatomegaly, and systemic venous distention, i.e., clinical manifestations of *right-sided heart failure*, are more prominent. However, when heart failure has existed for months or years,

such localization of excess fluid behind the failing ventricle may no longer exist. For example, patients with long-standing aortic valve disease or systemic hypertension may have ankle edema, congestive hepatomegaly, and systemic venous distention late in the course of their disease, even though the abnormal hemodynamic burden initially was placed on the left ventricle. This occurs in part because of the secondary pulmonary hypertension and resultant right-sided heart failure but also because of the retention of salt and water characteristic of all forms of heart failure (Chap. 37). The muscle bundles composing both ventricles are continuous, and both ventricles share a common wall, the interventricular septum. Also, biochemical changes that occur in heart failure and that may be involved in the impairment of myocardial function (Chap. 232), such as norepinephrine depletion and alterations in the activity of myosin ATPase, occur in the myocardium of *both* ventricles, regardless of the specific chamber on which the abnormal hemodynamic burden is placed initially.

BACKWARD VERSUS FORWARD HEART FAILURE For many years a controversy has revolved around the question of the mechanism of the clinical manifestations resulting from heart failure. The concept of *backward heart failure* contends that in heart failure, one or the other ventricle fails to discharge its contents or fails to fill normally. As a consequence, the pressures in the atrium and venous system behind the failing ventricle rise, and retention of sodium and water occurs as a consequence of the elevation of systemic venous and capillary pressures and the resultant transudation of fluid into the interstitial space (Chap. 37). In contrast, the proponents of the *forward heart failure* hypothesis maintain that the clinical manifestations of heart failure result directly from an inadequate discharge of blood into the arterial system. According to this concept, salt and water retention is a consequence of diminished renal perfusion and excessive proximal tubular sodium reabsorption and of excessive distal tubular reabsorption through activation of the renin-angiotensin-aldosterone system.

A rigid distinction between *backward* and *forward* heart failure (like a rigid distinction between right and left heart failure) is artificial, since both mechanisms appear to operate to varying extents in most patients with heart failure. However, the rate of onset of heart failure often influences the clinical manifestations. For example, when a large portion of the left ventricle is suddenly destroyed, as in myocardial infarction, although stroke volume and blood pressure are suddenly reduced (both manifestations of forward failure), the patient may succumb to acute pulmonary edema, a manifestation of backward failure. If the patient survives the acute insult, clinical manifestations resulting from a chronically depressed cardiac output, including the abnormal retention of fluid within the systemic vascular bed, may develop. Similarly, in the case of massive pulmonary embolism, the right ventricle may dilate and the systemic venous pressure may rise to high levels (backward failure), or the patient may develop shock secondary to low cardiac output (forward failure), but this low-output state may have to be maintained for some days before sodium and water retention sufficient to produce peripheral edema occurs.

REDISTRIBUTION OF CARDIAC OUTPUT The redistribution of cardiac output serves as an important compensatory mechanism when cardiac output is reduced. This redistribution is most marked when a patient with heart failure exercises, but as heart failure advances, redistribution occurs even in the basal state. Blood flow is redistributed so that the delivery of oxygen to vital organs, such as the brain and myocardium, is maintained at normal or near-normal levels, while flow to less critical areas, such as the cutaneous and muscular beds and viscera, is reduced. Vasoconstriction mediated by the adrenergic nervous system is largely responsible for this redistribution, which in turn may be responsible for many of the clinical manifestations of heart failure, such as fluid accumulation (reduction of renal flow), low-grade fever (reduction of cutaneous flow), and fatigue (reduction of muscle flow).

SALT AND WATER RETENTION (See also Chap. 37)

When the volume of blood pumped by the left ventricle into the systemic vascular bed is reduced, a complex sequence of adjustments occurs that ultimately results in the abnormal accumulation of fluid. On the one hand, many of the troubling clinical manifestations of heart failure are secondary to this excessive retention of fluid; on the other, this abnormal fluid accumulation and the expansion of blood volume that accompanies it also constitute an important compensatory mechanism that tends to maintain cardiac output and therefore perfusion of the vital organs. Except in the terminal stages of heart failure, the ventricle operates on an ascending, albeit depressed and flattened, function curve (Fig. 232-6), and the augmented ventricular end-diastolic volume and pressure characteristic of heart failure must be regarded as helping to maintain the reduced cardiac output, despite causing pulmonary and/or systemic venous congestion.

Congestive heart failure is also characterized by a complex series of neurohumoral adjustments. The activation of the adrenergic nervous system is discussed on p. 1285; there is also activation of the renin-angiotensin-aldosterone system and increased release of antidiuretic hormone. These influences elevate systemic vascular resistance and enhance sodium and water retention and potassium excretion. These actions are, to a minor extent, opposed by the release of atrial natriuretic peptide, which also occurs in congestive heart failure. Patients with severe heart failure may exhibit a reduced capacity to excrete a water load, which may result in dilutional hyponatremia. In the presence of heart failure, effective filling of the systemic arterial bed is reduced, a condition that initiates the renal and hormonal changes mentioned above.

The elevation of systemic venous pressure and the alterations of renal and adrenal function characteristic of heart failure vary in their relative importance in the production of edema in different patients with heart failure. The renin-angiotensin-aldosterone axis is activated most intensely by acute heart failure, and its activity tends to decline as heart failure becomes chronic. In patients with tricuspid valve disease or constrictive pericarditis, the elevated venous pressure and the transudation of fluid from systemic capillaries appear to play the dominant role in edema formation. On the other hand, severe edema may be present in patients with ischemic or hypertensive heart disease, in whom systemic venous pressure is within normal limits or is only minimally elevated. In such patients, the retention of salt and water is probably due primarily to a redistribution of cardiac output and a concomitant reduction in renal perfusion, as well as activation of the renin-angiotensin-aldosterone axis. Regardless of the mechanisms involved in fluid retention, untreated patients with chronic congestive heart failure have elevations of total blood volume, interstitial fluid volume, and body sodium. These abnormalities diminish after clinical compensation has been achieved by treatment.

CLINICAL MANIFESTATIONS OF HEART FAILURE

Dyspnea Respiratory distress that occurs as the result of increased effort in breathing is the most common symptom of heart failure (Chap. 32). In early heart failure, dyspnea is observed only during activity, when it may simply represent an aggravation of the breathlessness that occurs normally under these circumstances. As heart failure advances, however, dyspnea appears with progressively less strenuous activity. Ultimately, breathlessness is present even when the patient is at rest. The principal difference between exertional dyspnea in normal persons and in patients with heart failure is the degree of activity necessary to induce the symptom. Cardiac dyspnea is observed most frequently in patients with elevations of pulmonary venous and capillary pressures. Such patients usually have engorged pulmonary vessels and interstitial pulmonary edema, which may be evident on radiologic examination. This reduces the compliance of the lungs and thereby increases the work of the respiratory muscles required to inflate the lungs. The activation of receptors in the lungs results in the rapid, shallow breathing characteristic of cardiac dyspnea. The oxygen cost of breathing is increased by the excessive work of the respiratory muscles. This is coupled with the diminished delivery

of oxygen to these muscles, which occurs as a consequence of the reduced cardiac output and which may contribute to fatigue of the respiratory muscles and the sensation of shortness of breath.

Orthopnea Dyspnea in the recumbent position is usually a later manifestation of heart failure than exertional dyspnea. Orthopnea occurs because of the redistribution of fluid from the abdomen and lower extremities into the chest causing an increase in the pulmonary capillary hydrostatic pressure, as well as elevation of the diaphragm accompanying supine posture. Patients with orthopnea must elevate their heads on several pillows at night and frequently awaken short of breath or coughing (the so-called nocturnal cough) if their heads slip off the pillows. The sensation of breathlessness usually is relieved by sitting upright, since this position reduces venous return and pulmonary capillary pressure, and many patients report that they find relief from sitting in front of an open window. In far-advanced heart failure, orthopnea may become so severe that patients cannot lie down at all and must spend the entire night in a sitting position. On the other hand, in other patients with long-standing, severe left ventricular failure, symptoms of pulmonary congestion may actually diminish with time as the function of the right ventricle becomes impaired.

Paroxysmal (Nocturnal) Dyspnea This term refers to attacks of severe shortness of breath and coughing that generally occur at night, usually awaken the patient from sleep, and may be quite frightening. Though simple orthopnea may be relieved by sitting upright at the side of the bed with legs dependent, in the patient with paroxysmal nocturnal dyspnea, coughing and wheezing often persist even in this position. The depression of the respiratory center during sleep may reduce ventilation sufficiently to lower arterial oxygen tension, particularly in patients with interstitial lung edema and reduced pulmonary compliance. Also, ventricular function may be further impaired at night because of reduced adrenergic stimulation of myocardial function. *Cardiac asthma* is closely related to paroxysmal nocturnal dyspnea and nocturnal cough and is characterized by wheezing secondary to bronchospasm—most prominent at night. *Acute pulmonary edema* (Chap. 32) is a severe form of cardiac asthma due to marked elevation of pulmonary capillary pressure leading to alveolar edema, associated with extreme shortness of breath, rales over the lung fields, and the transudation and expectoration of blood-tinged fluid. If not treated promptly, acute pulmonary edema may be fatal.

Cheyne-Stokes Respiration Also known as *periodic* or *cyclic respiration*, Cheyne-Stokes respiration is characterized by diminished sensitivity of the respiratory center to arterial P_{CO_2}. There is an apneic phase, during which the arterial P_{O_2} falls and the arterial P_{CO_2} rises. These changes in the arterial blood stimulate the depressed respiratory center, resulting in hyperventilation and hypocapnia, followed in turn by recurrence of apnea. Cheyne-Stokes respiration occurs most often in patients with cerebral atherosclerosis and other cerebral lesions, but the prolongation of the circulation time from the lung to the brain that occurs in heart failure, particularly in patients with hypertension and coronary artery disease and associated cerebral vascular disease, also appears to precipitate this form of breathing.

Fatigue, Weakness, and Abdominal Symptoms These nonspecific but common symptoms of heart failure are related to the reduction of perfusion of skeletal muscle. Exercise capacity is reduced by the limited ability of the failing heart to increase its output and deliver oxygen to the exercising muscle. Anorexia and nausea associated with abdominal pain and fullness are frequent complaints and may be related to the congested liver and portal venous system.

Cerebral Symptoms In severe heart failure, particularly in elderly patients with accompanying cerebral arteriosclerosis, reduced cerebral perfusion, and arterial hypoxemia, there may be alterations in the mental state characterized by confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety. *Nocturia* is common in heart failure and may contribute to insomnia.

PHYSICAL FINDINGS (See Chap. 227) In moderate heart failure, the patient appears to be in no distress at rest except that he or she may be uncomfortable when lying flat for more than a few minutes. In more severe heart failure, the pulse pressure may be diminished, reflecting a reduction in stroke volume, and occasionally, the diastolic arterial pressure is elevated as a consequence of generalized vasoconstriction. In acute heart failure, hypotension may be prominent. There may be cyanosis of the lips and nail beds and sinus tachycardia, and the patient may insist on sitting upright. *Systemic venous pressure* is often abnormally elevated in heart failure and may be recognized by observing the extent of distention of the jugular veins. In the early stages of heart failure, the venous pressure may be normal at rest but may become abnormally elevated during and immediately after exertion as well as with sustained pressure on the abdomen (positive abdominojugular reflux).

Third and fourth heart sounds are often audible but are not specific for heart failure, and *pulsus alternans*, i.e., a regular rhythm in which there is alternation of strong and weak cardiac contractions and therefore alternation in the strength of the peripheral pulses, may be present. Pulsus alternans, a sign of severe heart failure, may be detected by sphygmomanometry and in more severe instances by palpation; it frequently follows an extrasystole and is observed most commonly in patients with cardiomyopathy or hypertensive or ischemic heart disease.

Pulmonary Rales Moist, inspiratory, crepitant rales and dullness to percussion over the lung bases are common in patients with heart failure and elevated pulmonary venous and capillary pressures. In patients with pulmonary edema, rales may be heard widely over both lung fields; they are frequently coarse and sibilant and may be accompanied by expiratory wheezing. Rales may, however, be caused by many conditions other than left ventricular failure. Some patients with long-standing heart failure have no rales because of increased lymphatic drainage of alveolar fluid.

Cardiac Edema (See Chap. 37) This is usually dependent, occurring in the legs symmetrically, particularly in the pretibial region and ankles in ambulatory patients, in whom it is most prominent in the evening, and in the sacral region of individuals at bed rest. Pitting edema of the arms and face occurs rarely and then only late in the course of heart failure.

Hydrothorax and Ascites Pleural effusion in congestive heart failure results from the elevation of pleural capillary pressure and transudation of fluid into the pleural cavities. Since the pleural veins drain into *both* the systemic and pulmonary veins, hydrothorax occurs most commonly with marked elevation of pressure in both venous systems but also may be seen with marked elevation of pressure in either venous bed. It is more frequent in the right pleural cavity than in the left. *Ascites* also occurs as a consequence of transudation and results from increased pressure in the hepatic veins and the veins draining the peritoneum (Chap. 46). Marked ascites occurs most frequently in patients with tricuspid valve disease and constrictive pericarditis.

Congestive Hepatomegaly An enlarged, tender, pulsating liver also accompanies systemic venous hypertension and is observed not only in the same conditions in which ascites occurs but also in milder forms of heart failure from any cause. With prolonged, severe hepatomegaly, as in patients with tricuspid valve disease or chronic constrictive pericarditis, enlargement of the spleen, i.e., congestive splenomegaly, also may occur.

Jaundice This is a late finding in congestive heart failure and is associated with elevations of both the direct- and indirect-reacting bilirubin; it results from impairment of hepatic function secondary to hepatic congestion and the hepatocellular hypoxia associated with central lobular atrophy. Serum transaminase concentrations are frequently elevated. If hepatic congestion occurs acutely, the jaundice may be severe and the enzymes strikingly elevated.

Cardiac Cachexia With severe chronic heart failure there may be serious weight loss and cachexia because of (1) elevation of circulating concentrations of tumor necrosis factor; (2) elevation of the metabolic rate, which results in part from the extra work performed by the respiratory muscles, the increased oxygen needs of the hypertrophied heart, and/or the discomfort associated with severe heart failure; (3)

anorexia, nausea, and vomiting due to central causes, to digitalis intoxication, or to congestive hepatomegaly and abdominal fullness; (4) impairment of intestinal absorption due to congestion of the intestinal veins; and (5) rarely, in patients with particularly severe failure of the right side of the heart, protein-losing enteropathy.

Other Manifestations With reduction of blood flow, the extremities may be cold, pale, and diaphoretic. Urine flow is depressed, and the urine contains albumin and has a high specific gravity and a low concentration of sodium. In addition, prerenal azotemia may be present. In patients with long-standing severe heart failure, impotence and depression are common.

ROENTGENOGRAPHIC FINDINGS In addition to the enlargement of the particular chambers characteristic of the lesion responsible for heart failure, distention of pulmonary veins and redistribution to the apices is common in patients with heart failure and elevated pulmonary vascular pressures. Also, pleural effusions may be evident and associated with interlobar effusions.

DIFFERENTIAL DIAGNOSIS The diagnosis of congestive heart failure may be established by observing some combination of the clinical manifestations of heart failure described above, together with the findings characteristic of one of the etiologic forms of heart disease. Table 233-1 shows the Framingham criteria, which are useful in the diagnosis of heart failure. Since chronic heart failure is often associated with cardiac enlargement, the diagnosis should be questioned, but is by no means excluded, when all chambers are normal in size. Two-dimensional echocardiography is particularly useful in assessing the dimensions of each cardiac chamber. Heart failure may be difficult to distinguish from pulmonary disease, and the differential diagnosis is discussed in Chap. 32. Pulmonary embolism also presents many of the manifestations of heart failure, but hemoptysis, pleuritic chest pain, a right ventricular lift, and the characteristic mismatch between ventilation and perfusion on lung scan should point to this diagnosis (see Chap. 261).

Ankle edema may be due to varicose veins, cyclic edema, or gravitational effects (Chap. 37), but in these patients there is no jugular venous hypertension at rest or with pressure over the abdomen. Edema secondary to renal disease can usually be recognized by appropriate renal function tests and urinalysis and is rarely associated with elevation of venous pressure. Enlargement of the liver and ascites occur in patients with hepatic cirrhosis and also may be distinguished from heart failure by normal jugular venous pressure and absence of a positive abdominojugular reflux.

Table 233-1

Framingham Criteria for Diagnosis of Congestive Heart Failure*

MAJOR CRITERIA
Paroxysmal nocturnal dyspnea
Neck vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure (>16 cmH_2O)
Positive hepatojugular reflux
MINOR CRITERIA
Extremity edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity reduced by one-third from normal
Tachycardia (≥120 bpm)
MAJOR OR MINOR
Weight loss ≥4.5 kg over 5 days' treatment

* To establish a clinical diagnosis of congestive heart failure by these criteria, at least one major and two minor criteria are required.

SOURCE: KKL Ho et al, Circulation 88:107, 1993.

TREATMENT

The treatment of heart failure may be divided logically into three components: (1) removal of the precipitating cause, (2) correction of the underlying cause, and (3) control of the congestive heart failure state. The first two are discussed in other chapters together with each specific disease entity or complication. An example is the treatment of pneumococcal pneumonia and acute heart failure (removal of the precipitating cause) followed by mitral valvotomy (correction of the underlying cause) in a patient with mitral stenosis. In many instances, surgical treatment will correct or at least alleviate the underlying cause. The third component of the treatment of heart failure, i.e., control of the congestive heart failure state, may, in turn, be divided into three categories: (1) reduction of cardiac work load, including both the preload and the afterload; (2) control of excessive retention of salt and water; and (3) enhancement of myocardial contractility. The vigor with which each of these measures is pursued in any individual patient should depend on the severity of heart failure. Following effective treatment, recurrence of the clinical manifestations of heart failure can often be prevented by continuing those measures that were originally effective.

While a simple rule for the treatment of all patients with heart failure cannot be formulated because of the varied etiologies, hemodynamic features, clinical manifestations, and severity of heart failure, insofar as the treatment of chronic congestive failure is concerned, the administration of an angiotensin-converting enzyme inhibitor (e.g., lisinopril 10 mg q.d.) has been shown to retard the development of heart failure and should be begun early in patients with cardiac dilatation and/or hypertrophy, even if they are asymptomatic. Then, as symptoms develop, simple measures such as moderate restriction of activity and sodium intake should be tried (Fig. 233-1). If these and the ACE inhibitor are insufficient, therapy with a combination of a diuretic, a vasodilator, and usually a digitalis glycoside is then begun. The next step is more rigorous restriction of salt intake and higher doses of loop diuretics, sometimes accompanied by other diuretics. If heart failure persists, hospitalization with rigid salt restriction, bed rest, intravenous vasodilators, and positive inotropic agents comes next. In some patients, the order in which these measures are applied may be altered.

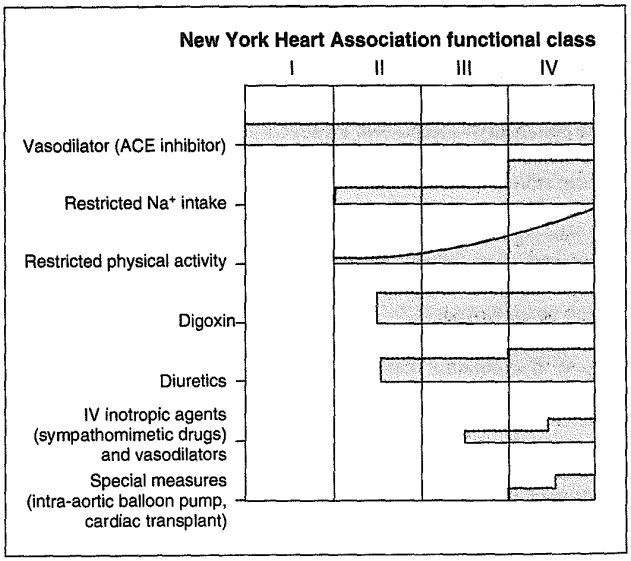

FIGURE 233-1 Overview of the treatment of heart failure. *[From RA Kelly, TW Smith: Treatment of stable heart failure: Digitalis and diuretics, in Heart Failure: Cardiac Function and Dysfunction, in WS Colucci (ed), Atlas of Heart Diseases, vol 4, E Braunwald (series ed), Philadelphia, Current Medicine, 1995.]*

COMPLICATIONS OF MYOCARDIAL INFARCTION AND THEIR TREATMENT

VENTRICULAR DYSFUNCTION Following myocardial infarction, the left ventricle undergoes a series of changes in shape, size, and thickness in both the infarcted and noninfarcted segments. This process is referred to as *ventricular remodeling* and generally precedes the development of clinically evident congestive heart failure in the months to years after infarction. Soon after myocardial infarction, the left ventricle begins to dilate. Acutely, this results from expansion of the infarct (i.e., slippage of muscle bundles, disruption of normal myocardial cells, and tissue loss within the necrotic zone, resulting in disproportionate thinning and elongation of the infarct zone). Later, lengthening of the noninfarcted segments occurs as well. The overall chamber enlargement that occurs is related to the size and location of the infarct, with greater dilation following infarction of the apex of the left ventricle and causing more marked hemodynamic impairment, more frequent heart failure, and a poorer prognosis. Progressive dilation and its clinical consequences may be ameliorated by therapy with ACE inhibitors and other vasodilators (e.g., nitrates) (Fig. 243-2). Thus, in patients with a lowered ejection fraction (less than 40 percent), regardless of whether or not heart failure is present, ACE inhibitors should be prescribed.

HEMODYNAMIC ASSESSMENT Pump failure is now the primary cause of in-hospital death from acute myocardial infarction. The extent of ischemic necrosis correlates well with the degree of pump failure and with mortality, both early (within 10 days of infarction) and later. The most common clinical signs are pulmonary rales and S_3 and S_4 gallop rhythms. Pulmonary congestion is also frequently seen on the chest roentgenogram. Elevation of left ventricular filling pressure and pulmonary artery pressure are the characteristic hemodynamic findings, but it should be appreciated that these findings may result from a reduction of ventricular compliance (diastolic failure) and/or a reduction of stroke volume with secondary cardiac dilation (systolic failure) (Chap. 232).

A classification originally proposed by Killip divides patients into four groups: class I, no signs of pulmonary or venous congestion; class II, moderate heart failure as evidenced by rales at the lung bases, S_3 gallop, tachypnea, or signs of failure of the right side of the heart, including venous and hepatic congestion; class III, severe heart failure, pulmonary edema; and class IV, shock with systolic pressure less than 90 mmHg and evidence of peripheral vasoconstriction, peripheral cyanosis, mental confusion, and oliguria. The expected hospital mortality rate of patients in these clinical classes when this classification was established in 1967 was as follows: class I, 0 to 5 percent; class II, 10 to 20 percent; class III, 35 to 45 percent; and class IV, 85 to 95 percent. With advances in management, the mortality rate has fallen, perhaps by as much as one-third to one-half, in each class.

Hemodynamic evidence of abnormal left ventricular function appears when contraction is seriously impaired in 20 to 25 percent of the left ventricle. Infarction of 40 percent or more of the left ventricle usually results in cardiogenic shock (see below). Positioning of a balloon flotation catheter in the pulmonary artery permits monitoring of left ventricular filling pressure; this technique is useful in patients who exhibit hypotension and/or clinical evidence of heart failure. Cardiac output can also be determined with a pulmonary artery catheter. With the addition of intraarterial pressure monitoring, systemic vascular resistance can be calculated as a guide to adjusting vasopressor and vasodilator therapy. Some patients with acute myocardial infarction have markedly elevated left ventricular filling pressures (>22 mmHg) and normal cardiac indexes [>2.6 and >3.6 L/(min/m^2)], while others have relatively low filling pressures (<15 mmHg) and reduced cardiac indexes. The former patients usually benefit from diuresis, while the latter may respond to volume expansion by means of intravenous administration of colloid-containing solutions.

Hypovolemia This is an easily corrected condition that may contribute to the hypotension and vascular collapse associated with myocardial infarction in some patients. Hypovolemia may be secondary to previous diuretic use, to reduced fluid intake during the early stages of the illness, and/or to vomiting associated with pain or medications. Consequently, hypovolemia should be identified and corrected in patients with acute myocardial infarction and hypotension before more vigorous forms of therapy are embarked on. Central venous pressure reflects right rather than left ventricular filling pressure and is an inadequate guide for adjustment of blood volume, since left ventricular function is almost always affected much more adversely than right ventricular function in acute myocardial infarction. The optimal left ventricular filling or pulmonary artery wedge pressure may vary considerably among patients. Each patient's ideal level (generally approximately 20 mmHg) is reached by cautious fluid administration during careful monitoring of oxygenation and cardiac output. Eventually, the cardiac output plateaus and further increases in left ventricular filling pressure only increase congestive symptoms and decrease systemic oxygenation without raising arterial pressure.

Rx TREATMENT

The management of heart failure in association with myocardial infarction is similar to that of acute heart failure secondary to other forms of heart disease (avoidance of hypoxemia, diuresis, afterload reduction, inotropic support) (Chap. 233), except that the benefits of digitalis administration in acute myocardial infarction are unimpressive. On the other hand, diuretic agents are extremely effective, as they diminish pulmonary congestion in the presence of systolic and/or diastolic heart failure. A fall in left ventricular filling pressure and an improvement in orthopnea and dyspnea follow the intravenous administration of furosemide. This drug should be used with caution, however, as it can result in a massive diuresis with associated decrease in plasma volume, cardiac output, systemic blood pressure, and hence coronary perfusion. Nitrates in various forms may be used to decrease preload and congestive symptoms. Oral isosorbide dinitrate, topical nitroglycerin ointment, or intravenous nitroglycerin all have the advantage over a diuretic of lowering preload through venodilation without decreasing the total plasma volume. In addition, nitrates may improve ventricular compliance if ischemia is present, as ischemia causes an elevation of left ventricular filling pressure. The patient with pulmonary edema is treated as described in Chap. 233, but vasodilators must be used with caution to prevent serious hypotension. As noted earlier, ACE inhibitors are an ideal class of drugs for management of ventricular dysfunction following myocardial infarction, especially for the long term.

CARDIOGENIC SHOCK In recent years, efforts to reduce infarct size and prompt treatment of ongoing ischemia and other complications of myocardial infarction appear to have reduced the incidence of cardiogenic shock from 20 percent to about 7 percent. Only 10 percent of patients with this condition present with it on admission, while 90 percent develop it during hospitalization. Typically, patients who develop cardiogenic shock have severe multivessel coronary artery disease with evidence of "piecemeal" necrosis extending outward from the original infarct zone.

It is useful to consider cardiogenic shock as a form of severe left ventricular failure. This syndrome is characterized by marked hypotension with systolic arterial pressure of <80 mmHg and a marked reduction of cardiac index [<1.8 L/(min/m^2)] in the face of an elevated left ventricular filling (pulmonary capillary wedge) pressure (>18 mmHg). Hypotension alone is not a basis for the diagnosis of cardiogenic shock, because many patients who make an uneventful recovery will have serious hypotension (systolic pressure of <80 mmHg) for several hours. Such patients often have low left ventricular filling pressures, and their hypotension usually resolves with the administration of intravenous fluids. In contrast to hypovolemic hypotension, cardiogenic shock is generally associated with a mortality rate of >70 percent; however, recent efforts to restore perfusion by coronary

AMERICAN ACADEMY OF PEDIATRICS

Committee on Fetus and Newborn

Use of Inhaled Nitric Oxide

ABSTRACT. Approval of inhaled nitric oxide by the US Food and Drug Administration for hypoxic respiratory failure of the term and near-term newborn provides an important new therapy for this serious condition. This statement addresses the conditions under which inhaled nitric oxide should be administered to the neonate with hypoxic respiratory failure.

ABBREVIATIONS. ECMO, extracorporeal membrane oxygenation; iNO, inhaled nitric oxide; FDA, US Food and Drug Administration.

Hypoxic respiratory failure in neonates born at or near term may be caused by such conditions as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, pneumonia or sepsis, and congenital diaphragmatic hernia. Conventional therapies, which have not been validated by randomized controlled trials, include administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation.[1] Despite aggressive conventional therapy, neonatal respiratory failure was associated with a high rate of mortality before the development of extracorporeal membrane oxygenation (ECMO).[2,3] Survival and short-term morbidity rates have been superior in term and near-term infants (≥34 weeks' gestation) treated with ECMO compared with conventional therapy[4]; however, questions remain about the long-term safety of ECMO.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator for which the mechanism of action involves guanylyl cyclase activation leading to production of cyclic guanosine monophosphate and subsequent smooth muscle relaxation.[5–7] Although several studies have suggested that iNO improves oxygenation,[8–14] the US Food and Drug Administration (FDA) evaluated 2 large randomized multicenter controlled trials of term and near-term neonates with hypoxic respiratory failure that demonstrated improved outcome with iNO therapy. The Neonatal Inhaled Nitric Oxide Study Group trial documented that iNO reduced the need for ECMO[15] without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age.[16] These results were strengthened by the Clinical Inhaled Nitric Oxide Research Group trial, in which iNO reduced the need for ECMO and the incidence of chronic lung disease.[17] iNO was not effective for infants with congenital diaphragmatic hernia.[18]

The limited data to date on hypoxic preterm neonates suggest that low-dose iNO improves oxygenation but does not improve survival.[14,19] Additional large randomized trials of iNO in premature neonates are required because they may experience more toxic effects than term and near-term infants.[14,19,20]

It is critical that infants with hypoxic respiratory failure in whom conventional ventilator therapy fails or is predicted to fail be cared for in institutions that have **immediate availability** of personnel, including physicians, nurses, and respiratory therapists, who are qualified to use multiple modes of ventilation and rescue therapies. Radiologic and laboratory support required to manage the broad range of needs of these infants is also essential.

iNO should be administered using FDA-approved devices that are capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle. Infants who receive iNO therapy should be monitored according to institutionally derived protocols designed to avoid the potential toxic effects associated with iNO administration. These effects include methemoglobinemia (secondary to excess nitric oxide concentrations), direct pulmonary injury (attributable to excess levels of nitrogen dioxide), and ambient air contamination.

In the trials of iNO therapy reported to date, the indication for use has been failure of ventilatory therapy. ECMO, a therapy of proven efficacy, usually is initiated if iNO therapy fails. Therefore, institutions that offer iNO therapy generally should have ECMO capability; if a center lacks ECMO capability, it should work in collaboration with an ECMO center to prospectively establish appropriate iNO failure criteria and mechanisms for the timely transfer of infants to the collaborating ECMO center. The diversity of geography, climate, and transport capabilities necessitates that the "timely transfer" be dictated by the location-specific transport limitations as well as the severity of the infant's illness. Because hypoxic respiratory failure is often rapidly progressive and abrupt discontinuation of iNO may lead to worsening oxygenation,[21] the risk of delayed provision of ECMO must be considered carefully when determining the appropriate time of transfer.

Plans for the care and referral of these infants should incorporate the following recommendations.

RECOMMENDATIONS

1. Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
2. iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label (http://www.fda.gov). An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
3. iNO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
4. Generally, iNO should be initiated in centers with ECMO capability. If iNO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of iNO therapy.
5. Centers that provide iNO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
6. Centers that provide iNO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, use of alternative therapies, and outcomes.
7. Administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

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POLICY STATEMENT

PEDIATRICS Vol. 106 No. 2 August 2000, pp. 344-345

AMERICAN ACADEMY OF PEDIATRICS:

Use of Inhaled Nitric Oxide

Committee on Fetus and Newborn

ABSTRACT

Approval of inhaled nitric oxide by the US Food and Drug Administration for hypoxic respiratory failure of the term and near-term newborn provides an important new therapy for this serious condition. This statement addresses the conditions under which inhaled nitric oxide should be administered to the neonate with hypoxic respiratory failure.

Hypoxic respiratory failure in neonates born at or near term may be caused by such conditions as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, pneumonia or sepsis, and congenital diaphragmatic hernia. Conventional therapies, which have not been validated by randomized controlled trials, include administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation.[1] Despite aggressive conventiona neonatal respiratory failure was associated with a high rate of mortality before the development of extracorporeal membrane oxygenation (ECM and short-term morbidity rates have been superior in term and near-term infants (≥34 weeks' gestation) treated with ECMO compared with conv therapy[4]; however, questions remain about the long-term safety of ECMO.

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator for which the mechanism of action involves guanylyl cyclase activation leading to cyclic guanosine monophosphate and subsequent smooth muscle relaxation.[5-7] Although several studies have suggested that iNO improves ox the US Food and Drug Administration (FDA) evaluated 2 large randomized multicenter controlled trials of term and near-term neonates with hyp respiratory failure that demonstrated improved outcome with iNO therapy. The Neonatal Inhaled Nitric Oxide Study Group trial documented that the need for ECMO[15] without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age.[16] These results were stre the Clinical Inhaled Nitric Oxide Research Group trial, in which iNO reduced the need for ECMO and the incidence of chronic lung disease.[17] iN effective for infants with congenital diaphragmatic hernia.[18]

The limited data to date on hypoxic preterm neonates suggest that low-dose iNO improves oxygenation but does not improve survival.[14,19] Add randomized trials of iNO in premature neonates are required because they may experience more toxic effects than term and near-term infants.[1]

It is critical that infants with hypoxic respiratory failure in whom conventional ventilator therapy fails or is predicted to fail be cared for in institutio **immediate availability** of personnel, including physicians, nurses, and respiratory therapists, who are qualified to use multiple modes of ventila rescue therapies. Radiologic and laboratory support required to manage the broad range of needs of these infants is also essential.

iNO should be administered using FDA-approved devices that are capable of administering iNO in constant concentration ranges in parts per m throughout the respiratory cycle. Infants who receive iNO therapy should be monitored according to institutionally derived protocols designed to potential toxic effects associated with iNO administration. These effects include methemoglobinemia (secondary to excess nitric oxide concentra pulmonary injury (attributable to excess levels of nitrogen dioxide), and ambient air contamination.

In the trials of iNO therapy reported to date, the indication for use has been failure of ventilatory therapy. ECMO, a therapy of proven efficacy, u initiated if iNO therapy fails. Therefore, institutions that offer iNO therapy generally should have ECMO capability; if a center lacks ECMO capab work in collaboration with an ECMO center to prospectively establish appropriate iNO failure criteria and mechanisms for the timely transfer of ir collaborating ECMO center. The diversity of geography, climate, and transport capabilities necessitates that the "timely transfer" be dictated by specific transport limitations as well as the severity of the infant's illness. Because hypoxic respiratory failure is often rapidly progressive and abr discontinuation of iNO may lead to worsening oxygenation,[21] the risk of delayed provision of ECMO must be considered carefully when determi appropriate time of transfer.

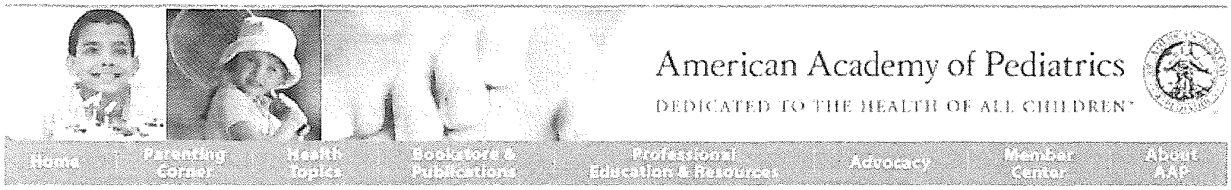
Plans for the care and referral of these infants should incorporate the following recommendations.

RECOMMENDATIONS

Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.

iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label (http://www.fda.gov). An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.

iNO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to pr



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Introduction

The Committee on the Fetus and Newborn studies issues and current advances in fetal and neonatal care; makes recommendations regarding neonatal practice; collaborates with the American College of Obstetricians and Gynecologists (ACOG) to consider perinatal issues on which the practices of obstetrics and pediatrics merge; and works cooperatively with ACOG on new editions of *Guidelines for Perinatal Care*.

Policy Statements

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PEDIATRICS Vol. 123 No. 6 June 2009, pp. 1606-1607 (doi:10.1542/peds.2009-0867)
This policy is a revision of the policy posted on June 1, 2003.

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Ventricular dysfunction clinical research in infants, children and adolescents

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Abstract

These two issues of *Progress in Pediatric Cardiology* comprehensively illustrate the wealth of currently available information on the pathophysiology of heart failure, age-related myocardial responsiveness, energy metabolism, cardiopulmonary interactions, the pressure-volume relationship, the systemic inflammatory response, the management of heart failure, pediatric pharmacology, the use of heart failure therapies including digoxin, ACE inhibitors, beta-adrenergic blockers, inotropic agents, diuretics, vasodilators, calcium sensitizers, angiotensin and aldosterone receptor blockers, growth hormone, and future gene therapy. The etiology and course of ventricular dysfunction in children is poorly characterized. Furthermore, many changing developmental properties of the pediatric myocardium and differences in the etiologies of ventricular dysfunction in children compared with adults are illustrated in these articles, invalidating the concept that children can safely be considered small adults for the purpose of understanding heart failure pathophysiology and treatment. However, these articles reveal that strikingly little research in children with ventricular dysfunction exists in terms of well-designed large-scale studies of the epidemiology or multicenter controlled clinical therapeutic trials. A future research agenda is proposed to improve understanding etiologies, course and treatment of ventricular dysfunction in children that is based on organized and funded cooperative groups since no one pediatric cardiac center treats enough children with a particular etiology of ventricular dysfunction. In conclusion, significant understanding of basic mechanisms of pediatric ventricular dysfunction and effective therapies for adults with ventricular dysfunction exist. A multicenter pediatric cardiac ventricular dysfunction network would allow improved understanding of diseases and treatments, and result in evidence-based medicine for pediatric patients with ventricular dysfunction.

Keywords: Congestive heart failure; Pediatrics; Ventricular function; Cardiomyopathy; Clinical trials

1. Introduction

The pathophysiology and pharmacologic treatment of ventricular dysfunction in infants, children, and adolescents have been reviewed in these two issues of *Progress in Pediatric Cardiology*. The large amount of work by contributors to highlight pediatric issues demonstrates many unique and potentially important aspects of ventricular dysfunction related to children. These articles, however, also illustrate how little has been done thus far to understand the pathophysiology and pharmacotherapy of ventricular dysfunction in this population. This summary of where the field of pediatric ventricular dysfunction stands will review unique aspects of pediatric research, challenges in the study of children with ventricular dysfunction, and principles of pediatric ventricular dysfunction. Tremendous opportunities exist to advance our understanding in this area at an unprecedented pace. However, many obstacles need to be overcome, including ourselves. I was recently approached by a respected colleague who explained at great length why he could not participate in an active double-blinded, placebo-

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controlled clinical trial of therapy for asymptomatic LV dysfunction in children because he just knew, without the benefit of a controlled clinical trial, that this was an effective therapy for his patients. Other pediatric cardiologists have lectured at national meetings stating it is sufficient to study, for example, pharmacologic agents for ventricular dysfunction in adults and, if benefit is found, use the drugs in children with the same illness without clinical trials in this age group. Some of the problems with this approach are that the disease processes resulting in ventricular dysfunction are often different in children than adults. Many pediatric conditions have no close analogies in the adult. Secondly, the effects of the intervention may be unlike those seen in adults. The pharmacokinetics of many drugs vary with age and their beneficial or adverse effects are different in children and adults. Thirdly, children differ from adults. Some therapies may not be tolerated by young children because they are unpalatable or difficult to administer. A final point is that, because the antecedents of many adult diseases are thought to have their origins in early life, studies in very young children, and even antenatally, may identify strategies for preventing diseases which have important public health consequences [1].

Tremendous advances in pediatric cardiology with catheter, surgical, and diagnostic procedures have occurred during the past four decades [2]. Unfortunately, the fields of prevention, therapeutics, and decision analysis based on very limited or biased data for all pediatric ventricular dysfunction have not kept pace. A network of cardiologists willing to participate and adequate funding for an infrastructural network would facilitate research in this area.

2. The current status of clinical research in pediatric ventricular dysfunction

2.1. Reliance on data from studies in adults

In many areas of pediatric practice, therapies have been studied only in adults, and pediatricians must consider whether it is appropriate to generalize from adult to child. Although some pediatric cardiologists have advocated that treatments proved effective for adults with myocardial dysfunction be used in pediatric patients based on data from adults this may not be prudent without further testing.

There appears to be real differences in incidence, implications, expectations, causes, treatment styles, and prevention between children and adults with ventricular dysfunction suggesting that for ventricular dysfunction, children should not be considered 'small adults'. Known ventricular dysfunction occurs frequently in adults and is extremely rare in childhood. Yet, for children there are greater productive years saved by preventing symptomatic ventricular dysfunction. There may be a higher potential for cure from ventricular dysfunction in children than in adults. As a result, the potential goal of pediatric therapy for ventricular dysfunction is more likely to be curative in intent, in contrast to the palliative intent of most adult therapies. Ventricular dysfunction in children is more likely to be due to genetic factors while in adults exogenous exposures predominate. At this time adult causes of ventricular dysfunction may be more amenable to prevention than pediatric causes.

2.2. Reliance on anecdotal experience

The art of learning medicine as a series of clinical anecdotes is important but an over reliance on anecdotal experience, to the exclusion of clinical research, has pitfalls as well [3].

2.3. A lack of appreciation for the need to consider the length of subsequent survival to understand disease process and therapeutic response

The longer a patient remains with LV dysfunction the worse the LV dysfunction becomes. Snapshot studies examining a high-risk population for LV dysfunction at a single point in time are inadequate to state that the population is normal or non-progressive. Natural history studies of LV dysfunction are particularly important in children where we have found that the long length of subsequent survival coupled with the need of the pediatric myocardium to grow in response to increasing somatic growth may result in accelerated progressive LV dysfunction. A small amount of LV dysfunction early in childhood may be particularly problematic later in life [4–40].

2.4. Paucity of data

The risk factors for (e.g. age, sex, ethnic origin and geographic differences) and course of myocardial dysfunction in infants, children, and adolescents have also been studied in a very limited fashion. Consequently, the results of studies to examine the effectiveness of therapies for the prevention, treatment, or beneficial alteration of the subsequent course of pediatric myocardial dysfunction are scarce. This is especially relevant for pediatric congestive heart failure where essentially no prospective multicenter controlled clinical trials have occurred. Yet, the consequences of mild left ventricular dysfunction may be more significant than in adults and due to growth and length of future survival. Heart disease remains the leading cause of death in the United States with

deaths from congestive heart failure on a steadily upward course.

2.5. Lack of evidence-based medicine

The emerging discipline of research synthesis (evidence-based healthcare) has led to greater awareness of the need to evaluate critically what is already known before either making recommendations for clinical practice or embarking on further research [41]. Evidence-based medicine is defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. By highlighting the strengths and weaknesses of clinical research in different specialities, this process of critical appraisal has shown that, by comparison with situations in adults, research questions relevant to the health of children may have been addressed not at all or only by small, poorly designed studies [42]. Reviews of randomized trials published during a 15-year period in one specialist pediatric journal showed that sample sizes were generally small (less than 20 in approx. one-half of the studies), only a small proportion were multicenter, and reporting of key quality indices was inadequate. When subspecialty areas have been reviewed, the conclusions have been similar. For example, one review characterized recent advances in pediatric cardiology that have led to improved outcomes for surgical repair of complex cardiac malformations to clinical trial-and-error and the common sense and accumulated wisdom of astute clinicians, rather than to basic science or epidemiology [42]. Clinical trial-and-error can occasionally lead to serious errors.

The four steps involved in translating research into practice include: (1) creating evidence through basic science research, phenotype–genotype correlations since different etiologies may lead to different phenotypic outcomes and a heterogeneous population is of limited value, randomized controlled trials, and observational studies; (2) summarizing evidence by published meta-analyses; (3) disseminating evidence by clinical practice guidelines; and (4) implementing evidence by clinical pathways [41].

The clinical effectiveness of therapy comes from randomized controlled trials [43–45]. Observational studies have several advantages over randomized, controlled trials, including lower cost, greater timeliness, and a broader range of patients. Although nonrandomized or observational studies have in the past been criticized for bias related to overestimating the true efficacy of a given therapy or leading to erroneous conclusions, recent comparisons to randomized, controlled trials suggest little evidence that estimates of treatment effects in well-designed observational studies (with either a cohort or a case–control design) are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials [43–45]. These prior concerns led observational studies to be limited in their use to the identification of risk factors and prognostic indicators and to situations in which randomized, controlled trials would be impossible or unethical.

The clinical data for non-therapeutic questions can be derived from observational studies with long follow-up periods to assess prognosis and from large cross-sectional or cohort studies to evaluate the validity and importance of diagnostic tests [41]. The validity of a diagnostic test frequently relies on surrogate endpoints rather than actual patient outcomes and its utility is its ability to meaningfully effect patient outcomes. Diagnostic tests are rarely evaluated in this manner.

Problems encountered in translating research into pediatric practice include a paucity of pediatric clinical trials, underfunding of pediatric research, lack of trained pediatric clinical investigators, frequency of small underpowered studies, heterogeneity of studies, inconsistency between meta-analyses and large randomized, controlled trials, lack of awareness of existing efforts, access to evidence, information overload, format not helpful, labor-intensive, expensive, and waning effectiveness [41].

A schism exists between laboratory-based medical scientists (who attempt to understand the biologic and molecular processes underlying health and disease) and epidemiologists (who try to assess health and disease states [outcomes] in groups of human subjects, exposure to factors that may increase or reduce the likelihood of health or disease, and the causal relationship between these outcomes and exposures), as well as between classical (population-based) and clinical (patient- and clinical intervention-based) epidemiologists [42].

Most pediatric subspecialists, including cardiologists, have not acquired the methodologic skills in research design and statistical analysis required to conduct fundable, hypothesis-driven research. Good science requires focus, depth, and a good question. Rigorous methods should be coupled to substantive expertise to ensure that the hypothesis tested is a useful one. Good epidemiologic science is time-consuming and often quite expensive, especially when it requires long-term follow-up. There are currently 1470 US board-certified pediatric cardiologists with approximately 38 new members each year that trained in the 46 certified US centers [46]. Most centers graduate 1–2 physicians each year and over the past decade the percentage of all pediatric cardiology graduates choosing careers in full-time academic medicine has fallen from nearly 65 to 40%, making it more

concerning whether research in pediatric cardiology will expand in the coming years without an organized research infrastructure [47]. An annual account of research grants funded by the NIH in 1998 showed that the number awarded on topics related to pediatric cardiology to be 117 [48]. Yet, only nine of them involved a pediatric cardiologist as the project's principal investigator [48]. This is occurring at a time when laboratory-based discoveries of new preventive or therapeutic interventions will continue to require demonstration of efficacy and safety in randomized trials. Although more and better epidemiologic studies are needed, so too are laboratory investigations that can confirm or undermine the associations observed in human populations, and explain the biochemical and cellular processes underlying them. Kramer points out that the future of pediatric research will depend on the collaboration of basic scientists and epidemiologists [42]. He cites as an example the use of molecular and other biologic markers that cannot only provide more valid and precise measurements of potentially causal exposures and disease outcomes but can also be used to assess causal mechanisms and pathways [42].

The 1990 US Department of Health and Human Services report entitled 'Healthy People 2000' noted that heart disease was among the five most common causes of death in childhood at any age [49]. An official policy report approved by the Board of Directors of the American Heart Association and written by the Task Force on Children and Youth of the American Heart Association noted that cardiovascular disease occurs more often in children than is generally appreciated [50,51]. More than 600 000 children in the United States have an abnormality of the cardiovascular system, including at least 40 000 whose life expectancy is shortened by an acquired disease such as cardiomyopathy. The annual cost of pediatric cardiovascular disease is > $8 billion in medical expenses and lost contributions to the gross national product. Cardiomyopathy accounts for an increasing number of the pediatric cardiac transplants. Genetic abnormalities in contractile proteins or energy-producing enzymes, among others, cause cardiomyopathy that becomes manifest in adulthood. Recent advances in genetics allow molecular diagnoses in fetal life. This report acknowledges that cardiomyopathy in children is increasing, and while the prevalence is unknown, 'Eventually more precise classification based on genetic advances will allow detection of people at risk and provide information about the basis of the disease.... With improved understanding of precise etiology, more effective and specific treatment can be developed' [50,51].

Children represent one-third of the United States population, yet they are virtually unrepresented in cardiovascular research. A paucity of funding for such research, including cardiomyopathy, is related in part to the small number of pediatric cardiovascular scientists. According to the Manpower Advisory and Pediatric Cardiology Committees of the American College of Cardiology, there were < 1000 certified specialists in pediatric cardiology in the United States in 1994, almost all of whom were centered on patient care and diagnostic or interventional techniques [52]. Only a limited number of them devoted a substantial effort to either clinical or basic biomedical research; furthermore, such research was largely retrospective, descriptive, and not controlled. Only 3% of responding certified pediatric cardiologists had completed ≥ 22 months of research training, suggesting that the growth of basic and clinical sciences within the field is limited. This was similar to a prior manpower study of pediatric cardiology that demonstrated that 20 years earlier only 6% of professional activities were devoted to research [53].

Cooperative groups in pediatric cardiology have been helpful at achieving research goals. The Pediatric Cardiomyopathy Registry, for example, has increased the likelihood of collaboration and research, since it allows prospective capture of cases and, in this era of molecular biology, permits new techniques to be applied to the study of pediatric cardiomyopathy [54]. It is hoped that many advances in the prevention, diagnosis, and treatment of cardiomyopathy in the young will be realized by the Registry. The field of pediatric cardiology has always worked well together on multicenter studies and registries. As evidenced by their publications, many of the most important clinical advances in pediatric cardiology have been done in the setting of multicenter studies, such as the New England Regional Infant Cardiac Program, the United States Multicenter Kawasaki Study Group, the Pediatric Cardiac Surgical Registry, the Northern Great Plains Regional Cardiac Program, the Baltimore–Washington Infant Study, the Electrophysiology Study Group, the Valvuloplasty and Angioplasty of Congenital Anomalies Registry, and the Pediatric Heart Transplantation Study Group.

Decoding the human genome will trigger developments that will change our daily lives [55–57]. The finding of genes responsible for diseases will require phenotypically well characterized populations of affected patients to determine patients whose genotypes reveal homogenous defects at high risk of disease and then to test etiology-specific therapies on these populations. Indeed, even at this time single-nucleotide polymorphisms of different genes can be studied by CHIP technology and determine, for example, whether a patient with ventricular dysfunction is likely to decline rapidly on standard drugs for the condition, and hence might need more aggressive treatment.

Dr Francis Collins, director of the Human Genome Research Institute, recently said at the 2000 AAP meeting that understanding the human genome will result in routinely predicting and preventing diseases, and treating patients with highly potent designer drugs tailored to their own genes. Collins said 'It's going to have a profound impact on the practice of medicine and probably nowhere more so than in pediatrics. Virtually all diseases have a genetic component and having the genome will accelerate finding genes for varied diseases.' Collins predicted that by 2010 there will be predictive genetic tests available for at least 10 disorders and treatments to lower risks for several conditions. By 2020 he predicted gene-based designer drugs targeted to the molecular fingerprint of the patient's problem will be available and doctors will be ordering genotype tests on patients before writing prescriptions. By 2030 Collins stated that individualized preventive medicine keyed to a person's genetic profile will be routine, infants will be tested at birth, and gene therapy and gene-based drug therapy will be available.

2.6. Lack of well-designed pharmaceutical industry sponsored studies

Pharmaceutical company placebo-controlled trials have been inadequately performed in children in the past. Prescriptions (25%) in pediatric wards were for drug courses that were either unlicensed or for off-label uses. In neonates, only 35% of prescription episodes were licensed [1]. Industry objectives are frequently more short-term in duration or low cost (e.g. survey data assembly if possible) to meet FDA requirements. However, a large increase in industry-sponsored pediatric drug trials is currently underway due to a new federal law and new FDA regulations that 2 years ago began requiring the pharmaceutical industry to test the effects of many adult products on children (pediatric drug-study proposals filed with FDA, 1999–2000: 184, expected number completed: 150). In December 2000 the FDA will require pediatric study of any adult disease-fighting drug that could be prescribed for children with the same disease. This is expected to increase the number of US children in clinical drug trials from < 1000 in 1990 to 18 000 by 2002. Prior to this legislation there were very few pediatric drug-study proposals filed with the FDA (1991–1997: 70, number completed: 11) [58–62].

3. The necessary clinical research agenda in pediatric ventricular dysfunction

3.1. Understanding heterogeneous etiologies in children

When trying to understand the proper therapy for children with ventricular dysfunction it is usually important not to view the child as a small adult and extrapolate the effects of ventricular dysfunction therapy for adult ischemia or post-infarction patients to the child where a multitude of non-ischemic, non-post-infarction etiologies exist. For example, in the article on angiotensin-converting enzyme inhibitors in this issue we reviewed the effects of this therapy based on the pathophysiology of the condition and found different reported effects of this therapy [63]. A goal is to have effective individualized, etiology-specific therapeutics. An individualized therapeutic approach, based on the etiology of ventricular dysfunction and possibly other factors, such as drug levels or the levels of neurohormones, could result in major progress in treating these patients. We have examined the effect of growth hormone replacement therapy in pediatric LV dysfunction following anthracycline therapy over a 10-year period and found that, unlike adults with LV dysfunction from other etiologies, there was not an improvement in LV dysfunction on growth hormone therapy compared to controls [64]. This suggests that the etiology is extremely important in determining whether the therapy will work. Similar to etiology-specific therapies for children with ventricular dysfunction we have utilized a similar etiology-specific preventive approach for pediatric

Table 1
Detection of doxorubicin cardiotoxicity during therapy by cause and comparison to late cardiotoxicity

Cause of cardiotoxicity	During therapy echocardiogram	During therapy serum cTnT[a]	Late echocardiogram
Depressed energetic (mitochondrial)	−2	0	±
Cytokine myocardial depressant	−2	0	-
Apoptosis	±	±	−1
Free radical injury	−1	≥ +1	≥ −1
Myocarditis	−2	+2	≥ −1

[a] cTnT, cardiac troponin T.

patients about to receive multiagent chemotherapy that includes doxorubicin. Current protocols employ multiagent cardioprotection targeted against specific etiologies of cardiotoxicity with the goal of no cardiac injury (Table 1).

Although dilated cardiomyopathy (DCM) may be caused by > 75 different disorders, the etiology in most cases is unknown (idiopathic). The course of DCM, almost regardless of etiology, is usually progressive (Fig. 1), with approximately 75% of these children dying within 5 years after the onset of symptoms. Most reports give 1- and 2-year mortality estimates of 25 and 40%, respectively. The cause of death in approximately 80% of cases is evenly divided between sudden cardiac death and congestive heart failure (CHF). Some authors believe that adults who survive more than 2 or 3 years have relatively good long-term survival, but no data have been reported in children. However, the natural history of incidentally discovered, asymptomatic DCM in adults cannot be considered a benign diagnosis, with a 7-year mortality rate approaching 50%, suggesting that an aggressive approach to the diagnosis and treatment of asymptomatic patients with DCM is clearly warranted (Fig. 1). Small single center series of pediatric DCM ranging from 24 to 81 children have suggested 14 factors predictive of poor outcomes: decreased LV systolic performance at presentation, persistent decreased LV systolic performance, a more spherical LV shape, an elevated LV end-diastolic pressure, increased LV mass, increased cardiothoracic ratio on chest radiograph, mural thrombi, age > 2 years, no LV hypertrophy by electrocardiogram (EKG), endocardial fibroelastosis, complex atrial or ventricular arrhythmias, persistent CHF, ST and T wave changes on EKG, a family history of cardiomyopathy. Most of these factors varied or were in conflict between these different studies making it impossible to understand risk factors for a poor prognosis in children with cardiomyopathy at this time. A report of 137 children with cardiomyopathy in Turkey from 1984 to 1989 noted that DCM improved or normalized for 38.5%,

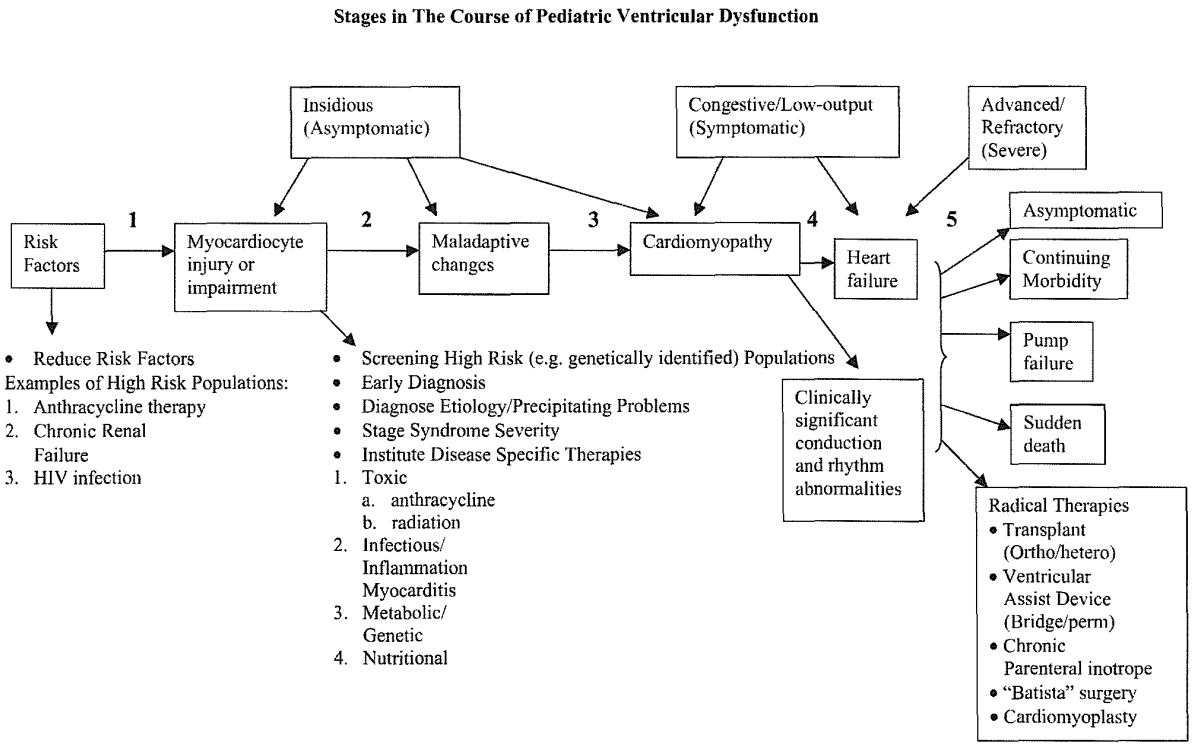

Fig. 1. Stages in the course of pediatric ventricular dysfunction. The identification of risk factors and high risk populations for ventricular dysfunction are highlighted where their use may lead to preventive or early therapeutic strategies. The determination of etiology may lead to etiology-specific therapies. The numbers 1–5 indicate stage-related points of intervention for preventive and therapeutic strategies and where biomarkers and surrogate markers may be used.

DCM remained stable or worsened for 50%, and 11.5% of children died; numbers that are virtually identical to the mean values for these parameters from all studies from more developed countries such as the United States, Canada, and England during similar time periods. This suggests that the enormous intensive and invasive resources spent on the treatment of children with DCM in more developed nations may not have had a significant impact on the morbidity or mortality of pediatric DCM, mandating the need to more completely understand the course, causes, factors predictive of adverse clinical outcomes, and newer etiology-specific therapeutics.

We have found that, in spite of large resources and advanced technology, the prognosis of DCM in developed nations is no better than in developing nations [65]. Furthermore, there has not been a significant improvement in outcome for DCM in children in published studies over the past four decades. We have been involved with studies of the myocardium from children with idiopathic dilated cardiomyopathy that specifically investigated disturbed myocardial energetics. We found a high percentage of these patients had abnormal mitochondrial enzyme function, mitochondrial deletions, or mitochondrial mutations [66,67]. This suggests that treating all children with symptomatic ventricular dysfunction in a similar fashion, regardless of etiology, may be detrimental since inotropes, for example, may not be the most efficacious therapy for a child with disturbed myocardial energetics from mitochondrial genetic or environmental abnormalities.

3.2. Understanding developmental differences in pharmacokinetics

Little is known about cardiovascular drug metabolism in children and this has implications for predicting clinically important drug interactions with the potential for either excessive drug exposure, effect, and toxicity or decreased drug exposure and loss of drug effect [58–62]. Historically this has been due to ethical, economic, regulatory, and technical issues. Dosing children by scaling adult doses based on body weight or surface area does not account for developmental changes that affect drug disposition (pharmacokinetics) or tissue/organ sensitivity to a drug (pharmacodynamics). The pharmacologic impact of these developmental changes is uncovered when unexpected or severe toxicity leads to pharmacologic studies [68,69]. Children metabolize drugs differently than adults. Therefore, drugs must be assessed in children in terms of increased risk of toxicity and reduced efficacy because they may act differently in children than in adults. We need earlier evaluation of drugs and approaches to make access available as soon as possible. In oncology, for example, in the past 20 years there have been 34 new drugs approved for use in adult cancers, but only one new drug approved to treat cancer in children [58]. Most FDA-approved drugs simply state 'safety and effectiveness in pediatric patients have not been established.'

Some of the goals of using combination therapy in children with ventricular dysfunction include: (1) To reduce morbidity and mortality with improved quality-of-life; (2) To treat different mechanisms contributing to ventricular dysfunction; (3) To treat for different effects (e.g. drugs to prevent functional deterioration, drugs to reduce mortality, and drugs to control symptoms); (4) To decrease underlying disease complications; (5) To reduce treatment toxicity by using lower doses; (6) To increase patient compliance; (7) To reduce drug dosage or dosing interval; and (8) To provide rational prescriptions (fewest drugs, fewest side effects, maximal compliance, and minimal cost).

3.3. Understanding unique aspects of pediatric recruitment, retention, compliance, and adherence with clinical studies

Children and their families have many unique issues regarding compliance, recruitment, and retention that have been challenging in pediatric studies of LV dysfunction [70–75]. Specific pediatric trial strategies for compliance, recruitment and retention must be developed. Some areas in need of further development and understanding to improve recruitment, retention, compliance, and adherence with clinical studies of ventricular dysfunction include supportive care, adolescent/young adult special issues, when the intention is not curative to stress the participation of the patient and family in the decision-making process, strategies to facilitate return to normal life, improve health-related quality-of-life and self esteem, quantity of life vs. quality of life tradeoffs, end-of-life care issues, minority affairs, underserved populations, alternative therapies, understanding, motivations, expectations, coping, fatigue, self-help, caregiver demands and level of burden, family financial burden, dietary factors, strategies to improve access to state-of-the-art therapy, diffusion into the community of knowledge in this area, develop rational surveillance and monitoring schedules for survivors of pediatric heart failure (determine effectiveness and cost-effectiveness), transition of care from pediatric cardiology to adult cardiology, greater understanding of health service outcome issues such as patient volume, payer differences, academic vs. other settings of care, protocol vs. no protocol care, race and ethnic issues and cultural factors.

3.4. Development of risk factors for pediatric ventricular dysfunction

Fig. 1 shows that the identification of risk factors for cardiomyopathy can help identify high risk populations that through screening may lead to: (1) early diagnosis, institution of disease-specific therapies, and alteration of the course of the disease and to; (2) primary prevention of disease by targeted strategies. Fig. 2 demonstrates independent risk factors identified in multivarible analyses of childhood anthracycline recipients [6,12,14,30]. Fig. 2 illustrates that similarities exist between risk factors for early cardiotoxicity during anthracycline therapy [14,30] and risk factors for late cardiotoxicity in anthracycline-treated long-term survivors of childhood cancer [6,12]. The importance of long-term longitudinal follow-up of high risk populations such as this to determine independent risk factors for late clinically significant outcomes cannot be overstated.

3.5. Development of clinically significant surrogate endpoints

Methodological difficulties that relate specifically to research in children include measuring clinically relevant outcomes. Where death is unlikely, or where research is done in the hope that it will benefit the participants, outcomes which may be surrogate markers for death are frequently used. The importance of identifying high-risk groups that may be detected early by validated biomarkers and surrogate endpoints cannot be overstated. Examples are p24 antigen and CD4 counts in HIV infection. These surrogate markers have many flaws and their ability to predict death has generally been established only in adults and the associations may be different in children. We have found that subclinical myocardial injury measured by serum cardiac troponin indicates that a low level of injury during doxorubicin treatment frequently translates to considerable echocardiographic abnormalities later in life (Table 1 and Fig. 3) [20,26,28,36,76–84].

Surrogate biomarkers have been useful for drug development and clinical safety assessment. A plethora of technological and conceptual advances in molecular biology and medicine, genetics and genomics, and related research has opened significant opportunities for development of an abundance of new therapies. These opportunities provide a challenge to the assessment of the safety and efficacy of these new candidate therapies. The current status of toxicology biomarkers in pediatric heart failure drug development and clinical safety assessments is in its very early development. A surrogate biomarker is defined as a reliable tool or measure that allows one to monitor and predict that exposure to a drug or

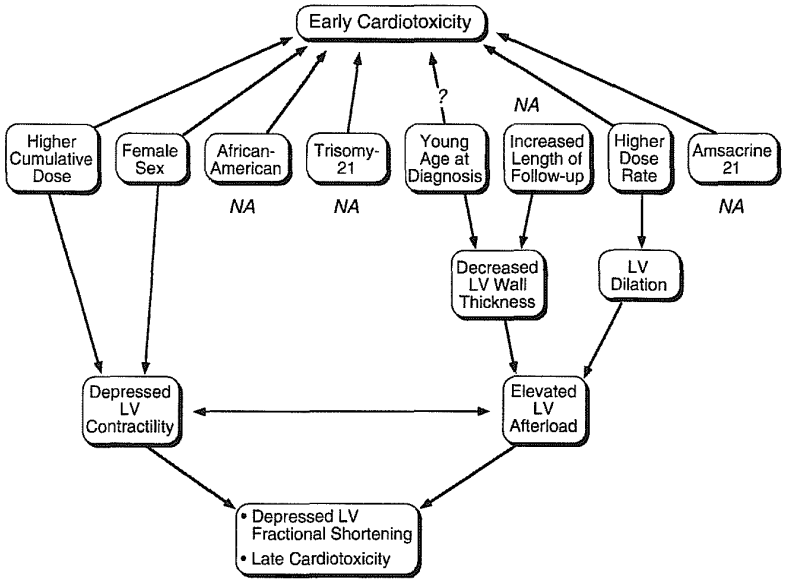

Fig. 2. Risk factors for the development of anthracycline-associated pediatric ventricular dysfunction. The upper part of the figure summarizes independent risk factors identified in multivariable analyses for early clinical cardiotoxicity developing during or in the first year following anthracycline therapy in > 6000 children treated on Pediatric Oncology Group protocols from 1974 to 1990 [14,30]. The lower part of the figure demonstrates the independent risk factors for late cardiotoxicity developing ≥ 2 years after the completion of anthracycline therapy in children treated for ALL or osteosarcoma. Median follow-up was 8 years [12]. The relation of these risk factors from late cardiotoxicity to the echocardiographic abnormalities found in these patients is illustrated and suggests two independent mechanisms of injury, each with distinct risk factors [12].

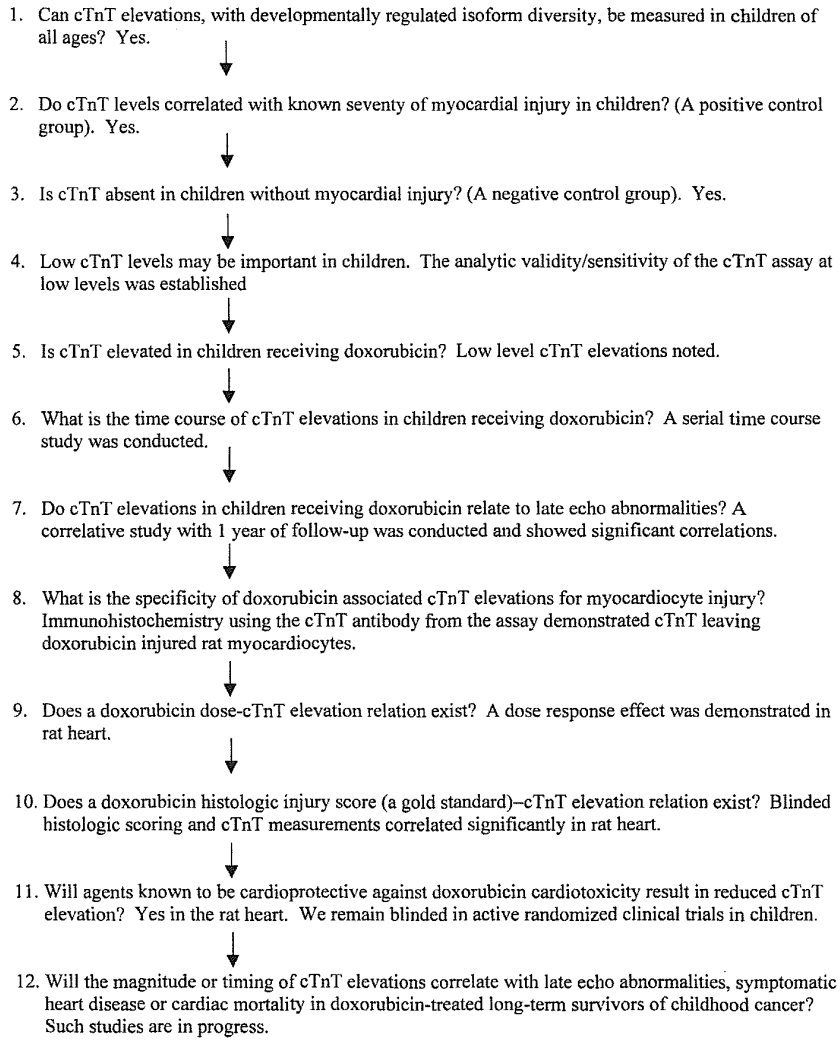

Fig. 3. Stages in the validation of serum cardiac troponin T as a biomarker of doxorubicin cardiotoxicity during therapy and as a surrogate endpoint for late doxorubicin cardiotoxicity in long-term survivors of childhood cancer. This figure illustrates the 12 stages we have undertaken during the past 6 years to determine whether elevations of serum cardiac troponin T represent doxorubicin myocardiocyte injury during therapy and whether these elevations during therapy can predict which children will have late doxorubicin cardiotoxicity. If that is found then cardiac troponin T would be validated as a surrogate endpoint for late doxorubicin cardiotoxicity. A multidisciplinary multispecies approach has been utilized [20,26,28,36,76–84].

environmental chemical may result in harm, illness, or pathology. Particular emphasis is on the demonstration that biomarkers can serve as early predictors of adverse effects and on the development of technological approaches to find more and better toxicology biomarkers.

High throughput technologies are enabling production of large numbers of new chemical entities to be evaluated as target-specific candidate therapies. Improved safety evaluation methods are needed to provide preclinical and clinical toxicity testing in an efficient and timely fashion. The use of biological markers, or biomarkers, defined as characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, is one approach to enhance toxicity testing.

Mass spectroscopy, cDNA microarray, protein expression, and imaging technologies are examples of basic discovery tools that may serve as platforms to evaluate predictive biomarkers of toxicity. These fundamental research discovery tools now provide opportunities to develop highly efficient assay systems to establish specific and sensitive indicators of cellular and molecular injury. For example, biomarkers may represent components of cell signaling pathways for apoptosis, growth factors, cytokines, and chemokines, and xenobiotic metabolic pathways. Establishment of

the linkage of biomarkers to clinical features of toxicity is critical to their application in drug safety testing.

Harnessing new technologies for toxicology testing will be expedited by cooperative efforts among government, universities, and private industry partners. These interactions will facilitate the development of a technology and information-based infrastructure that will support the standardization of testing methods, validation of assay systems, establishment of databases, and development of statistical analyses that are needed to better characterize toxicity biomarkers and establish linkage of biomarkers to clinical features of toxicity. These are critical to their application for drug safety testing.

The validation of a biomarker as a surrogate endpoint for children at risk of developing ventricular dysfunction is a long and consuming process. We have employed a multispecies, multidisciplinary approach to determine whether measurement of serum cardiac troponin T during doxorubicin therapy for childhood cancer can be considered a surrogate endpoint for the late echocardiographic abnormalities found in these patients when they become long-term survivors (Fig. 3) [20,26,28,36,76–84]. Not all cardiac abnormalities measured during therapy would be expected to relate to late echocardiographic abnormalities in this population (Table 1).

The use of biomarkers to tailor therapy based on mechanisms of injury for an individual child with unexpected new onset symptomatic ventricular dysfunction is a useful goal. Elevated serum cardiac troponin T indicates active myocardiocyte injury. In this setting such injury most likely represents infectious or inflammatory causes resulting in myocarditis. Recent work by Towbin and colleagues suggests that a positive PCR viral panel predicts subsequent adverse clinical outcomes following pediatric heart or lung transplantation [85–87]. Table 2 shows an example of a testable treatment strategy based on the presence or absence of active myocardiocyte injury, as measured by serum troponin, and the presence or absence of viral myocardial genome, as measured by PCR. This strategy, and others like it, may allow pediatric cardiologists to focus research efforts on whether etiology-specific therapies offer an advantage in outcome over anticongestive therapy alone.

The use of a biomarker for myocardiocyte injury, like serum cardiac troponin T, that may become a validated surrogate endpoint, allows for the identification of high-risk populations where subsequent LV dysfunction is likely to occur. We have found that 8% of young children presenting with acute, presumed viral, illnesses had evidence of active myocardial injury [88]. Similarly, we found that children with chronic renal failure frequently have active myocardial injury that relates to potentially modifiable factors [89,90]. Recently, we found that pediatric heart transplant recipients have myocardiocyte injury that does not necessarily correlate with histologic rejection [37]. Terbutaline cardiotoxicity for childhood asthma was found by us to be less cardiotoxic than previously thought by using serum cardiac troponin T [38].

The stages of biomarker development as a valid surrogate endpoint in pediatric patients at risk for ventricular dysfunction is illustrated in Fig. 3. The validation of a single biomarker, cardiac troponin T, as a surrogate endpoint for late doxorubicin cardiotoxicity has been a long and involved process [20,26,28,36,76–84].

Myocardiocyte injury may occur from disease or during therapy of childhood cancer. Injury should be detectable by screening for cardiac troponin-T, a myocardiocyte-specific contractile protein not normally present in serum except with myocardiocyte injury. Myocardiocyte injury in children with ALL relates not only to doxorubicin, but to other factors as well [79,80]. Low-level myocardial injury occurred in nearly 29% of doxorubicin-treated patients [79,80]. For patients with higher cardiac troponin T elevations, chronically active myocardiocyte injury over weeks to months was frequently noted [79,80]. Strategies to prevent or reduce cardiac injury during treatment for childhood cancer may be targeted, including individualized interventions, based on cardiac troponin T elevations.

Normal LV function does not indicate a lack of myocardial injury or damage (Table 1). The use of surrogate markers of subclinical disease is helpful since large sample sizes are needed to achieve endpoints of heart failure or death resulting in problems with recruitment and retention to conduct a placebo-controlled trial. Standard definitions of abnormal surrogate endpoints are imperative if they are to be

Table 2
Testable treatment strategies for children presenting with congestive heart failure

Viral polymerase chain reaction panel	+	+	–	–
Serum cardiac troponin	+	–	+	–
1. Immunomodulatory therapy	+	–	+	–
2. Anti-infective therapy	+	+	–	–
3. Anti-congestive or anti-remodeling therapy	+	+	+	+

adopted on a global basis. The pharmacokinetics of therapy and its pharmacodynamic outcome are important to consider when evaluating surrogate endpoints. Dose–response, add-on, sequential dose-escalation, or cross-over study designs may be useful in studies employing surrogate markers if the underlying disease or condition is stable (and often it is not in this population). Multi-arm and factorial study designs might explore dose and duration of tested therapies and the exploration of trends might be useful when surrogate markers are used. The use of a tiered approach to assess both the surrogate outcomes and a cluster of clinical related outcomes may also be helpful. The surrogate endpoints considered many times reflect the mechanism of action of the study drug. Studies that use clusters or composites of clinically-unproven outcomes for this patient population that are perhaps biologically related and may be affected by the same mechanism of action of the study drug are not acceptable. Unless the surrogate outcomes used are clearly reliable it becomes necessary to interpret results with extreme caution unless consistent results are observed on a range of related outcomes and even then the size of the treatment effect may be substantially overestimated. It is unclear whether in children with ventricular dysfunction, where there are multiple hormonal, nutritional, neurologic, and cardiovascular effects, among others, whether surrogate endpoints that have been validated in adults with ventricular dysfunction are also valid. Changes in surrogate markers should reflect changes in clinically meaningful endpoints such as heart failure or death for the surrogate marker to be valid. Surrogate endpoints that assess health-related quality-of-life are important. For example, if the use of a experimental therapy for pediatric ventricular dysfunction reduces non-fatal endpoints or events such as symptoms, decreases recurrent hospitalizations, or increases functional status, and that may be the only achievable goals for many of these patients, then the therapy's overall benefit to the patient may exceed its effects on objective surrogate markers of clinically significant outcomes.

3.6. Investigate the course of evolving disease processes

Fig. 1 reviews the stages in the course of pediatric ventricular dysfunction. The course is often followed by echocardiographic measurements of LV structure and function. The careful use of these measurements have enabled us to understand the mechanical mechanisms of developing ventricular dysfunction in different affected pediatric populations [11]. In children with HIV infection we have found that there are abnormalities of fractional shortening and contractility that independently predict mortality years before it occurs [39]. In this same population we found that inappropriately increased ventricular wall thickness or mass were also independent long-term predictors of mortality by different mechanisms [39]. This is in sharp contrast to anthracycline-treated long-term survivors of childhood cancer where we observed that inappropriately reduced ventricular wall thickness was the leading cause of late ventricular dysfunction by increasing ventricular afterload (Fig. 2) [6,12]. In children with chronic renal failure, ventricular dysfunction appears related in part to increased sympathetic cardiac tone [89,90]. Understanding the significance of measurements of ventricular structure and function is enhanced by considering a number of pediatric-specific issues including the normalization of echocardiographic measurements to age, body surface area, sex, and race/ethnic origin [12,91]. It becomes important to understand the effects of mechanical load and its potential implications for treatment options. Testable treatment strategies include whether all children with ventricular dysfunction should be treated similarly or whether afterload reducing strategies may be more beneficial for a child with ventricular dysfunction on the basis of elevated afterload with normal contractility and whether contractility enhancing strategies may be most appropriate for a child with ventricular dysfunction due to depressed contractility but normal loading conditions. We have found that in long-term survivors of childhood cancer treated with mediastinal radiation that many cardiac abnormalities are present including diastolic dysfunction with a restrictive cardiomyopathy [92]. Studies that have limited their assessment to global LV systolic performance have concluded that this is a population free of late dysfunction. The importance of understanding the comprehensive cardiovascular status of this high-risk population is clear and is the only way the patient's cardiac health will be accurately assessed.

3.7. Understanding that serious disability or death as endpoints are rare with intermediate follow-up

Genetic disorders that may lead to serious disability or death in childhood are rare and therefore there is difficulty in using objective clinical outcomes in pediatric research studies. Death is objective and has the advantage of being dichotomous but for most childhood illnesses death is unusual so very large sample sizes would be required.

3.8. Understanding what congestive heart failure is

For childhood congestive heart failure the diagnosis is often subjective or confounded by being linked to measurements of ventricular systolic function which

poses problems when establishing selection criteria or endpoints for clinical trials.

3.9. Understanding functional status and quality of life

There are few validated age-appropriate instruments. Quality-of-life assessment should be an important outcome in clinical trials. A recent review of nine quality-of-life measures developed for children found them to be insufficiently child-centered or family-focused, and few had been adequately validated or subjected to tests for reliability or responsiveness to change [1]. In one study we conducted of patient-perceived functional status of long-term survivors of childhood cancer treated with anthracyclines, we observed that the patients who had received the highest cumulative doses of anthracyclines and, as a result, had the worst ventricular function complained the least of decreased functional status but were the most impaired [6]. This is a complex and important area that needs more development. It is also important that as new therapies are tested in asymptomatic patients that quality-of-life be assessed to ensure that experimental therapies focused on treating ventricular dysfunction do not adversely affect overall quality-of-life.

3.10. Understanding development and progression of disease

It is only by studying the long term course of children with, or at risk for, ventricular dysfunction that we will be able to identify the genetic variations and environmental factors that predispose individuals to the development of heart disease and their subsequent modification [34]. We have found that even the fetal maternal environment may exert strong and lasting adverse effects on ventricular structure and function in infants and children, suggesting that long follow-up of at-risk populations should not only be thought of at the time of diagnosis of ventricular dysfunction, but also during the preceding time interval [17,93–96].

3.11. Proposed research in pediatric ventricular dysfunction

The relation of future research in pediatric ventricular dysfunction to existing guidelines in this area from the literature will be explored in this section. In addition, the ability of the NHLBI-supported Pediatric Cardiomyopathy Registry to facilitate these research objectives is listed [54].

The NHLBI Report of the Task Force on Research in Heart Failure published in May 1994 specifically suggests the formation of a national cardiomyopathy registry to encourage the establishment of working groups of scientists to: (1) investigate the genetics of cardiomyopathy by exchanging patient material, developing new genetic probes for candidate genes, and organizing a central center for data analysis: (2) integrate basic and clinical studies by using the availability of human cardiac tissue to elucidate the natural history of the biochemical and physiological changes that occur during the progression to heart failure and utilize this to monitor therapeutic interventions; and (3) create a national myocardial tissue bank to coordinate the distribution of tissue to facilitate studies of the pathophysiology of clinical heart disease. The report states that heart failure is a major and growing health problem in the United States; yet, scientists are at the brink of making major advances that could control this condition and reduce the toll of heart failure. The conclusion of the executive summary specifically calls for research on the genetic and cellular causes of heart failure and the development of a preventative strategy that includes identifying patients at risk of heart failure, both of which should be accelerated by the Pediatric Cardiomyopathy Registry [54]. Some of the specific recommendations noted throughout the report that are addressed by the Registry include the following:

- Use specific gene mutations associated with, and presumed responsible for, different cases of cardiomyopathy to allow for the genetic diagnosis of cardiomyopathy and to point the way to treating affected individuals in an early, 'preclinical' stage of disease in the hope of preventing heart failure.
- Efforts to elucidate the fundamental genetic abnormalities in idiopathic dilated cardiomyopathy are encouraged to yield information on the fundamental cause of heart failure and new methods of prevention.
- A major long-range goal that has potential for preventing and treating heart failure is the correction of abnormal cardiac gene expression by the introduction of foreign genes into the heart and by the restoration of myocyte cell division.
- To determine the causes of heart failure in different geographic locations and socioeconomic strata of a population.
- Identify candidate genes for familial forms of idiopathic dilated cardiomyopathy and other forms of hereditary heart disease that can lead to heart failure.
- To determine the relationship between the molecular abnormalities responsible for the synthesis of abnormal proteins and the abnormal clinical phenotype in the cardiomyopathies.
- Investigate potential infectious mechanisms of cardiac damage and cardiomyopathy.
- Determine whether development, race or gender

is a factor in the development or progression of ventricular hypertrophy or cardiomyopathy, and if so then what are gender, racial, and developmental-specific risk factors.
- Develop sensitive, reliable, and reproducible methods for early detection of functional, metabolic, and structural changes of the myocardium.
- Determine the factors that accelerate the progression of cardiac damage, and define the genetic and phenotypic characteristics that contribute to progression and regression of cardiac damage.
- Define the effectiveness of early therapeutic interventions, including their limitations and side effects, and determine ways in which to reduce the risks of early interventions.
- Develop and perfect simple, cost-effective, and yet accurate and reproducible non-invasive techniques suitable for patient care and epidemiological studies. These techniques should be improved sufficiently so that the need for expensive, invasive examinations can be greatly reduced.
- Define factors that constitute a high-risk profile among asymptomatic or mildly symptomatic patients with LV dysfunction.
- Determine how patients with LV dysfunction and heart failure who are at increased risk of sudden death can best be identified.
- Identify factors responsible for progression or lack of progression to symptomatic heart failure in individuals with asymptomatic abnormalities in cardiac structure or function. Clarify the interactions among predisposing factors, aging, and structural or functional cardiac abnormalities in increasing the risk of developing heart failure.
- Validate simplified, non-invasive imaging and cardiac function assessment methods for detecting abnormalities of cardiac structure and function. Evaluate the sensitivity of these methods for monitoring the progression of cardiac dysfunction.
- Identify markers in asymptomatic individuals with left ventricular dysfunction that are predictive of early morbidity and that therefore enable selection of patients who are more likely to benefit from aggressive therapy.
- Assess the relative importance of the relief of symptoms and disability vs. the increased risk of mortality in patients with end-stage heart failure.
- Define the role of cardiac transplantation in children with end-stage dilated cardiomyopathy and determine the risk factors that minimize long-term survival, including graft rejection, pulmonary vascular resistance, premature atherosclerosis, and ventricular diastolic dysfunction.

The NHLBI Report of the Expert Panel on Genetic Strategies for Heart, Lung and Blood Diseases predicts that many of the mutations causing disease will be identified in the next 10–20 years. Registries will allow that to happen for pediatric cardiomyopathy. The Registry should lead to an understanding of the pathogenesis of these disorders and offers the hope of having a major impact on the clinical practice of medicine in this area [54]. In reference to cardiomyopathy, the report notes 'a paucity of cardiovascular investigators and clinicians who are familiar with genetic principles and methodologies. Similarly, there are few molecular geneticists studying these vascular and myocardial diseases. It is therefore crucial to increase genetic expertise among cardiovascular investigators and to concurrently encourage the involvement of geneticists in this area.' These research priorities are some of the goals of the registry.

- Establish a disease-specific coordinated network to foster genetic studies among many investigators.
- Provide an infrastructure and ways to interact.
- Have the ability to share data and resources among network members.
- Develop and maintain appropriate databases.
- Provide a uniform, robust, and meaningful definition of the phenotype of cardiomyopathy.
- Have adequate facilities to store data.
- Have sufficient statistical and analytical expertise and resources.
- Result in the establishment of appropriate collections of patients and families of diverse ethnic and racial backgrounds.
- Provide detailed knowledge of relevant physiology to increase the power of genetic studies.

In June 1991, the NHLBI convened a Workshop on the Prevalence and Etiology of Idiopathic Dilated Cardiomyopathy (IDCM) (Am J Cardiol 1992; 69:1458–1466), in large part because there was limited information on pathogenesis and prognosis, few population-based estimates of incidence and prevalence were available, and few geographic areas were represented in previous publications. It was noted that IDCM was difficult to study owing to the relatively low prevalence, its potential pluricausal nature, and the fact that it is often a diagnosis of exclusion. The report summarized existing data on established IDCM, which notes 1-year survival rates of 48–77%, 2-year rates of 31–66%, and 3-year rates of 24–53% among more than 2000 adult patients. Because the mechanism of myocardial damage and the related etiologic and prognostic factors are virtually unknown, the workshop felt that it presented a significant challenge to the cardiovascular community. The workshop concluded by recommending several areas for future

observational and interventional studies of IDCM, all of which the Pediatric Cardiomyopathy Registry [54] will facilitate:

- Standardized diagnostic criteria should be developed.
- Population-based registries were given the highest priority among etiologic study designs to understand cardiomyopathy better. The workshop felt that this was an appropriate study design for tracking incidence and prevalence and to identify representative cases to study potential etiologic factors in subsequent case-control studies. Observational studies were recommended that would be able to address non-modifiable factors (e.g. age, sex, race or ethnicity, and genetic predisposition) and modifiable factors (e.g. viruses, diet, socioeconomic status, metabolic conditions, drugs, toxic or occupational exposure, obesity, and hypertension).
- Suggested measurements to be included in population-based studies in IDCM were stated. These included DNA polymorphisms and candidate genes, cardiac structure defined by echocardiography, immunologic markers, and neurohumoral factors). Echocardiography was recommended as the principal method of detection, diagnosis, and follow-up for population-based studies.

In May 1996 the NHLBI convened a Special Emphasis Panel on Research in Heart Failure whose suggestions included a number of areas applicable to clinical studies of children with ventricular dysfunction, some of which are highlighted below [97].

- 'More focused clinical trials in which the patient population is more homogenous. Although this approach may yield data that are viewed to be less broadly applicable, new understanding of a mechanism in a clearly defined subset of patients with heart failure may well be applicable to a larger population.'
- 'Future trials of heart failure treatments should plan to consider arrangements for ancillary basic studies and obtain blood, tissue, or other measurements to elucidate mechanisms of the disease and its progression. This information would form the origins of a database that would meet a critical need to establish the phenotypes and genotypes of the normal and failing hearts.'
- 'Large-scale clinical trials provide a rich population of patients with LV dysfunction that are monitored over time in a well-defined, standardized protocol. The opportunity to identify molecular, cellular, structural, neurohormonal, electrophysiological, bioenergetic, circulatory, or clinical markers of the progression of the ventricular dysfunction and of its response to the therapeutic interventions should not be lost.'

The list of clinical research studies in this area is large, in part because so little has been done so far. In general, research is needed to find the optimal therapy for correcting both systolic and diastolic ventricular dysfunction and left ventricular hypertrophy before irreversible changes ensue. In addition, more research is needed to find the means to combat the sudden death-promoting dysrhythmias of heart failure. It is also extremely important to consider the efficacy of preventive measures in heart failure candidates with normal systolic function. In adults improved heart failure treatment has resulted in improved outcomes but more work needs to occur to understand the physiological bases for potential sex, race, and age differences [98,99]. Clinical trials need to be designed out of need rather than expediency. Healthcare processes that deliver cost-effective treatments in a more uniform manner need to be implemented.

4. Obstacles to achieving clinical research goals in pediatric ventricular dysfunction

4.1. Smaller population

For many chronic diseases which affect both adults and children the number of patients in the adult population is much greater. This may lead to difficulties in obtaining statistical power to detect an effect of treatment.

4.2. IRBs may not allow pediatric studies where adult data exist

Institutional review boards have rejected pediatric proposals where the study has been done in adults. The same therapy may have different effects depending on the stage in the disease process that is used. Children receive special protection under federal regulations for biomedical research that require the potential for direct benefit to the child participating in a drug study. This limits participation since initial pharmacokinetic and safety testing in normal pediatric subjects is more difficult to obtain informed consent on than with adult studies.

4.3. Need for long-term follow-up to understand natural history and to examine subclinical drug effects

Studies in children are of particular interest where the drug may affect the natural history of a disease.

This is the case for many emerging therapies (i.e. gene therapy). Trials to determine safety and efficacy are initially important. However, the real outcomes of interest, such as rates of decline in function, should be examined over years, rather than months, and are of particular interest in patients with mild disease who may not yet have developed irreversible organ damage. The importance of maintaining cohorts of rare diseases to understand the natural history and response to therapy in children is clear [100,101]. The field of adult congenital heart disease is too narrowly focused on structural cardiovascular malformations and should include adults with onset of ventricular dysfunction in childhood either from genetic or environmental causes. In order to help these populations of patients more and better understand their diseases it becomes important to follow cohorts with specific rare diseases differently and a unified clinic is an ideal way to facilitate this. We found that using cross-sectional data at a single point in time demonstrated a significant correlation between immune dysfunction and ventricular dysfunction in HIV-infected children [23]. However, when we followed these children long-term and examined longitudinal correlations we found that there was not a significant correlation between immune and ventricular dysfunction [23]. Having been able to examine trends over time in this population at high risk for ventricular dysfunction enabled us to determine the truth.

4.4. FDA review and approval of pediatric ventricular dysfunction therapeutic studies utilizing death as the sole acceptable endpoint is not reasonable

The development of validated surrogate endpoints must be a priority. Mortality is not always an indicator of good or poor outcome in heart failure and may be the inevitable consequence of a long illness for which the patient may have received excellent care and had a good pharmacologic response to therapy. Suffering associated with this condition may be substantial, and health status measures may be as important as survival rates.

The FDA has made major changes to increase awareness and compliance with testing new drugs in children to develop pediatric dosing recommendations at an earlier stage in the development process and to improve the safety of new agents in children. Pediatric cardiologists must now devise more rational methods of selecting which new cardiac drugs to develop for children with ventricular dysfunction and to develop new and more efficient trial designs to evaluate safety, pharmacokinetics, and efficacy of new drugs in children with ventricular dysfunction, as more new drugs become available for testing in children at an earlier stage in the drug development process.

4.5. Participation by pediatric cardiologists is difficult

The Pediatric Cardiomyopathy Registry has > 220 centers that confirmed participation but only 44 have actually participated [54]. The agenda for pediatric cardiology should be to advocate for participation of pediatric cardiologists in clinical research studies because all is not well for us in this area. There was acknowledgement in the pediatric oncology field in the late 1960s that the outcome results were not good enough. We must first get that acknowledgement in pediatric cardiology and then get the buy-in of pediatric cardiologists around the country to participate on clinical trials. Recent drug company-sponsored studies of ACE inhibitors indicate that this can be done in this field [102,103].

Despite these difficulties there can be little progress in the clinical care of children without research in this age group, and the findings of studies in children may also be relevant to adult medicine.

Those concerned with the care of children have a duty to improve that care. One way of achieving that goal is through research. However, for research to be successful and to overcome difficulties pediatricians, parents, and children must all be convinced of its importance.

4.6. Reporting and recall bias by pediatric cardiologists

In several studies we have performed in pediatric ventricular dysfunction we have been surprised to find that the results were not what we would have expected a priori. For example, in 1993 we performed a written and telephone survey of 100 pediatric cardiology program directors to review cases of pediatric cardiomyopathy in their practices. The results of that survey are shown in Table 3. Five years later we presented the results of actual data that had been collected from many of these same programs and found major differences from the conclusions of the survey [98,99]. The actual incidence of pediatric cardiomyopathy and the percentage of children with a known etiology of their cardiomyopathy were both approximately one-half of what the survey had suggested [98,99]. This suggests that surveys of experts in pediatric cardiology may be misleading due to unintentional reporting and recall bias. The details of this survey on children with ventricular dysfunction are reviewed below.

Between September 1992 and June 1993, we conducted a self-administered mail survey of pediatric cardiologists associated with a range of health-care institutions and private practices throughout the United States and Canada. We took the sample of cardiologists from the American Academy of Pediatrics, 1991 Fellowship Directory, Section on Cardi-

Table 3
Results from cardiomyopathy survey (n = number of respondents; CM = cardiomyopathy)

Clinic profile	
Number of pediatric cardiologists on staff at responding institutions ($n = 94$)	538
Number of pediatric cardiology patients yearly ($n = 90$)	267889
Mean	3189
S.D.	1658
Race, ethnicity ($n = 74$)	
White	63%
Black	22%
Hispanic	10%
Other	5%
Sex ($n = 70$)	
Male	51%
Female	49%
Cardiomyopathy profile	
Number of patients seen yearly for CM (excluding Kawasaki disease and rheumatic fever) ($n = 84$)	5205
Mean	62
S.D.	104
Type of CM ($n = 82–84$)	
Dilated	58%
Hypertrophic	30%
Restrictive	5%
Arrhythmic	5%
Etiology ($n = 66–72$)	
Known or suspected	
Infectious	17%
Metabolic or genetic	13%
Cancer-related	12%
Immunologic	2%
No known etiology	57%
Cardiac catheterizations on patients with CM ($n = 89$)	1003
Mean	11
S.D.	12
Biopsies among catheterizations for CM ($n = 82$)	1075
Heart transplants on patients with CM ($n = 92$)	212
Deaths among patients with CM ($n = 78$)	218
Autopsies on patients who died with CM ($n = 82$)	190
Mean	2

ology. We initially identified 109 cardiologists from the United States and 15 from Canada. These physicians represented 38 large, 27 medium, and 14 small university hospitals in the United States, 30 private-practice settings in the United States, and 15 hospitals in Canada. Of the cardiologists identified from the United States, 1 was not a pediatric cardiologist, 1 was retired, and 1 was deceased. The remaining 121 pediatric cardiologists were eligible to participate in the survey.

We designed the questionnaire to provide estimates on the number of cardiomyopathy cases that might be submitted to a national pediatric registry and the willingness of respondents to participate in such a registry. Specific questions included the number of cardiologists on staff; annual number of pediatric cardiology patients seen by their group or institution; gender and racial distribution of patients; number of patients with a cardiomyopathy seen yearly; annual number of cardiac catheterizations, biopsies, and transplants performed on these patients; and annual number of deaths and autopsies. In addition, respondents were asked whether they would be willing to participate in a voluntary pediatric cardiomyopathy registry and, if so, what proportion of cases would realistically be reported. The response rate to the survey was 79% ($n = 96$). Twelve pediatric cardiologists from the United States and one from Canada declined to complete the questionnaire and also declined to participate in a voluntary registry on telephone follow-up.

Ninety pediatric cardiologists responded affirmatively to their group or institution participating in a voluntary registry; three respondents reported that they would not participate; and three responses were missing.

The results of this survey suggested a strong nationwide interest in and need for a voluntary registry for pediatric cardiomyopathy. The large number of cases also suggested that the magnitude of the disease is great. Furthermore, the percentage of cases with an unknown etiology and the number likely to be symptomatic (cardiac catheterizations) or to have intractable disease (transplants and deaths) reinforced the need to study this disease and discover common etiologies and disease mechanisms so as to develop appropriate treatments.

4.6.1. Availability of patients and evidence of access to patients

The centers responding to the survey represented a high percentage of pediatric cardiologists in the United States and Canada and encompassed almost all major centers of pediatric cardiology. The responding and participating centers collectively followed 267 889 pediatric cardiology patients. The 1991 Fellowship Directory of the American Academy of Pediatrics listed 580 pediatric cardiologists from the United States and Canada as members. The survey reported here represents the participation of 538 pediatric cardiologists, 95% of the number listed in the academy directory. Survey respondents noted that they refer only 2.5% of cardiomyopathy patients elsewhere for evaluation and management. The respondents stated that realistically, 83% of their pediatric cardiomyopathy patients would be reported to the registry. Therefore, the availability of and access to data from infants and children with cardiomyopathy appears quite strong.

4.6.2. Wide geographic distribution

Participating centers represent 43 states plus the District of Columbia, eight Canadian provinces, and Puerto Rico. These states or provinces encompass 94% of the population. Survey respondents stated that they capture 70% of pediatric cardiology patients in their region, with 80% of new patients having been referred from elsewhere.

4.6.3. Women and minorities

Females represented 49% of all pediatric cardiology patients followed at responding centers. The racial and ethnic composition was 63% white, 22% black, 10% Hispanic, and 5% other.

4.6.4. Importance of the Medical Question

IDCM, or primary myocardial disease, is poorly understood. The annual incidence of IDCM is estimated at 2–8/100 000 in the United States. Overall survival of patients with IDCM is poor (~ 50–60% at 2 years). As exemplified by the known forms of inherited cardiomyopathy, factors such as age, coexisting illnesses, diet, and additional genetic loci may play a part in determining the expression of the cardiomyopathy phenotype.

4.6.5. Prevalence of pediatric cardiomyopathy

The mean number of active pediatric cardiomyopathy patients followed at 84 respondents' centers is 62, for a total of 5205 patients, or 1.9% of the mean number of all pediatric cardiology patients followed (3189). This figure is close to the 2.7% prevalence of pediatric cardiomyopathy followed by pediatric cardiologists in the New England Regional Infant Cardiac Program. The actual prevalence of pediatric cardiomyopathy (diagnosed and undiagnosed) is not known.

Cardiomyopathy is functionally classified as hypertrophic, dilated, restrictive, or arrhythmic. The survey noted that DCM was most common (58%), followed by hypertrophic (30%), restrictive (5%), and arrhythmic (5%). In the majority of cases reported here (57%), the etiology was unknown. For those where the etiology was known or suspected, respondents reported that 17% had an infectious etiology, 13% were metabolic or genetic, 12% were related to toxic exposures (e.g. anthracycline chemotherapy or irradiation), and 2% had immunologic causes.

4.6.6. Incidence of pediatric cardiomyopathy

The annual number of new cases of pediatric cardiomyopathy reported by 88 centers was 4098, with a mean of 47. A comparison of 47 with the mean number of total cases per reporting center [62] suggests that the length of follow-up for infants and children with cardiomyopathy is short, approximately 1.4 years. Other studies on cardiomyopathy have suggested that the 1-year survival rate for infants and children is 20–80% and the 5-year survival rate for adults is 25%, supporting the possibility that short survival is likely. Other factors that may have contributed to the similarity between prevalence and incidence could be patient improvement and discharge from follow-up, patients lost to follow-up, and the methods for data collection used in this survey.

This survey suggests that the incidence of cardiomyopathy based on 60 million children $\leq$ 18 years of age is 0.9/10 000 children (4512/60 million). This compares closely with the 1/10 000 incidence noted in the first year of life in the Baltimore-Washington study. This suggests that a steady number of new cases of cardiomyopathy continues throughout childhood to keep the incidence constant.

4.6.7. Severity of pediatric cardiomyopathy

Children with clinically symptomatic cardiomyopathy usually undergo cardiac catheterization with endomyocardial biopsy. The 90 centers reported 1075

cardiac catheterizations for cardiomyopathy in the preceding year, excluding post-transplants, suggesting that 24% of children become clinically symptomatic during the first year after diagnosis of cardiomyopathy. Cardiac catheterizations for cardiomyopathy in children represented 5% of all catheterizations at these centers. Cardiac transplantation, indicating a failure of medical management, was done for 20% of infants and children with symptomatic cardiomyopathy during the first year after presentation. Two hundred eighteen infants and children (20%) died of symptomatic cardiomyopathy in the preceding year at these 90 centers. Together, this suggests that up to 40% (430/1075) of infants and children with symptomatic cardiomyopathy will fail medical or surgical management in the first year following diagnosis.

4.7. What may be intuitive may not be correct

Another prospective study we performed looked at the development of abnormal left ventricular structure or function in children receiving antiretroviral therapy [7,40]. Based on data in animals and adult patients suggesting that cardiac abnormalities may develop in some HIV-infected patients treated with antiretroviral therapy, recommendations were made in children and adults that potentially life-saving antiretroviral therapy be discontinued if ventricular dysfunction develops. When we studied this prospectively in a multicenter design over 10 years we found that unlike animal and adult studies there was no measurable effect of antiretroviral therapy on the myocardium [40].

Another example of where an accepted therapy in adults to reduce the incidence of developing left ventricular dysfunction became the standard-of-care in many pediatric oncology treatment protocols without demonstrating that the therapy resulted in cardioprotection in children was the use of 48 h continuous infusion of anthracycline chemotherapy. We compared continuous infusion therapy with previously conventional bolus anthracycline infusion over less than 1 h duration [104]. To our surprise, after completing a multicenter, prospective randomized blinded study over 5 years duration we concluded that 18 months after the completion of anthracycline chemotherapy there was no difference in left ventricular structure or function between the two groups and that both groups had significantly deteriorated since their initial cardiac assessment [104]. In addition, the continuous infusion cohort had substantially more hospitalization days and other complications [104]. This was unexpected based on adult studies, but was only found by performing a prospective study in children. Knowing the results of this study enabled us to stop giving false hope to our patients with ALL and their families and allows us to investigate other cardioprotective strategies that may be of benefit. Again, what we have seen many times is that not everything that makes sense biologically, or is based on animal or adult studies, has been useful in the treatment of children.

4.8. Reliability of multicenter pediatric cardiology data

There is a need to know how good your tests are. We determined that locally measured echocardiographic reliability is poor in pediatrics on multicenter studies [105]. There is a need for central remeasurement. Clinical management of children with cardiac disease is frequently based on echocardiographic measurements of LV structure and function. In multicenter pediatric studies of cardiac status associated with experimental treatments or disease processes, the determination of efficacy, toxicity, and course is frequently based on echocardiographic measurements of LV structure and function. Despite the clinical and research importance placed on pediatric echocardiographic measurements, little has been published about the reliability of these measurements.

This may have implications for the planning and conduct of research studies, and as well as for the management of individual patients. The importance of reliable and accurate LV measurements cannot be over-emphasized. For example, expert panel standards of cardiology practice have been used to recommend withholding potentially lifesaving chemotherapy in asymptomatic children with cancer when fractional shortening drops below a specified value [10]. Presenting similar problems, are an increasing number of standard-of-care guidelines that differentiate acceptable from unacceptable care in some settings based on a one percentage point difference in LV function. However, our data show that despite attempts to standardize echocardiographic techniques, the determination of fractional shortening from the same tracing varies considerably among centers [105].

Our study would suggest that these precautions are very important when a single echocardiographic measurement, but not longitudinal changes in z-scores in the same child where any systematic bias in the same child would be subtracted out, are to be used in clinical care [105]. Also, comparing a study sample's data with a data set generated by other researchers may lead to inappropriate normative data for multicenter clinical studies and could result in misleading group averages.

Our study showed that echocardiographic measures of LV structure and function calculated locally are subject to heterogeneity in data acquision and assessment [105]. Measurements differed so much that a central echocardiographic facility is needed to provide

consistent and reliable data for research studies, and repeat measurements on individual children are recommended to provide clinically meaningful results. To improve inter-institutional agreement, we recommend standardizing how images are acquired and read. Though core laboratories increase the labor and expense of clinical trials, they provide more consistent and probably accurate analysis than do local measurements. Future pediatric clinical trials should arrange for independent evaluations of echocardiographic data.

4.9. Animal models of pediatric ventricular dysfunction

Animal models of pediatric ventricular dysfunction can often augment and expedite controlled clinical trials. For example, the rat model we have used to assess biomarkers for the detection of anthracycline cardiotoxicity enabled us to determine histologic myocardial status in ways not possible in children [20,26,28,36,76–84]. The rat model has allowed us to rapidly test the effectiveness of different anthracycline cardioprotective strategies since we are only able to perform one controlled clinical trial to test an anthracycline cardioprotection strategy in children approximately every 5 years due to accrual and follow-up issues. An animal model has been very helpful for us to identify the most promising strategy to bring to a human clinical trial.

However, it becomes very important to realize that all findings in animal studies are not directly translatable to children. For example, the newborns of pregnant monkeys treated with zidovudine exhibit profound myocardiocyte damage. This resulted in the suggestion that pregnant HIV-infected women should not receive zidovudine to substantially reduce HIV transmission from mother to child. In contrast to the monkey model, when we examined zidovudine cardiotoxicity in infants and children we were unable to demonstrate adverse effects [40]. In this case, human studies are likely to have resulted in many saved lives of uninfected children born to HIV-infected mothers who received zidovudine and who otherwise would have died of HIV infection.

5. How to achieve clinical research goals in pediatric ventricular dysfunction

5.1. Advocacy, representation and participation

Out of frustration with the current voice pediatric cardiology has, a call for an organization devoted entirely to the field of pediatric cardiology has been recommended to provide a 'legitimate body' that can speak out on behalf of pediatric cardiologists [106]. The stated goals would be to create a platform for scientific discussions, propagate knowledge and standards of care, as well as advocate for the advancement of patient care and the professional goals of the medical profession of this field.

Examples of where increased organizational efforts on this field may lead to more attention to the clinical and research needs of children with heart disease are abundant. One example is, on 17 October 2000 the President signed into law the Children's Health Act of 2000 with > $50 million in FY 2001 earmarked to it. This is a package of provisions related to children's health that promotes additional research on disease and disabilities specific to children, among other topics. Research in many important areas are included such as muscular dystrophy, lead poisoning, infant mortality, traumatic brain injury, autism, fragile X, juvenile arthritis, juvenile diabetes, asthma, hearing loss, childhood cancer, and epilepsy. No mention of pediatric cardiovascular diseases is part of this major federal legislation for children's health.

As another example, NHLBI has had no pediatric cardiology representation on SPARK, Strategic Plan, Epidemiology Task Force, Heart Failure Task Force, Genetics Task Force, Dilated Cardiomyopathy Task Force, Heart Failure Special Emphasis Panel, and very little representation on any NHLBI Study Section listed on the NHLBI web site during the past year, yet this is the major research funding organization for the field of pediatric cardiology in the US. Of the 58 members of the SPARK Working Group, a select group of accomplished scientists convened to assist the NHLBI by identifying research areas that constitute extraordinary opportunities and that would merit substantial increases in resource investment, assembled in May 1998 to formulate a strategic plan for the NHLBI funding the years FY2001-2005 not a single pediatric cardiologist was included.

In spite of this, largely through the efforts of NHLBI internal program staff, an important 2001 initiative was included. This initiative is to 'Investigate diagnostic and therapeutic approaches for congenital and acquired pediatric cardiovascular conditions from fetal life into adulthood. Approximately 32 000 infants are born each year with congenital cardiovascular malformations, one of the leading causes of infant mortality. In addition, acquired pediatric cardiovascular conditions, including arrhythmias, inflammatory conditions, cardiomyopathies, hypertension, and hyperlipidemia affect several million children and adolescents. Treatment of congenital and acquired pediatric cardiovascular disease involves drug and surgical therapies. Yet, most standard therapeutic drugs have not been tested in randomized controlled trials in children. Surgical correction has side effects in children about which much is still unclear. Important

clinical questions remain unanswered. Most treatment decisions concerning pediatric heart disease are not evidence-based. In the past 25 years, fewer than 40 randomized clinical trials have been conducted, of which nearly half dealt with patent ductus arteriosus in preterm infants. The medical, emotional, social and economic consequences of pediatric heart disease are profound. Medical therapy is employed widely to treat pediatric heart disease. Few standard therapy agents, however, have been tested in randomized trials in pediatrics. Agents of choice used in the treatment of adult heart failure are used in children, but have not been studied in a systematic fashion. Emerging adult therapies may benefit children but are virtually untested in them despite their requirement by FDA regulations. A pediatric myocarditis agent has never been evaluated in a prospective randomized trial. A collaborative network of up to six clinical research centers and a data coordinating center will evaluate standard and new diagnostic and therapeutic strategies in pediatric cardiovascular medicine. The network approach can also promote training of investigators in pediatric clinical research and provide a way to ensure rapid dissemination of research findings... The major barriers to clinical studies in pediatric heart disease include the heterogeneity of conditions, the small numbers of individuals with a particular malformation or condition at any one center, differences in treatment approaches to particular problems, the absence of systematic centralized databases, and the lack of resources to provide national coordination of collaborative efforts. Efficiencies will be achieved through a common infrastructure for recruiting, monitoring, and following patients whose conditions will be characterized in a standard fashion' [107]. This is an extremely important landmark advance for pediatric cardiology. Hopefully some of the selected protocols will apply to pediatric ventricular dysfunction.

5.2. Prevention of ventricular dysfunction has to start in childhood

As illustrated in Fig. 1, we should not wait until symptomatic LV function is present to initiate preventive strategies. The studies of Barker and colleagues have demonstrated retrospectively that antenatal events influence morbidity and mortality in adult life (e.g. coronary heart disease and hypertension). The definition of preventive cardiology is too narrow and should include reducing the subsequent risk of developing symptomatic myocardial disease.

For more than 2000 years, cardiac failure has been recognized as a clinical entity, but within the past 15 years it has been identified as a major public health concern [108]. Thus, the national hospital discharge service estimated that 4.8 million US adults have heart failure and that nearly 500 000 US adults develop it each year, making this condition the leading diagnosis for hospitalization of persons older than 65-years-old. The healthcare expenditure for heart failure in the US in 1993 was $17.5 billion, which amounts to 11% of the total budget for cardiovascular disease in 1997. Approximately 60% of the healthcare expenditure for heart failure is for hospital care. Heart failure accounts for more than 3 000 000 office visits annually at a cost of $3 billion yearly for out-of-hospital care. Heart failure is a common chronic condition that impairs quality of life and results in loss of independence.

Kannel has reviewed the prospects for prevention of heart failure in adults that is noted below [108]. Fig. 1 demonstrates how these preventive strategies may be helpful in children at-risk of, or with, ventricular dysfunction. 'The epidemiology and the vital and health statistics concerning heart failure indicate that is a major burden on victims, their families, and the health care system. Evidence indicates that treatment of the overt condition continues to be inadequate because of an unacceptably poor survival rate. Those who may have this condition must be detected and treated while the process is still evolving. Treatment of presymptomatic left ventricular dysfunction, correction of the dysfunctional maladaptive changes of vasoconstriction, increased afterload, and salt and water retention; and timely myocardial revascularization and valve surgery hold great promise for high-risk heart failure candidates. In addition to the proven efficacy of ACE inhibitors, recent growing evidence indicates that beta-blockade can reverse and slow the progression of left ventricular dilatation that characterizes heart failure and reduces all-cause mortality in patients with overt heart failure.

From a population perspective the most cost-effective approach to the problem is to correct the modifiable risk factors as early as possible. The high population-attributable risks imposed by hypertension, diabetes, and coronary disease indicate the priority areas. Detection and control of hypertension and coronary disease have proven efficacy, but these measures are not being fully implemented. Only 45% of hypertensive persons have their blood pressure optimally controlled, and ACE inhibitors, beta-blockers, lipid-correcting therapies, and thrombolytic therapies are far from optimally employed. Major hypertension trials indicate clearly that treating hypertension reduces the risk of heart failure, and a recent meta-analysis indicates that antihypertensive treatment in the elderly can reduce heart failure incidence by 47%, an estimate close to the population-attributable risk estimated by the Framingham study. Although clinical

trials indicate that medical interventions can improve survival in overt heart failure, survival is still poor' [108].

Despite recent innovations in the treatment of predisposing conditions for heart failure, the condition remains highly prevalent and lethal once established in adult patients. Improvements in the treatment of clinically overt heart failure — the end stage of uncontrolled hypertension, myocardial ischemia, and valvular disease — have made only a small improvement in the poor survival in patients with this diagnosis. Therapy introduced at this late stage appears unlikely to substantially prolong life. Preventive measures must be taken before ventricular dysfunction becomes symptomatic and before maladaptive compensatory phenomena ensue. Clues to the methods needed to detect persons vulnerable to heart failure and prevent the progression of conditions predisposing to myocardial decompensation are emerging from recent epidemiologic research.

The goals of preventive strategies for pediatric ventricular dysfunction are: (1) to reduce the incidence of pediatric ventricular dysfunction; (2) to continue basic, clinical and population research into causes of pediatric ventricular dysfunction for interventions; (3) to increase risk factor reduction; (4) to establish data-based interventions; (5) to extend risk reduction to entire populations even though this may be less intensive to individual patients; and (6) to develop systems to monitor surveillance nationally through partnerships and collaborations.

5.3. Network infrastructure

Pediatric oncology is a notable exception to many areas of pediatrics in that high-quality clinical trials (multicenter randomized) are regularly performed [109–114]. Also, some successes have occurred in perinatal medicine where the NICHD Neonatal Research Network was established in 1986 to conduct multi-center clinical trials in neonatal medicine and management that is funded by a cooperative agreement between 14 clinical centers, the data coordinating center, and the NICHD. The neonatal research network has included therapies for sepsis, intracranial hemorrhage, chronic lung disease, and pulmonary hypertension. In addition, the Network has implemented a standardized follow-up program of extremely low birthweight infants and supports a registry of infants less than 1500 g at birth with $> 29\,000$ enrolled babies. Four of the Network centers also support a Maternal Lifestyle Study that investigates the effect of prenatal maternal drug abuse on neonatal and long-term outcomes. The NHLBI has recently established a pediatric asthma clinical network and a thalassemia clinical research network. In identifying the reasons for the relatively low standard of research in children, it is instructive to examine areas where there has been more success, to try and establish where certain difficulties may not exist or may have more easily been overcome.

Acute lymphoblastic leukemia (ALL) is rare, occurring in 1 in 2000, but the success achieved over the past 30 years in improving survival in ALL has been attributed largely to evaluation of therapy by multicenter trials [109–114]. Over the past 30 years, 5 year event-free survival for high risk ALL has improved from approximately 10% to nearly 90% due to multicenter clinical trials. The small field of pediatric oncology agreed over the past three decades to voluntarily regulate themselves and provide experimental procedures only to patients who participate in valid research. The availability of a pool of test subjects assures that new ideas for treatments are rapidly tested, allowing them to be adopted nationwide if they work, or tossed aside if they prove useless. As a result, the advances in this field have been phenomenal, far outpacing anything seen in adult medicine. In adult oncology for example a giant leap from developmental therapeutics and early underpowered clinical trials to community-wide applications of high-dose therapy for breast cancer circumvented essential scientific scrutiny and the well-intentioned but premature enthusiasm of patients and advocates was used at a time when physicians knew the therapy was toxic, expensive, and experimental [115]. For controlled clinical trials to succeed they must be designed to define the most effective, least morbid, and/or least expensive treatment. The payers must be brought initially into the process to fund the appropriate trials rather than be forced to pay for unproven, perhaps well-intentioned, treatments. The scientific importance of 'approved clinical trials' must be accepted by patients, physicians, and the payers. It must be agreed that the new treatments are unproven and therefore must be a subject for clinical investigation. Patients who are on such approved trials may get better care and closer observation; they should be reassured that they are not receiving a known inferior control therapy. Whether they are the beneficiaries of the experimental therapy is the goal of the trial. If the process can be efficiently undertaken, then resources will be saved. Knowledge, negative or positive, will be accumulated in a timely fashion. Ultimately the patient would be the beneficiary of the progress and not the victim of unproven innovation. This gives further importance to the role of intergroup participation to maximize patient accrual. Small or statistically minute differences in the continuous follow-up may be encountered. There have been few studies comparing the

costs of a clinical trial that defines the correct approach to a particular disease with the consequence of widespread use of an unproven treatment [115].

Advances in childhood cancer therapies have been dramatically aided by the willingness (even eagerness) of parents, children, physicians, nurses, and other health care workers to enroll patients on research studies that attempt to advance knowledge in the field. This degree of cooperation and collaboration among various groups has led to studies that have shown that participation in clinical trials leads to better therapy outcomes than those treated off-protocol using 'the doctor knows what's best' therapy [113]. This has resulted in third party payers reimbursing children on oncology protocols and in some cases not reimbursing those being treated off-protocol. A recent study of adult cancer patients treated at the Kaiser Permanente health maintenance organization demonstrated that participation in cancer clinical trials did not result in substantial increases in the direct costs of medical care [116]. Other costs that were not taken into account include recruiting patients, assuring that treatment protocols are followed, collecting and managing data, and supporting the infrastructure for research. Other benefits to HMOs for participating in clinical trials are enhanced appeal of an HMO to patients and physicians and earlier adoption of new treatments.

Over the past 16 years I have been fortunate to work closely with two oncology groups, the large (> 100 clinical sites) Pediatric Oncology Group (now merged to form the even larger Children's Oncology Group) and the smaller (10 clinical sites) Dana Farber Childhood Leukemia Group. I have observed different strengths of large and small multicenter clinical trials groups. Large groups are able to enroll more patients with quicker accrual and obtain answers sooner, there is often more missing data and less complex protocols, and there is longer protocol development periods to obtain consensus. However, effective therapies more rapidly become standard of care when tested on large group protocols. The smaller groups can perform more complex testing with better quality control and with more frequent testing. Effective therapy on smaller group studies frequently becomes the pilot data for larger group studies.

I have similarly been involved with the care of HIV-infected children during the past 16 years and have been impressed with the major therapeutic advances that have resulted from the NIH sponsored Pediatric AIDS Clinical Trials Group (ACTG). For example, the ACTG protocol 076 demonstrated that transmission from mother to infant could be virtually eliminated by maternal zidovudine use during pregnancy, an amazing result that created life from death. The value of cooperative group participation in pediatric AIDS speaks for itself.

5.4. Database derived clinical research

Databases derived from clinical trials or registries contain more detailed clinical information than administrative databases but have a selection bias that limit their usefulness in providing a true reflection of ventricular dysfunction across the population. Administrative databases can provide uniform information across a broad population over a long time frame and can track the onset of heart failure within a population [117].

5.5. Registry derived data

Large prospective studies of pediatric cardiomyopathy have not been previously conducted in North America, resulting in little population-based data. The NHLBI-sponsored Pediatric Cardiomyopathy Registry was established to: (1) describe epidemiology and clinical course of cardiomyopathy in patients ≤ 18 years; and (2) to promote the development of etiology-specific treatments [54]. A large database of sociodemographic and clinical information on children with pediatric cardiomyopathy has been established through the cooperative efforts of cardiology centers in North America, allowing precise estimates of the incidence of pediatric cardiomyopathy and a better understanding of the natural history of this disease [98,99].

5.6. Clinical practice guidelines

Practice guidelines have emerged in recent years as an important means of translating the results of clinical trials into specific recommendations for the treatment of patients [118–121]. Such guidelines describe the indications for use of medications and the optimal approach to the management of specific clinical problems. Guidelines help to limit inappropriate care, decrease the magnitude of geographic variations in practice patterns, and enhance the effective use of healthcare resources. In addition, guidelines are an invaluable tool for quality assurance and can assist in the development of coherent plans for inpatient and outpatient treatment. Advances in medicine occur so rapidly that practice guidelines may be out of date shortly after they are issued. Thus, there is a continuing need to update existing recommendations so that recent advances in therapy can be brought to the attention of physicians in a timely fashion. Currently practice guidelines cannot be developed for the pharmacologic management of pediatric patients with

chronic heart failure due to left ventricular systolic dysfunction, the use of surgical approaches or devices or the management of acute heart failure or of heart failure associated with preserved left ventricular systolic function due to the fact that there are virtually no well-controlled studies on the effect of therapy on outcomes in these patients. Practice guidelines are very popular in pediatric cardiology and are useful but potentially dangerous. Guidelines may codify and make rigid algorithmic approaches to the treatment of patients and thereby reduce or even eliminate good clinical judgement or inhibit research [10]. Guidelines can take on a power of their own and have medicolegal ramifications when not followed even if they are based on weak or no data [10]. In adult patients with myocardial infarction critical pathways in hospitals did not have increased use of proven medical therapies, shorter lengths of stay, or reductions in mortality compared with other hospitals that commonly used alternative approaches to quality improvement [122]. A recent survey of general pediatricians found that most use practice guidelines, but no specific guidelines, except those for asthma, are used by $> 27\%$ of pediatricians [118]. The results of this survey suggested that practice guidelines are most likely to be followed if they are simple (practical and feasible), flexible to allow for clinical judgement, rigorously tested and shown to improve outcome, not used punitively, and are motivated by desires to improve quality, not reduce costs.

Guidelines are not performance measures. Guidelines are written to suggest diagnostic or therapeutic interventions for most patients in most circumstances. Performance measures are standards of care that imply that physicians are in error if they do not care for patients according to these standards. Performance measures define how to practically identify those patients for whom a specific action should be taken.

For adult patients with heart failure four structural measures were recommended as quality indicators [123]. These include: (1) clear, evidence-based guidelines for the care of patients with heart failure; (2) a mechanism to systematically monitor patient care and outcomes; (3) providers should recognize that many require different levels of care and there must be an organizational structure to move patients to the appropriate level of care; and (4) patients would benefit by having specific programs to address the end-of-life needs of many patients with heart failure.

Four process measures were also recommended as quality measures for adult patients with congestive heart failure [123] including: (1) the medical record should document left ventricular systolic function; (2) patients with heart failure, LV systolic dysfunction, and no contraindications to ACE inhibitors should be prescribed ACE inhibitors; (3) patients hospitalized with heart failure and LV systolic dysfunction should be treated with digoxin; and (4) patients with NYHA class II and III heart failure, LV systolic dysfunction, and no contraindication to beta-blockers should be prescribed beta-blockers. Similar measures cannot be developed for pediatric heart failure at this time due to lack of data.

6. Summary

Heart-muscle disease is an area of pediatric cardiology where we are often unable to help patients with either knowledge or action. These are rare patients, the number of institutions studying them well is small, and among those studied, the great majority have non-specific findings. Thus, to make progress, there is a need to pool case-study information among institutions. Data sharing makes it possible for all users to profit quickly from knowledge, experience, insights, and hypotheses that may be gained from material from other institutions, even though it may be too scanty, unproved, or speculative for publication.

At this point, a multidisciplinary approach is needed to study longitudinally the variety of pathogenic mechanisms in pediatric cardiomyopathy, as well as diagnostic, therapeutic, and preventive approaches. Given that this group of diseases is relatively rare, with a variety of suggested etiologies and new possibilities for diagnosis and treatment, we have felt that the best way to change the past piecemeal approach to a more constructive one is by a cooperative effort. It is for this reason that we helped established a national registry for pediatric cardiomyopathy [54].

The available literature on pediatric cardiomyopathy lacks good data on incidence and prevalence, survival, and prognostic factors, largely because of variable selection criteria and case definitions, small numbers, inclusion or exclusion of myocarditis, whether clinically asymptomatic cases are included, and the methods used. These inconsistencies mean that little of the natural history (especially survival and prognosis) is really known. The collection of large numbers of cases in the registry can help identify specific rare defects. The Pediatric Cardiomyopathy Registry provides a clearer understanding of the relationship between myocarditis and DCM and may help determine whether cases of cardiomyopathy in adults may have originated as myocarditis in childhood. The Pediatric Cardiomyopathy Registry has the potential of making a large impact on establishing various etiologies of pediatric cardiomyopathy. Molecular biology has brought new understanding of HCM; similar advances should be forthcoming for other types of cardiomyopathy. Eventually, molecular insight into

the multiple causes of cardiomyopathy will facilitate the diagnosis of these conditions. In the absence of molecular biological testing, there is likely to be serious underestimating of the impact of cardiomyopathy. Distinguishing between some of the types of cardiomyopathy and other cardiac problems is a major diagnostic challenge. Because the human body is almost always host to viral infections, it is likely that subclinical viral cardiovascular involvement is common and not limited to histologically documented myocarditis associated with congestive heart failure. As most past research concentrates on symptomatic myocarditis, the best characterized type of viral heart disease, we are left with the frustration that our level of understanding of this field is still quite limited.

The literature illustrates how poor our existing knowledge is of the clinical epidemiology of viral heart involvement. One can only settle for clinically overt heart disease. Viral heart involvement is often incorrectly captured, owing to difficulties in definition and diagnosis, precluding a good understanding of the spectrum and course of viral heart disease. Classic histologic, serologic, and culture techniques for defining viral heart disease have problems with sensitivity, specificity, and positive and negative predictive values. The histologic diagnosis of myocarditis also has many pitfalls. The limited availability of premorbid tissue for diagnostic purposes further hampers our understanding. Unfortunately, newer techniques such as in situ hybridization and PCR may also have problems with sensitivity and specificity [124]. At this time, the isolated finding of a positive PCR for a specific viral probe may not reliably indicate active viral cardiac involvement. In the absence of an understanding as to what constitutes viral cardiac involvement, it is impossible to understand the clinical epidemiology of viral heart involvement and the response to therapy. Thus, whether a continuum exists from viral myocarditis to DCM remains unanswerable. More than 90% of HIV-infected children have echocardiographic abnormalities, yet chronic congestive heart failure occurs in 10%, transient congestive heart failure in another 10%, and cardiac arrest or sudden death in 10% [4,8]. One-third of HIV-infected children who have died did so in the setting of severe ventricular dysfunction [8]. Therefore, just relying on symptomatic heart disease to capture cardiomyopathy underestimates the impact of this problem. The registry provides the opportunity to capture asymptomatic cardiomyopathy [54].

This registry should help establish the usefulness of endomyocardial biopsy in diagnosing pediatric cardiomyopathy and in determining the course and prognosis of the various types of pediatric cardiomyopathy. It should also allow assessment of newer, less invasive diagnostic imaging techniques to determine whether the diagnosis of specific types of cardiomyopathy can be made without the need for biopsy. The registry should facilitate treatment trials of immunosuppression and immunomodulation for cardiomyopathy, as well as other therapies. The registry could identify cases for inclusion in trials.

The proposed Pediatric Heart Disease Clinical Research Network [107] is a very exciting development in this field that offers a tremendous opportunity to rigorously investigate important clinical questions in pediatric cardiology at a limited number of centers. Hopefully, some of the clinical studies of this network will focus on issues related to pediatric ventricular dysfunction. Future planning should focus on expanding this network to more completely allow the participation of more pediatric cardiology providers in the US. The tremendous successes in pediatric oncology and pediatric HIV are benchmarks that such efforts are invaluable in improving outcomes for affected children and their families.

The articles in these two issues of *Progress in Pediatric Cardiology* on pediatric heart failure demonstrate how much has been learned to allow us to conclude that the pathophysiology, pharmacology, etiologies, and clinical course of pediatric heart failure differs from adults with heart failure in many ways. The pediatric literature reviewed in these issues has been largely observational studies that support the next steps to embark on multicenter controlled clinical trials, natural history studies, and translational studies to advance this field further.

It is extremely difficult to accept children failing medical management for ventricular dysfunction in the year 2000 and to be able to say to their families that we have done everything possible when, in fact, there have been virtually no controlled clinical trials that have been performed in this area. For the good of our patients, for our personal integrity, and for the future of our subspeciality, the time for active multicenter clinical research in pediatric ventricular dysfunction is now.

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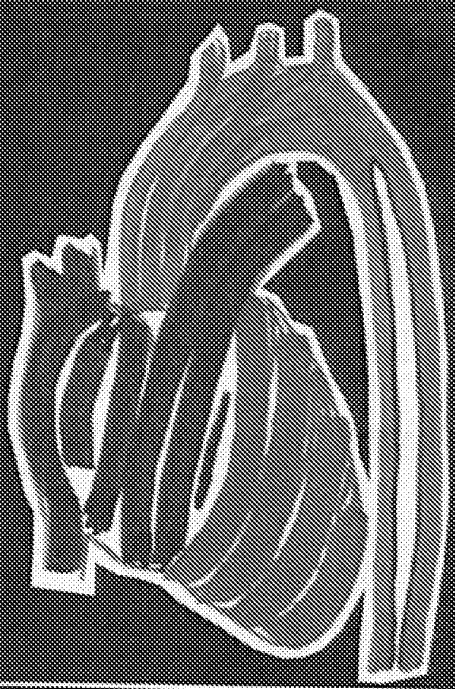
CLINICAL APPLICATION OF THE INTRA-AORTIC BALLOON PUMP



Third Revised Edition

By

Hooshang Bolooki, MD, FRCS(C)

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loids. Colloids include blood transfusion, plasma, and plasmanate®. Output volume includes gastric drainage, urinary output, amount or number of times of bowel movements, and any evidence of excessive insensible loss (sweating, hyperventilation, etc.).

9) Laboratory studies are done on a daily basis or as ordered. Blood gas analysis and serum potassium levels are measured more frequently.

Prolonged Intra-Aortic Balloon Pump for Chronic Left Ventricular Dysfunction

In these patients, nursing care is somewhat different because of the slow process of recovery. Here, attention is directed mainly to improving the patient's cardiac function through various therapeutic interventions and to preventing major complications such as leg ischemia and balloon rupture. Working toward these goals, it becomes clear that care of the monitoring lines is the prime function of the nurse who also ensures accurate measurement of hemodynamic data. These patients are cared for in an ICU for days or weeks.

After 7 to 10 days when patients are stable, but still are balloon dependent and are awaiting implantation of a cardiac assist device or heart transplantation, radial artery pressure monitoring by pressure cuff may be sufficient. At this stage, they may have a peripheral intravenous line. These patients may ambulate around their bed with the nurse's assistance if there is sufficient improvement of cardiac function in conjunction with IABP assist.

Intra-Aortic Balloon Pump for Reversal of Acute Coronary Ischemia

In these patients, intra-aortic balloon pumping frequently is done for one or a combination of the following indications:

1) To decrease the episodes of angina pectoris that are unresponsive to nitroglycerin infusion.

2) To suppress and control malignant ventricular arrhythmias that are unresponsive to drug therapy.

3) To improve and reverse the acute LV dysfunction due to oxygen supply/demand imbalance.

The main purpose is to *reduce myocardial oxygen consumption and to redistribute the coronary blood flow*. Here, hemodynamic monitoring is of academic interest. The nurse should observe the balloon augmentation curves and record the number and severity of episodes of angina, as well as their duration and response to therapy. The type and frequency of ventricular arrhythmia are also recorded. Since the conditions may alleviate quickly with IABP, psychologic support becomes an important task for the nurse. In contrast to patients who are in chronic LV failure, patients with acute ischemia are awake and alert and are very inquisitive of their condition and prognosis. They are psychologically depressed because of chest discomfort or ventricular arrhythmia which interrupts their rest and may occur unheralded. Frequent discussion with the patient and the family plays an important role. These patients should be sedated more frequently than patients in chronic congestive heart failure where sedation is rarely needed and at times contraindicated.

In these situations, measurement of pulmonary artery pressure and cardiac output should be done at the start of each nursing shift. Once cardiovascular stability is achieved, IABP should be discontinued. The average assist time in these patients is less than 3 days. Pharmacologic therapy includes drugs that increase myocardial oxygen

supply by coronary vasodilatation (calcium channel blockers and nitroglycerin) and drugs that decrease myocardial oxygen consumption (propranolol, ACE inhibitors, and nitroprusside). Since most patients are fully alert and may not be respirator dependent, they generally require less exhaustive nursing care. Nursing care of patients with preinfarction or postinfarction angina in whom LV function is minimally depressed, becomes difficult if distal leg ischemia develops. Ischemic leg pain requires frequent administration of strong sedatives and prompt surgical intervention. A change in the balloon catheter to the opposite leg or a decision to discontinue balloon pumping or to proceed with cardiac surgery may be required. The period of balloon pumping in these patients frequently is short and a decision toward cardiac catheterization and surgical intervention is reached quickly.

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Inhaled nitric oxide therapy in neonates and children: reaching a European consensus

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Abstract Inhaled nitric oxide (iNO) was first used in neonatal practice in 1992 and has subsequently been used extensively in the management of neonates and children with cardiorespiratory failure. This paper assesses evidence for the use of iNO in this population as presented to a consensus meeting jointly organised by the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology. Consensus Guidelines on the Use of iNO in Neonates and Children were produced following discussion of the evidence at the consensus meeting.

Keywords Inhaled nitric oxide · Pulmonary hypertension · Persistent pulmonary hypertension of the newborn · Extracorporeal membrane oxygenation · Vasodilator · Pulmonary

Introduction

Inhaled nitric oxide (iNO) has been used in Europe to treat a variety of conditions in neonates and children since 1992, foremost in persistent pulmonary hypertension of the newborn (PPHN), which has remained a major therapeutic challenge in the NICU [1, 2]. Introduction of iNO into clinical use was virtually unregulated in Europe, where supplies of industrially produced gas were freely available. Subsequently clinical trials have established roles for iNO therapy in the treatment of term neonates with severe respiratory failure and a pharmaceutical quality product has recently become available in Europe and the United States. The high cost of the licensed product, compared to previous industrial supplies, and the narrow scope of the drug's licensed indications suggested to our group that a consensus should be established on the use of iNO therapy in neonates and children covering both its approved and potential indications.

Methods

An Advisory Board was established under the auspices of the European Society of Neonatal and Paediatric Intensive Care to co-ordinate the scientific programme of the meeting. The board consisted of experts with proven scientific or clinical expertise relevant to the clinical use of iNO. The board identified a further panel of experts who were invited to act as section leaders whose role was to review the literature in their designated subject area. Section leaders were asked to produce written summaries of their subject area, which were then circulated to delegates prior to the meeting and which formed the basis of the evidence presented to delegates at the consensus meeting itself.

A further panel of opinion leaders were invited to attend the meeting on the basis of their known interest in the use of iNO or their status as opinion leaders in the field of neonatal and paediatric intensive care. The European Society of Paediatric Research and the European Society of Neonatology were officially represented at the meeting. At the consensus meeting each subject area was presented in summary by the section leader(s), following which open discussion led to the composition of draft consensus statements. These were then edited and re-presented to delegates with further discussion leading to final agreement on the individual consensus statements.

Results

Inhaled nitric oxide in term and near-term neonates

Neonatal hypoxaemia may result from *intra-pulmonary shunting*, from *extra-pulmonary shunting* (so-called PPHN) or from cyanotic congenital heart disease. The presence of interstitial pulmonary infiltrates or a low volume lung (<6–7 ribs) on chest X-ray strongly suggests parenchymal lung disease. Alveolar recruitment has been shown to render babies with severe hypoxaemic respiratory failure responsive to iNO, when they were previously unresponsive [2]. Exogenous surfactant and ventilatory manoeuvres [3] should therefore be deployed to optimise lung volume before iNO is introduced. If cyanosis persists after any necessary lung recruitment manoeuvres have been applied, an echocardiogram should be obtained to confirm or exclude the presence of congenital heart disease or pulmonary hypertension as causes of cyanosis. Inhaled NO is most likely to benefit babies with PPHN with recruited lung volume and is unlikely to benefit babies with cyanotic heart disease.

The recent Cochrane Review was used as a framework in this discussion [4]. The review, last updated in December 2000, included 12 relevant trials in its analysis, all of which used random allocation [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. One further on-going study received limited analysis since, at the time of review, it was on-going and published only as an abstract [16]. A literature search up to October 2003 failed to reveal any new randomised, controlled trials not already included in the Cochrane review.

The limitations of the studies presented within the Cochrane review were highlighted. Of major importance, the entry criteria differed markedly between trials as did dosage and ventilatory strategies, there being a suggestion that high frequency oscillatory ventilation (HFOV) appears beneficial in achieving a response to iNO [10]. Eight of the 12 clinical trials studied the effect of iNO on the overall clinical course of the babies included and, in particular, whether the need for extracorporeal membrane oxygenation (ECMO) was reduced. Only six trials did not allow crossover [6, 7, 8, 11, 12, 13]. Of the six studies which did not allow crossover, three [6, 11, 12] found a statistically significant reduction in the combined outcome of death or requirement for ECMO in the NO group. A meta-analysis of all six studies found that iNO treatment resulted in a reduction in the incidence of death or requirement for ECMO (relative risk 0.65) [4].

Inhaled nitric oxide therefore appears to improve outcome in hypoxaemic term and near-term infants. The improvement is due mainly to a reduction in the need for ECMO, since mortality was not reduced. The two largest studies [6, 11] included infants with congenital diaphragmatic hernia as sub-groups. A separate analysis has been presented from one of these studies [17]. There was no evidence that outcome was improved in these babies through the use of iNO, even if short-term improvements in oxygenation did occur. It is important to note that whilst iNO reduced the need for ECMO, the majority of mature babies in these studies went on to ECMO.

Only one study has considered long-term follow-up as a primary or secondary hypothesis. In this study, the incidence of disability, the incidence of deafness and infant development scores were all similar between tested survivors who received NO and those who did not [18].

The major randomised, controlled trials of iNO in term or near-term babies have used echocardiography to

exclude congenital heart disease as a cause of hypoxaemia prior to exposure to iNO. Babies with such lesions are at best unlikely to benefit from iNO, as cyanosis is due to extra-pulmonary shunting. Inhaled NO exposure may even be harmful in some babies with congenital heart disease, such as those with obstructed total anomalous pulmonary venous drainage or severe left ventricular dysfunction with right-to-left ductal shunting [19], in whom pulmonary arteriolar vasoconstriction may be clinically beneficial by reducing left heart filling.

Dosage and response to inhaled nitric oxide treatment in term and near-term neonates

Decisions regarding continued use of iNO therapy cannot be based on the primary end points used in the pivotal studies, such as reduced mortality or 'avoidance' of ECMO. Instead clinicians must use surrogate physiological end points in order to establish whether an initial test exposure to iNO is effective. Improvement in oxygenation of approximately 20% over baseline values at 30–60 min has been used in many studies as an indicator of early response to iNO including six of the studies in the Cochrane review [5, 6, 7, 9, 11, 12].

Four published studies have reported dose-response data for this group of babies [7, 20, 21, 22]. All four studies suggest that a maximal beneficial effect of iNO is already seen at concentrations of less than 30 ppm. Further increases of iNO (to 80–100 ppm) do not appear to result in further improvement of oxygenation above that achieved at 20–30 ppm. The large NINOS study [11] used initial doses of 20 ppm iNO, but exposed 'partial responders' to 80 ppm. Only 6% of these partial responders were converted to full response by 80 ppm iNO.

In the small study published by Tworetzky et al. a maximum reduction of pulmonary artery pressure was observed at 20 ppm NO, whereas maximal improvement in oxygenation occurred at 5 ppm [23]. Response to the introduction of iNO usually occurs rapidly in 'responders'. Some investigators attribute clinical improvements seen several hours later to iNO administration [24]. However it was the expert group's view that there is a serious danger that babies with very severe hypoxaemia could be harmed if ECMO referral were to be delayed whilst waiting for a 'late' response.

If no substantial effect has been achieved during a trial of iNO, treatment with iNO should be rapidly discontinued or the baby transferred on iNO to a level 3 or tertiary neonatal unit. This should occur as soon as the clinician is convinced that iNO is not inducing a beneficial effect judged by improving oxygenation. The trial to improve oxygenation with NO should not last longer than 4 h. The reason not to prolong NO therapy unnecessarily is that NO synthase is down-regulated, with suppression of endogenous NO production. Down-regulation of endogenous NO synthase by the use of iNO has been suggested [25, 26, 27].

We were unable to identify studies establishing the optimal regime for maintenance of iNO therapy once an initial response has been established. It is, however, logical in clinical practice to seek to minimise iNO exposure by lowering the iNO dose, provided the beneficial effects on oxygenation and general clinical stability are maintained. This approach was described by Kinsella et al. [28] in the early stages of the clinical exploration of iNO therapy and further validated by Clark et al. [6].

Discontinuation and weaning

Some information is available on strategies for weaning patients from iNO as clinical improvement occurs. In a prospective study, Demirakca et al. evaluated the clinical response to iNO in neonates and children with acute respiratory distress syndrome (ARDS) [21]. Attempts to discontinue iNO were made as soon as a stable respiratory status (PEEP<6 cmH_2O, inspiration/expiration ratio of 1:2, FiO_2 <0.8 and an iNO concentration of 5 ppm) had been achieved. Oxygenation index (OI) values of less than 5 predicted successful withdrawal with a sensitivity of 75%, a specificity of 89%, a positive predicted value of 69% and a negative predictive value of 91% [21].

Aly et al. [29] adopted a weaning strategy for babies with PPHN which included step-wise 5 ppm decrements of iNO doses. Discontinuation of iNO was performed as soon as the patient was stable with an FiO_2 less than 0.5. Weaning was successful at the first attempt in 9 out of 16 patients. In the remaining seven neonates, major signs of deterioration (oxygen saturation drop >10% or below 85%) prompted a reinstitution of iNO treatment for 30 min. Subsequently, FiO_2 was raised by 0.4 and a successful withdrawal of iNO was then obtained. Interestingly, FiO_2 could be returned to the pre-weaning value in a few hours. Sokol et al. [30] noted that significant deterioration of PaO_2 occurred in some babies even when weaned from 1 to 0 ppm, suggesting that iNO is physiologically active even at very low concentrations. There may be a role for other vasodilators such as epoprostenol, iloprost, endothelin antagonists or selective phosphodiesterase inhibitors [31] when weaning babies from iNO after treatment courses of sufficient duration to down-regulate NO synthase.

Toxicity

Nitric oxide reacts with oxygen to form nitrogen dioxide (NO_2) where the reaction rate is proportional to the square of the NO concentration and directly proportional to the

oxygen concentration. Whilst NO itself is a relatively reactive molecule, NO_2 is demonstrably more reactive and toxic and is a radical (it has an unpaired electron). Due to the fact that NO is usually administered in combination with high inhaled oxygen concentrations and that NO_2 in animal experiments is damaging to the lungs already at low concentrations when administered with other oxidants, the main toxicological concern should be focused on NO_2 exposure and this should be kept to a minimum. In long-term exposure lung damage may occur at 0.5 ppm NO_2 and acute lethal effects are seen from 100 ppm. Human subjects inhaling 2–3 ppm NO_2 for 5 h demonstrated reductions in antioxidant defences and an increase in alveolar permeability [32]. Reactive species such as peroxynitrite formed from NO_2, as well as being implicated in short-term toxicity, have the potential to cause damage to DNA, raising the possibility of mutagenic or carcinogenic effects. However, the concentrations of iNO and NO_2 to which patients are exposed clinically are largely within the permitted limits for occupational exposure [33]. There is as yet no evidence that inhalation of NO has any lasting adverse effects. Long-term follow-up of children exposed to iNO therapy will be required to establish any late adverse effect.

When NO reacts with haemoglobin, methaemoglobin (metHb) is formed. MetHb is not directly toxic, but is unable to carry oxygen. If metHb is allowed to accumulate it can significantly reduce the oxygen-carrying capacity of blood. The monitoring and management of metHb during clinical iNO therapy is discussed below.

Inhalation of NO has been shown by some investigators [34], but not by others [35], to inhibit platelet function. The randomised controlled neonatal trials have, however, not shown any difference in bleeding complications between groups administered iNO or control gas [4].

Delivery and monitoring

Nitric oxide administration systems should deliver constant concentrations of iNO within the respiratory gas mixture independent of ventilator mode or settings, ensure a rapid mixing and minimise contact time between NO and oxygen, thereby reducing the possibility of generating high NO_2 levels [36, 37, 38]. The delivery system should display the pressure within the NO cylinder to permit timely cylinder changes to be undertaken without loss of gas supply. The system should ideally encompass a backup power supply for use in the event of mains failure or during intra-hospital transport. A manual backup or 'hand bagging' facility must be provided for use in the event of ventilator failure or other indications for hand ventilation, as sudden discontinuation of iNO therapy can be life-threatening [36, 37, 39].

The safest approach to iNO delivery is probably to use only pharmaceutical grade NO stored in cylinders and at concentrations and conditions approved by drug regulatory bodies and delivered by devices tested and approved according to the appropriate medical device legislation.

In the clinical setting, measurement of iNO and NO_2 concentrations can be undertaken using chemiluminescence or electrochemical devices. There are a number of practical disadvantages of chemiluminescence analysers in the clinical setting, including their high cost, their need for relatively high sample volumes, noise, their need for regular calibration and their relative inaccuracy in measuring NO_2 due to the "quenching" effect [37]. Electrochemical analysers use two separate fuel cell sensors for NO and for NO_2, placed either in the gas mainstream or side stream of the ventilatory circuit. Electrochemical devices do not underestimate NO_2 levels, are inexpensive, silent, easy to calibrate and require very low gas sample volumes. Most devices are portable. Electrochemical analysers are, however, relatively insensitive (resolution 0.5 ppm) and their measurements may be affected by temperature, pressure, humidity and the presence of other gases in the environment [37]. Although many early studies of iNO delivery systems were constructed by investigators for their own studies, a number of delivery and monitoring systems have been developed for clinical use and are commercially available [39, 40].

Inhaled NO_2 concentrations should be kept to a minimum. Clinical and experimental evidence show that it is possible to administer 20 ppm iNO whilst generating NO_2 concentrations of less than 0.2 ppm [38]. Direct comparisons with tolerable environmental NO_2 concentrations should take into account that the awake person inhaling NO_2 is exposed to at least 50% lower NO_2 concentrations in their trachea due to efficient scavenging of NO_2 in the upper airways.

Nitric oxide has been supplied for clinical use by a number of suppliers as a compressed gas diluted in a balance of nitrogen with final NO concentrations of between 100 and 1000 ppm. The gas is supplied in aluminium cylinders filled to pressures of 150–200 bar. Very concentrated preparations may be difficult to deliver accurately whilst mixtures with low NO concentrations can reduce FiO_2 excessively [41]. The final choice of cylinder NO concentration will, therefore, depend on the characteristics of the delivery system in use and the required FiO_2 and FiNO. The future availability of iNO as a pharmaceutical within Europe may encourage standardisation.

Environmental safety

The US National Institute for Occupational Safety and Health (NIOH) suggest a "Permitted Exposure Limit" for

NO_2 of 5 ppm and NO 25 ppm over an 8-h period for these potentially toxic substances [33]. Several European countries have regulated maximal occupational exposure to 2 ppm NO_2. Extrapolating this to the ICU in which iNO would be administered for a 24-h period, it would be prudent to aim for environmental levels of NO_2 in the ICU below 1.5 ppm. Environmental NO contamination can occur from two sources during iNO administration: dumped waste ventilator gas and accidental leakage of concentrated gas from a delivery system or cylinder. The US Food and Drug Administration state, in their specification for medical delivery of NO, that such delivery "does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required" [42]. A similar ruling is applied by the UK National Health Service, which states that scavenging of waste NO is unnecessary provided that ventilation in the ICU meets required standards [43]. Several studies confirm that this advice is sound [44, 45]. There must, however, be a small risk of high environmental levels occurring from uncontrolled release of a large volume of concentrated gas from a cylinder in the event of a serious error or accident. For this reason, the consensus group suggest that it is reasonable to measure environmental levels of NO_2 continuously.

Transport

In 30–50% of babies given a trial of iNO the therapy does not result in a sustained positive oxygenation response [4]. Most babies who fail to respond to iNO are potential ECMO candidates. Since acute withdrawal of iNO may be associated with severe rebound hypoxaemia, even in babies who apparently respond poorly [46, 47], arrangements must be in place for these babies to be transferred to an ECMO centre without interruption of iNO delivery. Occasionally non-neonates may require transport within or between hospital whilst receiving iNO.

Apart from the ability to deliver iNO safely to the baby during transport, consideration must also be given to safety of the staff and crew within the transport vehicle, and compliance with any regulations governing such use. Kinsella et al. recently reported concentrations of NO and NO_2 in the cabin environment of various transport vehicles during iNO use and confirmed them to be negligible. Furthermore, they calculated the effects of uncontrolled release of a full US D-type NO cylinder containing 350 l NO gas. In this " worst case scenario" environmental NO levels were unlikely to reach dangerous levels (maximum 40 ppm fixed wing aircraft, 34 ppm ground ambulance, 94 ppm small helicopter) [48].

The expert group recommend that equipment for delivery and monitoring of iNO during transport should comply with standards for medical devices and the safety and test requirements of the specific aircraft or other transport vehicle used. Several delivery systems have been used during transport and at least two portable systems are commercially available, one of which is specifically designed as a transport system [48].

Staff training

Clinical use of iNO involves potential hazards for both staff and patients, mainly from the risk of exposure to toxic levels of NO and NO_2, but also issues such as safe handling of gas cylinders. The safe and appropriate use of medical equipment requires adequate preparation and training. Regulatory authorities frequently recommend standards for training in the use of medical equipment, typically stating that training should include both theoretical and practical instruction [49]. US guidelines for neonatal use recommend physician training [50] and some nursing authors have discussed the need for training [51]. It has also been recommended that protocols or guidelines should be compiled by hospitals using iNO, covering all aspects of its use including responsibility for off-label prescription. Such protocols should aim to help staff deliver iNO therapy that is both safe and effective [52].

Use of inhaled nitric oxide in preterm neonates

For the purposes of this paper, 'preterm' neonates are defined as those babies too premature to be considered for ECMO should their condition require it, i.e. babies less than 34 weeks completed gestation [53].

Inhaled NO may improve oxygenation in preterm neonates with hypoxaemic respiratory failure in one of two ways: (1) it may reverse extra-pulmonary shunting by selectively decreasing pulmonary vascular resistance (PVR) and (2) it may reduce intra-pulmonary shunting (and/or V/Q mismatch) by redistributing pulmonary blood flow. The former mechanism is likely to be the most important in infants with primary or secondary PPHN, whereas the latter will be more important in the majority of preterm infants who have parenchymal lung disease as the primary cause of their hypoxaemic respiratory failure.

There are three published, randomised, controlled trials (RCTs) of iNO therapy in preterm infants [14, 54, 55], overviews of which have been reported in the form of two systematic reviews [53, 56]. A total of 207 infants have been studied in these RCTs. Other RCTs (such as the UK INNOVO trial, NICHD Preemie iNO trial and other US trials) are either on-going or have only just completed recruiting and results are not yet available. One small RCT has reported the long-term neurodevelopmental outcome following iNO therapy [57].

A Cochrane Review has summarised the results of the three RCTs in preterm infants [53]. The study of Kinsella

et al. [55] is the single most useful trial in that it recruited neonates with hypoxaemic respiratory failure early in the course of their respiratory disease, the intervention was masked, an important primary outcome (mortality) was chosen, there was no crossover treatment with iNO and infants were carefully evaluated for intraventricular haemorrhage (IVH). There is no evidence of an effect of iNO on mortality or chronic lung disease (CLD) at 36 weeks, or on survival without CLD in preterm infants with hypoxaemic respiratory failure. Doses of between 5–20 ppm iNO appear to be effective in improving arterial oxygenation within the first 2 h of treatment. One study showed a reduction in days of ventilation with 5 ppm iNO in survivors [55] whilst another study reported no difference [14].

Sufficient data are lacking for evaluation of the possible effects of iNO on periventricular haemorrhage or on long-term neurodevelopmental outcome. Thus, with the data currently available, the consensus group do not recommend the routine use of iNO in the preterm infant and strongly recommend its use in this indication only within controlled clinical trials. The use of iNO could, however, be justified as rescue therapy in life-threatening hypoxaemia after lung recruitment has been optimised.

Use of inhaled nitric oxide in paediatric acute lung injury and acute respiratory distress syndrome

Acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) may result from many systemic disease processes, and affects people of all ages. No drug therapy has been found to impact substantially on survival in ALI cases. Inhaled NO has been used in this setting principally because of its effect in improving oxygenation as therapy commences, due to improved ventilation-perfusion matching.

The comments in this section are aimed at guiding the clinical use of iNO in paediatric practice. Recommendations on ALI and ARDS had to be formed on a very limited base of information as, apart from case series and anecdotes about children, almost all data on such clinical use of iNO were only available for adult patient populations. Five randomised controlled trials were evaluated (Dellinger [58], Dobyns [59], Lundin [60], Troncy [61], Michael [62]) in a recent Cochrane review [63] assessing 535 patients, with only one trial focused on children [59]. Inhaled NO had no impact on mortality in trials without crossover (relative risk 0.98, 95% confidence intervals 0.66, 1.44) or with crossover of treatment failures to open-label iNO (RR 1.22, 95% CI 0.65, 2.29). Evidence published in one study demonstrated that iNO resulted in a transient improvement in oxygenation in the first 24 h of treatment: the oxygenation index (OI) showed a mean difference of −3 (95% CI −5.354, −0.646), and PaO_2/FiO_2 ratio and a mean difference of 35 (95% CI 20.236–49.764) [58]. Other clinical indicators of effectiveness, such as duration of hospital and intensive care stay, were inconsistently reported. There were no complications reported to be directly attributable to this treatment.

Based on these data, it appears that iNO has no effect on mortality and only transiently improves oxygenation in ALI/ARDS. There is insufficient data to assess other end points. The authors of the Cochrane review suggest that any further trials of iNO in this indication must stratify for underlying disease, since outcome is thought to be more related to this than to respiratory failure alone.

Use of inhaled nitric oxide in children with cardiac disease

Pulmonary hypertension is an important problem in many children with acquired or congenital heart disease. As a selective pulmonary vasodilator, as in neonatal PPHN, iNO has the potential to improve the management of these patients. Numerous reports of iNO usage in such patients have been published including its use in the assessment of the reversibility of pulmonary hypertension as a diagnostic procedure [64, 65] and in the perioperative management of pulmonary hypertension or RV afterload reduction [66, 67, 68]. Inhaled NO has also been shown to complement standard methods of differentiating reactive from fixed pulmonary vascular disease [64, 65].

Inhaled NO has been shown to be effective in the management of some patients with severe reactive pulmonary hypertensive episodes following cardiac surgery [69, 70]. In these patients, iNO is believed to replace endogenous NO production, which is temporarily impaired due to the effects of cardiopulmonary bypass on the pulmonary endothelium. One randomised, controlled trial [71] reported that the prophylactic administration of 10 ppm iNO was associated with a significant reduction in pulmonary hypertensive events and a reduction in time to meeting extubation criteria. Mortality and length of ICU stay were, however, unaffected. Another similar, but smaller, study failed to demonstrate any benefit from prophylactic iNO [72]. The view of the consensus meeting experts was that data from other clinical trials was required before the routine prophylactic use of iNO could be recommended in children at risk of pulmonary hypertensive events after repair of congenital heart surgery. Inhaled NO has also been shown to improve the haemodynamic status in patients with elevated PVR after the Fontan operation [73] and in those with failing right ventricles [74]. There are no RCT's in this group of patients.

In summary, there are few RCTs on the use of iNO in children with cardiac disease from which to draw evidence-based conclusions. There is insufficient evidence to recommend the routine use of prophylactic

postoperative iNO in congenital heart patients at risk of pulmonary hypertension. The expert group felt that there is, however, sufficient evidence (from large case series) to support a trial of 20 ppm iNO for 10 min, increasing to 40 ppm if no response to the lower dose, in patients with clinically significant pulmonary hypertension complicating their perioperative course. In this setting it is recommended that iNO should only be continued if there is documented evidence of important haemodynamic improvement. After a 30-min trial of iNO at 20 ppm, increasing to 40 ppm, consideration should be given to discontinuing the drug if no clinically significant response has occurred.

Conclusion

These guidelines, "Use of iNO in neonates and children: consensus guidelines from the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology", (please see ESM), were compiled by a group of practitioners with knowledge of iNO therapy drawn from the majority of European states. The guidelines are designed to allow the safe use of this therapy, within both its permitted and its potential uses. It is hoped that these guidelines will encourage evidence-based practice and further clinical trials on the use of iNO therapy.

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Critical Care Medicine Department

Critical Care Services

The CCMD provides the following clinical services:

Intensive Care Unit (ICU)

The Intensive Care Unit (ICU) at the NIH is located on the third floor of the Mark O. Hatfield NIH Clinical Center. This is a 12-bed Medical/Surgical ICU with an adjoining 6-bed intermediate care unit. The unit can provide hemodynamic monitoring, diagnostic ultrasound, ventilatory, renal replacement, and cardiovascular support. In addition, all medical patients and some surgical patients with predominantly medical problems are cared for by Critical Care Medicine Department (CCMD) senior physicians and medical fellows. The ICU team physicians, nurses, respiratory therapists, and a pharmacist, nutritionist, and social worker dedicated to the management of CCMD patients. The department also provides a diagnostic pulmonary service for patients with bronchoscopy and elective pulmonary artery catheterization. The CCMD accepts patients from any service within the Clinical Center. Admission of patients for CCMD care can be requested by contacting the CCMD physician on-call via the page operator or by calling (301) 451-0567.

Code Team

"Code Blue" procedures a have been established to obtain emergency medical assistance for patients, visitors, and employees. The code team serves as a mobile emergency response team, rendering lifesaving first aid, and making appropriate referrals to any needed services including outside facilities. The Critical Care Medicine Department (CCMD) fellow serves as the team leader. Other members of the code team include the surgery oncology fellow, two intensive care nurses, two respiratory therapists, and the CCMD attending physician. The team responds typically to respiratory and cardiac arrests, anaphylaxis, respiratory distress, severe seizures, and hypotensive/ syncopal episodes.

A Rapid Response Team (RRT) had been established to obtain early access to critical care consultation for any inpatient or outpatient if their condition appears to be deteriorating. This service is provided to improve recognition and response to a change in patient condition and to enhance a culture of safety for the patient. The RRT team consists of the CCMD fellow and the ICU charge nurse. The patient's physician, nurse, or respiratory therapist may call for this assistance whenever needed. Patients and families may also use the service when requested through their health care provider.

Procedures, Vascular Access, and Conscious Sedation (PVCS) Services

The Procedures, Vascular Access, and Conscious Sedation (PVCS) Services are staffed by critical care fellows and the Nursing Service and provides temporary vascular catheters to those patients requiring continuous vascular access for long periods of time.

The service places multilumen jugular, subclavian, and femoral vascular catheters as well as peripherally inserted central catheters. All catheters are placed using ultrasound guidance. This service also provides conscious sedation when necessary for procedures such as vascular access, bronchoscopy, and bone marrow biopsies. Patient care providers may call (301) 451-0336 to make an appointment for their patients to have catheters placed.

Critical Care Therapy and Respiratory Care Section (CCTRCS)

The Critical Care Therapy and Respiratory Care Section (CCTRCS) was established, with specially cross-trained respiratory therapists, to provide respiratory critical care and essential support to accomplish specific therapeutic goals. In 1999, the CCTRCS expanded its staff and clinical services to support all areas of the Clinical Center. In addition to our patient care responsibilities, the CCTRCS provides monthly Basic Cardiac Life Support recertification classes to all allied healthcare personnel and has developed a weekly lecture series to foster continued professional growth and development of our staff.

Critical Care Nursing

The critical care nurses provide care to critically ill patients and their families. The nurses provide this highly skilled care in close collaboration with the critical care physicians, critical care respiratory therapists, and other members of the multidisciplinary health care team. The scope of practice for critical care nurses encompasses patients of all ages, from infancy through adulthood, with a variety of potentially life-threatening problems. These nurses provide care for patients on protocols from any of the institutes of the NIH through complex and vigilant assessment and interventions. Although the patient population is widely variable, the nurses are particularly skilled in caring for immunosuppressed patients with life-threatening infections and/or respiratory failure and for patients requiring continuous renal replacement therapy for acute renal failure.

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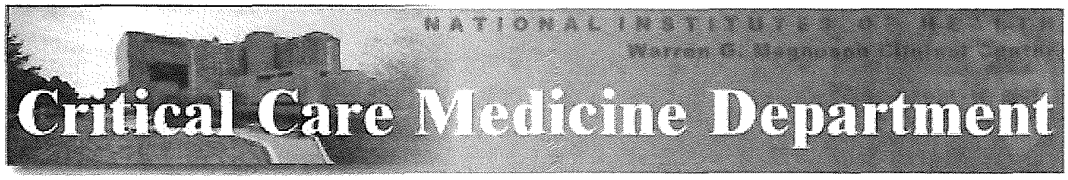

Critical Care Therapy and Respiratory Care Section

Category:	Clinical
Section:	Ventilator Management
Title:	Standard of Practice: Care of the Mechanically Ventilated Patient
Policy #:	01
Revised:	03/00

1.0 DESCRIPTION

1.1 Definition: Mechanical ventilatory support may be provided to a patient through a wide variety of mechanical, pneumatic, electronic, and microprocessor-driven devices for the purposes of life support during acute respiratory failure, therapeutic support of suboptimal cardiopulmonary function, or therapeutic support of chronic ventilatory failure. Ideally, mechanical ventilatory support should:

- Maintain alveolar ventilation to ensure adequate elimination of carbon dioxide.
- Maintain arterial oxygenation to ensure adequate delivery of oxygen to the tissues.
- Minimize the risk of adverse pressure and volume effects on the lungs (eg, baro-/volutrauma) and cardiovascular system.
- Aim for patient comfort.
- Provide appropriate reconditioning workloads as well as muscle rest during recovery.
- Specific instruction for the use of any of the devices of ventilatory support should be obtained from the Operator's Manuals for the devices. Additionally, specific indications and procedures exist for some devices (see the corresponding procedures in References), and Section policies still apply. The purpose of this Standard of Practice is to provide a *guideline* for proper care of the patient whose medical management includes the use of any of the devices of mechanical ventilatory support.

1.1 Indications

1.1.1 Hypercapnic respiratory failure resulting from:
- 1.1.1.1 Decreased respiratory drive
- 1.1.1.2 Increased dead space
- 1.1.1.3 Right-to-left shunt
- 1.1.1.4 Mechanical failure
- 1.1.1.5 Hypermetabolism with resulting increases in carbon dioxide production

1.1.2 Hypoxic respiratory failure resulting from:
- 1.1.2.1 Right-to-left shunt
- 1.1.2.2 Ventilation-perfusion mismatch

1.1.2.3 Diffusion defect
1.1.2.4 The acute respiratory distress syndrome (ARDS)

1.1.3 Refer to the operator's manual and/or procedure for device-specific indications (see References).

1.2 Contraindications:

1.2.1 Documented refusal to be mechanically ventilated as per an advance directive signed by the patient or an acceptable surrogate

1.2.2 Device-specific contraindications may exist. Refer to the operator's manual and/or procedure

1.3 Potential Complications

1.3.1 Pulmonary barotrauma

1.3.2 Ventilator-associated pneumonia

1.3.3 Cardiovascular compromise

1.3.4 Increased intracranial pressure

1.3.5 Device-specific complications may exist. Refer to the operator's manual and/or procedure.

1.4 Precautions

1.4.1 Mechanical ventilatory devices are highly sophisticated requiring understanding of the technical components of their design, the pathophysiology of the respiratory system, and the patient-ventilator interaction. Personnel who are primarily responsible for implementing mechanical ventilation or associated changes to the parameters of mechanical ventilation must demonstrate competence in:
1.4.1.1 The technical setup and operation of the device
1.4.1.2 Cardiopulmonary physiology and pathophysiology
1.4.1.3 Interpretation of the results of arterial blood gas analysis
1.4.1.4 Assessment of the need for mechanical ventilatory support, therapeutic response, and adverse reactions
1.4.1.5 The ability to respond appropriately to adverse reactions as well as to make recommendations to improve the ventilator plan of care
1.4.1.6 Appropriate application of universal precautions

1.4.2 Mechanical ventilatory devices should not be adapted for uses other than those intended by the manufacturer.

1.4.3 Any device which fails to perform according to the manufacturer's specifications should not be used for patient care. Refer all equipment failures and malfunctions to appropriate service personnel.

1.5 Adverse Reactions and Interventions

1.5.1 If mechanical ventilation results in life-threatening cardiopulmonary compromise, or the mechanically ventilated patient exhibits life-threatening physical signs, appropriate life support measures must be implemented. Specifically, the caregiver must:

1.5.1.1 Ensure that the patient has an adequate airway.
1.5.1.2 Ensure that ventilation is supported via the use of a manual resuscitator.
1.5.1.3 Ensure that oxygenation is optimized.
1.5.1.4 Ensure that steps are taken to preserve cardiac function.

1.5.2 If a malfunction of the device is suspected, remove the patient from the device and ensure appropriate oxygenation and ventilation. Do not reinstitute mechanical ventilation with the device until troubleshooting maneuvers prove proper function. Secure an alternate ventilatory device when necessary.

1.5.3 Device-specific interventions may exist. Refer to the operator's manual and/or procedure.

2.0 EQUIPMENT AND SUPPLIES

2.1 Manual resuscitator and appropriate size mask

2.2 Cardiopulmonary monitor and supplies

2.3 Pulse oximeter and supplies

2.4 Suction equipment and supplies

2.5 Intubation equipment and supplies

2.6 Stethoscope

2.7 Oxygen analyzer

2.8 Pressure monitor

2.9 Volume monitor

2.10 Timepiece

2.11 Device-specific humidification system

2.12 Device-specific patient interface and circuit including a water trap system capable of closed disposal of condensation (when necessary) **NOTE: Pediatric circuit shall be utilized on pts. weighing < 20kg.**

2.13 Test lung

2.14 Continuous Ventilation Record

2.15 Universal precautions attire

2.16 Calibration equipment and preventive maintenance documentation as per the manufacturer's specifications and departmental policy

3.0 PROCEDURE

3.1 Assure device readiness for use through evidence of calibration/performance verification.

3.2 Assess appropriateness of physician's orders and set ventilatory parameters accordingly. Initial settings as well as changes to ventilatory parameters must be accompanied by physician's orders.

3.3 Ensure proper device function with a test lung.

3.4 Connect the patient to the device. Assess the patient for tolerance and the patient-ventilator system for good coordination and proper function. Set all applicable alarms including alarms for thermal regulation of the humidification system.

3.5 Perform a thorough assessment of the patient-ventilator system according to the CCTRCS Patient Assessment Policy. Document ventilator data (see 5.0. Documentation) as well as cardiopulmonary data according to CCTRCS policy on the Continuous Ventilation Record. Perform repeat patient-ventilator checks as per policy.

3.6 Monitor the patient continuously via cardiopulmonary monitor and pulse oximetry. Perform arterial pH and blood gas analysis and/or capnometry or transcutaneous monitoring as necessary and per physician order.

3.7 Make recommendations for changes to the ventilatory care plan as appropriate.

3.8 Perform suctioning and other airway care interventions as clinically indicated to ensure optimal pulmonary management of the patient.

3.9 Perform routine circuit and related equipment changes as per Section policy and whenever required to restore integrity of the circuit or when the circuit is visually soiled.

3.10 Ensure that ventilator readiness data are filed according to Section policy.

4.0 POST PROCEDURE

4.1 Refer to the operator's manual and/or procedure for specific cleaning instructions.

4.2 After appropriate disinfection and reassembly, perform a pre-use functional check according to Section policies.

5.0 DOCUMENTATION

5.1 A proper record of ventilator care should include documentation of at least the following every two hours:

5.1.1 Ventilator settings comply with physician orders

5.1.2 The ventilator is functioning properly as evidenced by a check of measured volumes, rates, pressures, and FiO2

5.1.3 Alarms are appropriately set

5.1.4 Measured inspired gas temperature

5.1.5 Transcutaneous oxygen saturation (SpO2), carbon dioxide, or end-tidal carbon dioxide values (when available)

5.1.6 The signature or initials of the person performing the patient-ventilator system check and the person's credentials are documented at the time of the check.

5.2 A proper record of ventilator care should include documentation of the following, at least every twelve hours:

5.2.1 Alarms are activated and respond appropriately

5.2.2 The patient's artificial airway is secure and positioned as previously documented

5.2.3 A manual resuscitator and appropriate size mask are available at the bedside and functional

5.2.4 Physician's orders for ventilator parameters as written are up-to-date

5.2.5 Physical assessment results are documented (see the CCTRCS Patient Assessment Policy).

5.3 A proper record of ventilator care should include documentation of the following as needed:

5.3.1 Ventilator circuitry and/or manual resuscitation equipment is changed according to policy or as needed when visibly soiled or leaky

5.3.2 Changes to the ventilatory parameters are documented at the time of change, and circled for easy identification

5.3.3 Airway care maneuvers (including suctioning) are documented when performed

5.3.4 Transport parameters, adverse events, weaning parameters, care plan information, etc. are documented as needed to ensure the most complete information on the patient and a good continuity of care.

5.4 This documentation shall be made on the patient's Continuous Ventilation Record and/or the nursing flowsheet.

5.5 See the CCTRCS Patient Assessment Policy for specific information on the communication and reporting of pertinent patient information to the oncoming shift.

6.0 REFERENCES

6.1 CCTRCS Policy "Patient Assessment, Documentation and Communication of Patient Care Information"

6.2 CCTRCS Policy "General Standards for Mechanically Ventilated Patients"

6.3 AARC Clinical Practice Guideline "Patient-Ventilator System Checks"

6.4 AARC Clinical Practice Guideline "Humidification during Mechanical Ventilation"

6.5 AARC Clinical Practice Guideline "Ventilator Circuit Changes"

6.6 AARC Clinical Practice Guideline "Transport of the Mechanically Ventilated Patient"

6.7 Servo Ventilator 900C - Operating Manual

6.8 Servo Ventilator 300 - Operating Manual

6.9 BiPAP® Ventilatory Support System Clinical Manual

6.10 CCTRCS Procedure "Use of the Respironics BiPAP® Ventilatory Support System"

6.11 Ambu TransCARE Series Ventilators Operator's Manual

6.12 CCTRCS "TransCARE I Transport Ventilator Procedure"

6.13 CCTRCS "Equipment Change Policy"

6.14 CCTRCS "Ventilator Weaning Procedure"

6.15 CCTRCS "Receiving and Implementing of Physician Orders Policy"

6.16 CCTRCS "Infant, Pediatric and Adult Ventilator Circuit Size Guidelines Policy"

6.17 CCTRCS "Servo Calibration Policy"

6.18 CCMD "Pressure Control Setting Policy"

6.19 CCMD "Pressure Support Mode Ventilation Policy"

6.20 CCMD "Ventilator Settings Change Policy"

6.21 CCTRCS "Compliance Measurements Policy"

6.22 CCMD "Physician Section Patient Transport Policy"

SIGNATURE:_____ DATE:_____
Assistant Section Chief, CCTRCS, CCMD

SIGNATURE:_____ DATE:_____
Section Chief, CCTRCS, CCMD

SIGNATURE:_____ DATE:_____
Medical Director, CCTRCS, CCMD

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Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn

David L. Wessel, Ian Adatia, Linda J. Van Marter, John E. Thompson, Janie W. Kane, Ann R. Stark and Stella Kourembanas

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Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn

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ABSTRACT. *Objective.* To determine the effect of inhaled nitric oxide (NO) on clinical outcome in newborns with persistent pulmonary hypertension (PPHN).

Design. A prospective, randomized trial of patients referred to a level 3 nursery in a single large center. Clinicians were not masked to group assignment. Crossover of patients from control to NO treatment was not permitted.

Methods. We randomized 49 mechanically ventilated newborns, transferred to our center with clinical and echocardiographic evidence of severe PPHN (arterial oxygen tension [Pao_2] <100; fractional inspired oxygen = 1) to treatment with or without NO. Patients with gestational age <34 weeks or with congenital heart disease or diaphragmatic hernia were excluded. High-frequency oscillatory ventilation was used but not allowed concomitantly with NO. Primary outcome variables were oxygenation, mortality, and use of extracorporeal membrane oxygenation (ECMO).

Results. Meconium aspiration syndrome and isolated PPHN were the most common diagnoses (32/49) and were distributed equally between groups. The median age at the time of entry into the study was similar between groups, 25 hours for control patients and 18 hours for NO patients. Median baseline oxygenation index (OI) was similar in 23 control (OI = 29) and 26 NO (OI = 30) patients. Mortality (8%), use of ECMO (33%), median days on mechanical ventilation (9 days), and duration of supplemental oxygen (13 days) were not different between treatment groups. Pao_2, oxygen saturation, and OI improved in the NO group compared with baseline and to control patients at 15 minutes. The median percent change in OI (−31%) in the NO group was significantly different from baseline and from the control group. The difference in oxygenation between treatment groups was still apparent 12 hours after baseline. Before cannulation for ECMO, oxygenation was better in the NO group compared with control patients. Among patients who were placed on ECMO, the median time from baseline to ECMO cannulation was 2.4 hours (range, 1 to 12 hours) among control patients and 3.3 hours (range, 2 to 68 hours) for those randomized to receive NO. There was a tendency to observe fewer adverse neurologic events (seizure and intracranial hemorrhage) in the NO group (4/26 vs 8/23). One child with alveolar capillary dysplasia confirmed by postmortem examination could not be weaned from 80 parts per million of NO and transiently developed methemoglobinemia (peak methemoglobin level = 17%). No other side effects were observed.

Conclusions. Although mortality and ECMO use were similar for both treatment groups using this study size and design, sustained improvement in oxygenation with NO and better oxygenation at initiation of ECMO may have important clinical benefits. We speculate that modification of treatment to include specific lung expansion strategies with NO treatment and recognition that early improvement of oxygenation may be sustained with NO may lead to reduced use of ECMO in NO treated patients compared with controls. *Pediatrics* 1997; 100(5). URL: http://www.pediatrics.org/cgi/content/full/100/5/e7; *persistent fetal circulation, extracorporeal membrane oxygenation, high-frequency oscillatory ventilation, alveolar capillary dysplasia, methemoglobin.*

ABBREVIATIONS. PPHN, persistent pulmonary hypertension of the newborn; ECMO, extracorporeal membrane oxygenation; NO, nitric oxide; ppm, parts per million; Pao_2, arterial oxygen tension; Fio_2, fractional inspired oxygen; $Paco_2$, arterial carbon dioxide tension; OI, oxygenation index; HFOV, high-frequency oscillatory ventilation.

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by increased pulmonary vascular resistance, right to left shunting of blood, and severe hypoxemia.[1–3] PPHN is frequently associated with pulmonary parenchymal abnormalities, including meconium aspiration, pneumonia, sepsis, lung hypoplasia, and dysplastic alveolar capillary structure. In some instances, there is no evidence of pulmonary parenchymal disease and the etiology is unknown. Treatment strategies, including alkalinization, hyperventilation, and use of intravenous vasodilators are aimed at lowering pulmonary vascular resistance but are associated with adverse effects and are not always successful.[4] Extracorporeal membrane oxygenation (ECMO) has improved survival for neonates with refractory hypoxemia but may be associated with hemorrhagic, neurologic, and other complications.[5–7] Although survival for PPHN has improved, better treatment would further reduce mortality rates and morbid outcomes.

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator.[8,9] Early investigations suggested that this drug improved oxygenation in patients with PPHN who were administered 6 to 80 parts per million (ppm) of NO with oxygen.[10,11] Although promising, these initial studies were small case series

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with physiologic rather than clinical outcomes and lacked a control group. Subsequent trials were informative but until recently were still limited by lack of controls, extensive treatment crossover designs, or inherent limitations of multicenter trials with varying definitions of standard clinical practice.[12–17] Although the efficacy of NO in the treatment of PPHN has been recently affirmed in multicenter randomized trials,[18,19] results of other studies may add to our understanding of this new therapy. We conducted a prospective, randomized trial of NO for treatment of PPHN among patients referred to a single large center. Our objective was to systematically introduce this investigational therapy in a randomized fashion to all patients with PPHN, allowing for an interim analysis and protocol modification, until we or others could demonstrate sustained improvement in oxygenation and superior outcome with NO.[20] Our primary hypothesis was that treatment with inhaled NO would improve oxygenation compared with controls and reduce mortality and utilization of ECMO.

METHODS

Patients

We screened all newborns with a clinical diagnosis of PPHN admitted to Children's Hospital between September 1, 1992 and September 1, 1994. Qualifying criteria for enrollment included gestational age ≥34 weeks and Pao_2 <100 mm Hg during mechanical ventilation on FIO_2 = 1 after optimization of ventilatory and pharmacologic strategies. Patients were sedated with narcotic and administered muscle relaxants, with efforts made to achieve moderate hyperventilation ($Paco_2$ = 30 to 40 mm Hg). Sodium bicarbonate was infused to correct metabolic acidosis and raise pH to 7.45 to 7.60. Systemic blood pressure was supported with colloid infusions, dopamine, and dobutamine. Intravenous vasodilators such as tolazoline or prostaglandin E1 were not used.

Echocardiographic evidence of pulmonary hypertension was required and included right to left or bidirectional shunting at the ductus arteriosus or foramen ovale. Evidence of systemic pressure in the pulmonary artery was inferred by Doppler assessment of tricuspid regurgitation or by ventricular septal position.

Patients were excluded from study if they had major anomalies including congenital heart disease or congenital diaphragmatic hernia, or if echocardiography demonstrated evidence of low pulmonary vascular resistance (eg, continuous left to right flow through a patent ductus arteriosus or isolated right ventricular dysfunction without pulmonary hypertension). Previous treatment with surfactant therapy or high-frequency oscillatory ventilation (HFOV) at the referring institution was permitted.

Patients were randomly assigned to control or NO treatment. Randomization schemes were developed using a permuted-blocks design with blocks of size 10. Primary outcome variables were oxygenation, mortality, and use of ECMO. The initial study design predicted that a reduction in ECMO utilization from 40% to 15% would require 50 patients in each treatment group to achieve 80% power. For continuous variables [oxygenation index (OI) and Pao_2], a 20% reduction would require 25 patients in each group. Additional outcomes included oxygenation before ECMO, duration of mechanical ventilation, duration of exposure to supplemental oxygen during hospitalization, and need for supplemental oxygen after discharge from the hospital. We recorded and analyzed continuous variables including oxygenation, airway pressures, heart rate, and systemic blood pressure during the 24 hours after baseline measurements were obtained. Measures of oxygenation were: Pao_2, Pao_2/FIO_2, OI (OI = $FIO_2 \times$ mean airway pressure $\times 100 \div Pao_2$), and oxygen saturation by pulse oximetry. For patients who were supported with ECMO, we recorded the last Pao_2 before preparation for ECMO and the last oxygen saturation before initiation of ECMO. The clinical course was also noted for occurrence of seizures treated with anticonvulsants or for abnormalities on head ultrasound described as intracranial hemorrhage more severe than grade 1. Head ultrasounds were obtained at the discretion of the responsible clinician and for all patients before and after initiation of ECMO.

Protocol

We obtained informed consent from the parents of all patients using a protocol approved by the Clinical Investigation Committee of Children's Hospital with an investigational new drug number assigned by the United States Food and Drug Administration. Patients were randomized either to receive NO or to continue conventional therapy. Patients randomized to receive NO had the FIO_2 reduced to 0.97. After randomization, patients were continued in the study even though the baseline Pao_2 may have exceeded 100 mm Hg. Arterial blood gases, heart rate, blood pressure, pulse oximetry, and all ventilator settings were recorded at baseline and 15 minutes later. During this interval no change in pharmacologic or mechanical support was permitted except as a resuscitative maneuver. All clinical variables were again recorded and analyzed at 1, 2, 6, 12, and 24 hours after baseline and daily thereafter until hospital discharge.

All patient care decisions were made by the clinical care team according to standard practice guidelines and were not altered by the investigators. In both the treated and control groups attempts to wean mean airway pressure and FIO_2 were made after a stable Pao_2 >60 mm Hg had been achieved. Patients assigned to the NO group received a starting dose of 80 ppm. NO was weaned according to a preset protocol which lowered the NO dose from 80 ppm to 40 ppm after 1 hour. If tolerated, this dose was continued up to 12 hours and dose reductions to 5 ppm were attempted each morning. NO was discontinued when the dose could be successfully reduced to 5 ppm for at least 12 hours while Pao_2 was sustained >60 mm Hg with an $FIO_2 \leq 0.5$.

Alternatively, NO was discontinued when a patient was cannulated for ECMO or when the attending physician chose to convert from conventional mechanical ventilation to HFOV. The protocol permitted use of NO only during conventional mechanical ventilation. HFOV was allowed before randomization, or if NO treatment was discontinued in favor of HFOV, or at any time in patients randomized to control. Concomitant treatment with HFOV and NO was not permitted because of early theoretical concerns about toxicity when NO at 80 ppm was combined with HFOV. Criteria for initiation of ECMO included an OI >40 for at least 1 hour or hemodynamic instability despite inotropic support. If a patient failed to wean from an FIO_2 of 1.0 after persistent attempts during 2 to 3 days, ECMO was then utilized even though the OI was still just below 40.

We have described our NO delivery system previously.[21,22] We used NO gas (Scott Specialty Gases, Plumsteadville, PA and Ohmeda Pharmaceutical Division, Liberty Corner, NJ) of medical grade quality which conformed to United States Food and Drug Administration standards. The source tank concentration of NO was either 2200 ppm (45 patients) or 800 ppm (4 patients, later in the study). NO, nitrogen dioxide, and inspired oxygen were continuously monitored from a sampling port on the inspiratory limb of the ventilator circuit (Thermoenvironmental Instruments, chemiluminescence model 42H, Franklin, MA). Methemoglobin levels were measured by cooximetry (Ciba model 2500) in all patients receiving NO after the first 15 minutes of exposure and then every 12 hours.

Statistical Analysis

Data are represented by median values and ranges along with mean and standard error of the mean where appropriate. After a Friedman's analysis of variance by ranks, a paired nonparametric test (Wilcoxon signed rank test) was used to compare the difference between baseline hemodynamic variables and after 15 minutes of inhaled NO and five subsequent times up to 24 hours with correction for multiple comparisons. Comparison between patients in the control and NO treatment groups was made using the Mann-Whitney test. Binary variables were compared using Fisher's exact test.

RESULTS

We enrolled 51 patients. Two patients were promptly disqualified for study because on review of the echocardiogram shortly after enrollment 1 pa-

tient was noted to have total anomalous pulmonary venous connection; the other patient had an erroneously reported entry Pao_2. Neither patient received treatment under this protocol. Among the remaining 49 patients, 23 randomized to conventional treatment and 26 were assigned to receive NO. There were 3 departures from the intended protocol. One patient in the NO group received only conventional therapy. In 2 patients who randomized to NO, the drug was administered for only 15 minutes; conventional therapy was continued for 12 and 14 hours, respectively, before initiation of ECMO in both patients. Outcomes for these 3 patients were analyzed according to the intention to treat. There were no differences between groups for age at entry, gestational age, weight, or baseline Pao_2 (Table 1).

Associated conditions including meconium aspiration syndrome, isolated PPHN, pneumonia, sepsis, and rare patients with hydrops fetalis, respiratory distress syndrome, or pulmonary hemorrhage were similar between groups (Table 2). Surfactant therapy was permitted at any stage during hospitalization. Four patients received surfactant therapy including 1 after enrollment in the study.

Overall Outcome

Four (8%) of the 49 patients died, 2 in each group. Two had alveolar capillary dysplasia identified at a postmortem examination, and a third patient had clinical features consistent with alveolar capillary dysplasia but we were unable to obtain permission to perform an autopsy of this child. One child who died with alveolar capillary dysplasia while receiving NO had an intracranial (thalamic) hemorrhage which precluded use of ECMO. A fourth patient had poor left ventricular function and a right ventricular dependent circulation with echocardiographic evidence of a small left atrium and left atrial hypertension with continuous right to left ductal flow, but continuous left to right flow across the foramen ovale. Her clinical presentation and echocardiographic assessment were consistent with PPHN. Severe pulmonary hypertensive changes were identified microscopically during the autopsy. NO was administered to this patient for 15 minutes and then discontinued because of clinical deterioration. Hypoxemia and hypotension persisted with conventional therapy and ECMO was initiated. The patient died on ECMO with an intracranial hemorrhage 16 hours after baseline.

Sixteen (33%) of the 49 patients required ECMO, one half in each group (relative risk = 1). One-quarter of our patients had either seizures or intracranial hemorrhages more severe than grade 1. No patient was discharged home requiring supplemental oxygen (Table 3).

Differences Between Treatment Groups

There were no differences between groups with respect to death, use of ECMO, days on mechanical ventilation, or days receiving supplemental oxygen (Table 3). However, measures of oxygenation after baseline were markedly different between the two groups. The median percentage change in Pao_2/Fio_2 at 15 minutes compared with baseline for the control patients (−2%, range −37% to 249%; $P = .57$) compared with patients assigned to NO (+45%, range −33% to 539%; $P = .001$) was significant ($P = .03$ between groups, Fig 1).

Similarly, the percentage change in OI at 15 minutes compared with baseline was significant for the NO group and it had improved compared with control patients (Fig 2). Baseline OI was similar between the two groups but dropped dramatically in the treated NO patients compared with baseline (−31%, range −84 to 38%; $P = .003$) and also compared with the control population (5%, range −71 to 101%; $P = .39$) ($P = .009$ between groups). This observation was related to changes in oxygenation and not mean airway pressure or Fio_2; the median percentage change in Pao_2 was 43% (range, −35 to 539%; $P = .002$) for patients receiving NO and −2% for control patients (range, −37 to 247%; $P = .57$) ($P = .04$ between groups). The median change in mean airway pressure at 15 minutes compared with baseline was zero. Oxygen saturation by pulse oximetry increased by 4% (range, −9% to 21%; $P = .0003$) in NO

TABLE 1. Comparative Data at Baseline, Median (Range)

	Control (n = 23)	Nitric Oxide (n = 26)
Age at entry (hours)	25 (3–63)	18 (5–83)
Gestation (weeks)	40 (36–42)	40 (35–42)
Weight (kg)	3.4 (2.2–5.2)	3.5 (2.5–5.0)
Heart rate (beats per min)	165 (139–200)	175 (135–195)
Mean blood pressure (mm Hg)	54 (39–80)	53 (35–76)
Pao_2 (mm Hg)	64 (27–212)	47 (24–113)
pH	7.48 (7.23–7.62)	7.51 (7.14–7.66)
$Paco_2$ (mm Hg)	34 (18–58)	31 (13–75)
Mean airway pressure (cmH_2O)	15.2 (8.3–32)	16.3 (10.8–25.6)
Oxygenation index	29.4 (10.5–114)	30.4 (10.4–84.5)

TABLE 2. Diagnostic Categories and Associated Conditions

Diagnosis	All (n = 49)	Control (n = 23)	Nitric Oxide (n = 26)
Meconium aspiration syndrome	22 (45%)	9	13
Persistent pulmonary hypertension of the newborn	11 (23%)	7	4
Pneumonia	8 (16%)	3	5
Sepsis	4 (8%)	3	1
Hydrops fetalis	2 (4%)	1	1
Respiratory distress syndrome	1 (2%)	0	1
Pulmonary hemorrhage	1 (2%)	0	1

TABLE 3. Outcome

	All (n = 49)	Control (n = 23)	Nitric Oxide (n = 26)
Mortality	4 (8%)	2 (9%)	2 (8%)
Extracorporeal membrane oxygenation	16 (33%)	8 (35%)	8 (31%)
Seizure or intracranial hemorrhage	12 (25%)	8 (35%)	4 (15%)
Median days on ventilator	9	10	9
Median days on oxygen	13	12	13
Home oxygen	0	0	0

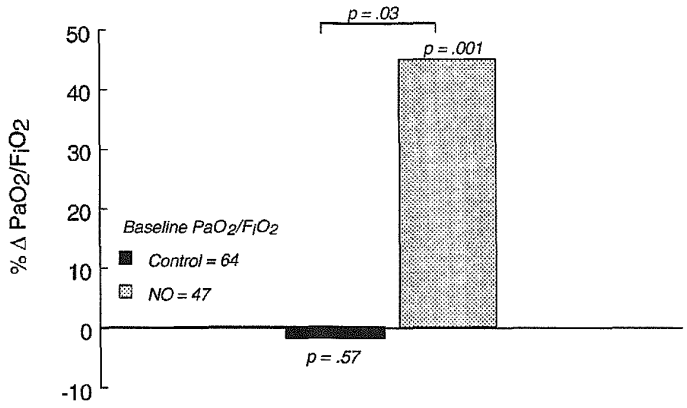

Fig 1. Median percentage change in Pao_2/Fio_2 at 15 minutes compared with baseline for control patients and patients treated with NO. Oxygenation significantly improved in NO patients compared with the control population (P = .03).

treated patients and 0 (range, −22 to 41%; P = .97) for control patients (P = .006 between groups). There was no change in heart rate or blood pressure within groups compared with baseline or between groups.

Fifteen patients who received NO increased their Pao_2 at 15 minutes by more than 20% from baseline. Only 2 of these patients were subsequently placed on ECMO. One of these patients, with the diagnosis of pulmonary hemorrhage, saw improvement in Pao_2 from 29 to 42 mm Hg at 15 minutes and to 55 mm Hg 2 hours later just before cannulation for ECMO (OI = 49). The second patient had improvement in Pao_2 from 43 to 54 mm Hg 15 minutes after NO was started. Pao_2 was sustained in the 60s in this patient. However, after 68 hours the Fio_2 still could not be weaned from 0.97 without reduction in the Pao_2 below 60 mm Hg; the child was placed on ECMO (Pao_2 = 63 mm Hg, OI = 28). Thus, no child had a positive response (more than 20% change) to NO followed by marked deterioration and need for ECMO.

The improvement in oxygenation among patients treated with NO was sustained. Figure 3 shows the median percentage change in OI for both treatment groups during the first 24 hours of study. The reduction in OI seen at 15 minutes with NO was sustained compared with baseline and was significantly different from controls at later time points. After 12 hours of treatment, the median percentage change in OI among NO treated patients was −50% (range, −86 to 30%; P = .0007) compared with control patients' change of −19% (range, −81 to 97%; P = .20) (P = .03 between groups). OI was excluded from analysis after patients were placed on ECMO. Because the number of patients treated with ECMO was the same in each group (n = 8), and because the number of patients treated with HFOV at any point in their treatment (n = 18, controls vs n = 15, NO) was not different between groups, the data suggest that the immediate and sustained improvement in oxygenation was attributable to NO inhalation. Analysis of oxygenation data with ECMO patients excluded at all times demonstrates similar findings, as does separate statistical analysis which excludes patients assigned to but not treated with NO. The median time receiving NO was 22.5 hours (range, 0.25 to 137 hours).

For those patients who were placed on ECMO the Pao_2 and oxygen saturation were higher in the NO group just before cannulation (Table 4). In control patients, the median value of the last recorded Pao_2 was 38 mm Hg, similar to the baseline value. Before ECMO the oxygen saturation by pulse oximetry had fallen from 86% to 82%. In contrast, in NO treated patients the median Pao_2 rose from 41 mm Hg at baseline to 55 mm Hg before ECMO (P = .02, between groups) and oxygen saturation rose from 87% to 91% (P = .02, between groups). The median time from baseline to ECMO cannulation was 2.4 hours (range, 1 to 12 hours; mean = 3.9 ± 1.3 hours) among control patients and for the NO group it was 3.3 hours (range, 2 to 68 hours; mean 17.7 ± 8.9 hours).

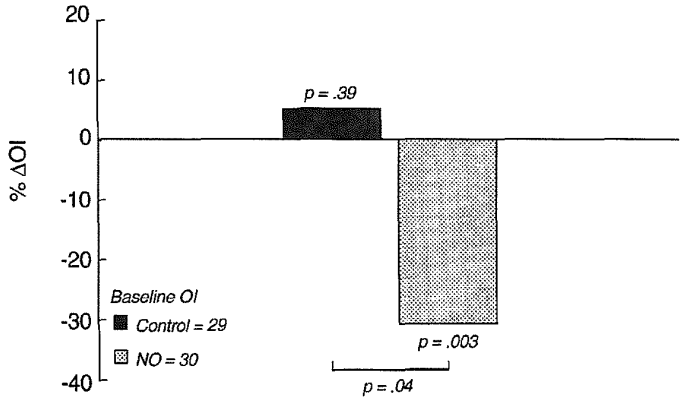

Fig 2. Median percentage change in OI at 15 minutes compared with baseline for control patients and for patients treated with NO. In NO treated patients, OI was reduced and was significantly different from control patients (P = .04).

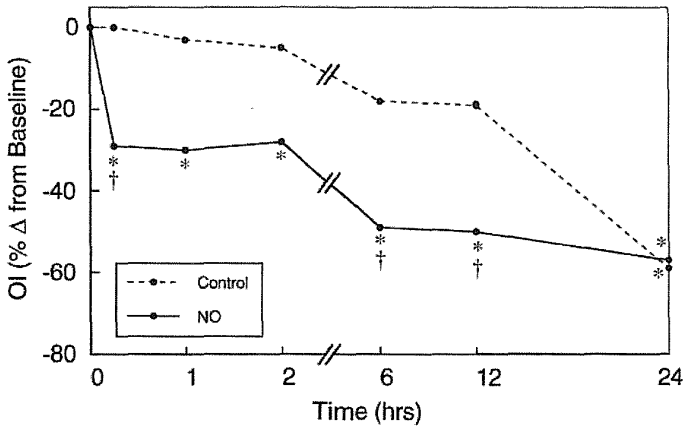

Fig 3. Median percentage change in OI during the first 24 hours of study. The reduction in OI during the first 15 minutes was sustained during subsequent times compared with baseline (*) or to control patients (†) ($P < .05$). OI data were not included in this figure after patients were cannulated for ECMO.

There was a tendency toward fewer neurologic complications in the NO treatment group. Eight of 23 control patients suffered from intracranial hemorrhage or seizures compared with 4 of 26 in the NO group including the incompletely treated patient with left atrial hypertension who died on ECMO ($P = .1$ by Fisher's exact test; Table 4).

Toxicity

The median peak methemoglobin level was 1.7% (range, 0.1 to 17%). One patient with subsequently documented alveolar capillary dysplasia could not be weaned to <80 ppm of NO and developed a peak methemoglobin level of 17% after 25 hours of treatment. The methemoglobin level was reduced below 8.0% with vitamin C therapy and transfusion with packed red blood cells. The patient died suddenly on 80 ppm of NO, 4 days after enrollment with a tension pneumothorax and intracranial hemorrhage.

Peak nitrogen dioxide levels of 1 ppm or less were recorded in 19 out of 26 patients who received NO. One patient had a spurious nitrogen dioxide level of 9 ppm which could not be subsequently confirmed using backup chemiluminescence devices. No other patient had nitrogen dioxide levels that exceeded 5 ppm.

DISCUSSION

This study showed that inhaled NO improved oxygenation in patients with PPHN compared with control patients. This confirms earlier reports from smaller uncontrolled trials of NO and supports the contention that improved oxygenation can be sustained with NO. The OI improved not only during the first 15 minutes of therapy, but was also reduced compared with control patients at 6 and 12 hours after initiation of therapy. Because the number of patients treated with ECMO or HFOV was not different between groups one cannot attribute these oxygenation differences to drop out of ECMO patients or artifact of mean airway pressure measurements during HFOV compared with conventional therapy.

However, sustained improvement in oxygenation was not sufficient in all cases to avoid treatment with ECMO. Thus, we could not demonstrate any difference in use of ECMO between the two treatment groups. Several possible reasons may account for this finding including: 1) lack of important clinical benefit of the drug, 2) insufficient sample size to detect clinical benefit, 3) poor patient selection for optimal NO effect, 4) physician preference to pursue strategies utilizing ECMO despite clinical improvement with NO, and 5) incomplete utilization of optimal ventilatory strategies to facilitate NO effect.

It seems unlikely that NO has no clinical benefit whatsoever other than a transient effect on Pa_{O_2}. Several studies, including ours, have shown sustained improvement in oxygenation with NO.[10–12,14] Severe hypoxemia is usually the main indication for ECMO. Along with cardiac output, oxygenation is the primary determinant of oxygen delivery and, therefore, of end organ function and clinical well being. If better oxygenation can be obtained without increased risk, it is likely to be desirable in PPHN. Use of NO did not prolong exposure to mechanical ventilation or supplemental oxygen. We did not increase the risk of intracranial hemorrhage and seizures. In fact, there was a tendency to observe fewer such events in patients treated with NO, although the number of patients affected was too small to predict improvement in neurologic outcome with confidence. We did not observe patients who had favorable transient responses, but then deteriorated to require ECMO support. This circumstance has been described more characteristically in patients with severe pulmonary parenchymal disease or lung hypoplasia rather than those predominantly affected by profound elevation in pulmonary vascular resistance.[13–16]

TABLE 4. Extracorporeal Membrane Oxygenation Patients (n = 16)

	Control (n = 8)		Nitric Oxide (n = 8)	
	Base	Pre-ECMO	Base	Pre-ECMO
Pa_{O_2} (mm Hg)	38	38	41	55*
Oxygen saturations (%)	86	82	87	91*
Time to extracorporeal membrane oxygenation (hours)		2.4		3.3

* $P = .02$ compared to control patients.

Is it possible that within this study design, there was an observable effect on clinical outcome and we enrolled too few patients to reveal this effect? If we exclude patients who were randomized to receive NO, but who were prematurely withdrawn from NO therapy or never received the drug, then the differential use of ECMO (6/23 vs 8/23) still does not reach statistical significance. A 25% reduction in risk of ECMO at this rate of utilization would require 438 patients in each group to achieve a statistical power of 80%. Because many centers are now using NO, such a study design would have little chance of successful completion. It is unrealistic to assume that a larger enrollment with the same study design and clinical algorithms for care would have demonstrated differences in clinical outcome.

Exclusion of patients with congenital diaphragmatic hernia and selection of patients who had clinical and echocardiographic confirmation of high pulmonary vascular resistance should have optimized the likelihood of beneficial response to NO.[14] Nonetheless, this study included patients who retrospectively were thought to be unsuitable candidates for successful use of NO, including those with alveolar capillary dysplasia[23] and a patient with severe left ventricular dysfunction.[24] Better selection of patients may further enhance our ability to detect beneficial uses and effects of NO.

It is possible in this early limited experience with NO, clinicians were uncertain about the clinical course with the drug and were inclined to utilize ECMO despite improvement in oxygenation. We observed that the precannulation Pao_2 and oxygen saturation for patients who went to ECMO were better in the NO group. Pao_2 rose to the middle 50s in NO patients as they were directed to ECMO, but stayed between 30 and 40 mm Hg among control patients who went to ECMO. This improvement in oxygenation did not dissuade clinicians from utilizing ECMO during this phase of our NO experience. Our institution has reported a large ECMO experience with low mortality; new therapies may be accepted slowly.[25] It may be argued that although patients who were receiving NO and cannulated for ECMO were still receiving an Fio_2 of 0.97, the median Pao_2 of 55 mm Hg before ECMO was adequate to defer cannulation in at least one-half of the patients. This idea is supported by the short time between enrollment and cannulation for those patients who were supported by ECMO. It was also noted that NO patients had a tendency to undergo cannulation for ECMO at a slightly later time but generally within the first 24 hours of life. An aggressive mind set among clinicians toward utilization of ECMO may have hindered our evaluation of the clinical efficacy of NO but may also have accounted for the low incidence of chronic lung disease among our patients; no patient was discharged to home on supplemental oxygen.

It is most likely in our opinion that the study design of this investigation precluded the optimal effect of NO by excluding the concomitant use of HFOV with NO in any patient, including those with findings of pulmonary parenchymal disease and loss of lung volume on chest radiograph. As has been suggested by Abman and Kinsella[26] and others, lung recruitment strategies facilitated by HFOV ventilation may enhance the efficacy of NO. With this in mind, our protocol was reevaluated after 2 years of enrollment when this interim analysis was conducted. NO is now used in conjunction with HFOV when clinically indicated.

Limitations

Some limitations of the study have already been mentioned. The exclusion of HFOV and the low power to detect small differences in clinical outcomes are apparent.

The trial was unmasked which may introduce observer bias. Although it is possible that investigators may be biased toward overstating the benefits of the therapy, the timing of the first hemodynamic record and blood gas sampling was rigidly enforced at 15 minutes and 1 hour and then subsequently left to the execution of the bedside clinicians according to preset times. Thus the measures of oxygenation were objective and less susceptible to bias. On the other hand, the purported rapid onset of action of NO may lead more easily in an unmasked trial to premature and incorrect clinical assumption of treatment failure.[12,17] Investigators have recently suggested that the clinical benefit of NO may be manifest throughout several hours. An unmasked trial may permit clinicians to condemn slow responders to a category of failure to respond after a few minutes of NO therapy and therefore reinforce the perceived need for ECMO. Although indications for ECMO may be reasonably stated to include a sustained OI >40, many factors play a role in the timing and utilization of this resource.

We did not investigate the dose response relationship for NO nor did we establish the minimum effective dose of this drug. Based on earlier animal and human infant experience, we chose the initial dose of 80 ppm as the likeliest tolerable dose of NO able to achieve maximal pulmonary vasodilation.[8,27,28]

Methemoglobinemia was observed in 1 patient who was the only patient who could not be weaned from 80 ppm. This patient had postmortem evidence of alveolar capillary dysplasia. All other patients tolerated reduction in NO dose to 40 ppm. Although nitrogen dioxide levels did not exceed 3.5 ppm in any patient, these measurements were performed with chemiluminescence technique before our appreciation that quenching effects in high oxygen environments may contribute to falsely low (or even negative) measurements of nitrogen dioxide.[21] Modification of chemiluminescence technology for clinical use, along with improvements in electrochemical detection devices may be combined with the use of 40 ppm or lower doses of NO, to minimize toxicity without significant compromise of any potential therapeutic efficacy.[29] Nonetheless, the full range of potential toxicity of NO and its metabolites such as peroxynitrite, and the potential effects of adverse interaction with free radical scavenging among normal processes in immature and diseased lungs, have not been fully tested. This will require further study

with randomized trials which implement appropriate follow-up of patients and do not permit crossover of treatment.

Finally, we have seen that mortality for reversible causes of PPHN is low in an ECMO center. At most, 2 and probably only 1 patient in this series died with reversible pulmonary hypertension. This low event rate will make it unlikely that mortality is a realistic outcome variable for single-center randomized trials of the efficacy of NO in PPHN. Considering the potential to achieve zero mortality in this disease, centers without ECMO capability may need to re-evaluate the timing of patient referrals, especially if withdrawal of NO (during transport) may be associated with rebound pulmonary hypertension.[30]

The improvement in oxygenation and low incidence of identifiable side effects with inhaled NO in this study encouraged us to proceed with continued randomization in a second phase of the trial using lower NO doses and combined therapy with NO and HFOV when indicated. This phase has just been completed and confirms the value of HFOV. These and other studies will be required before one can conclude with certainty whether NO improves outcome in patients with PPHN.

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Improved Oxygenation in a Randomized Trial of Inhaled Nitric Oxide for Persistent Pulmonary Hypertension of the Newborn

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Inhaled Nitric Oxide in the Neonate With Cardiac Disease

Andrew M. Atz and David L. Wessel

As a selective pulmonary vasodilator, inhaled nitric oxide is an important diagnostic and therapeutic agent for the treatment of pulmonary hypertension in patients with congenital heart disease. Among 400 patients treated in our center with nitric oxide, 37% were newborns. Hemodynamic benefit was shown in newborns with total anomalous pulmonary venous connection, in those with congenital mitral stenosis, and in postoperative patients with preexisting left to right shunts and other lesions. It can be used to help discriminate anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction, and it may be used in the treatment or prevention of pulmonary hypertensive crises after cardiopulmonary bypass. However, none of the purported benefits of inhaled nitric oxide in children with congenital heart disease have been studied in a randomized, placebo-controlled manner.

Pulmonary Hypertension and Congenital Heart Disease

Prevalence

Among causes of infant mortality in the United States, congenital anomalies account for the largest diagnostic category, and structural heart disease leads the list of congenital malformations.[1] Approximately one third of pediatric intensive care admissions are for children with cardiovascular disorders.[2] Compared with the number of adults with coronary and rheumatic heart disease, the number of Americans with congenital heart disease is relatively small, but one quarter of this number are sufficiently affected by the disease to require intervention within the first month of life.[3] The number of neonates with pulmonary hypertensive disorders further complicating their congenital heart disease is difficult to precisely quantify, but likely represents about 25% of those who require early intervention.[4] Their severity of illness, demand on resources, and the previously limited success of therapeutic options have focused attention on this population of patients.

Importance

Pulmonary hypertension is often a crucial factor in determining the timing or type of intervention, and has been invoked as the primary determinant of mortality in many lesions.[5,6] The assessment of pulmonary vascular reactivity forms an important part of the preoperative and postoperative management of patients with congenital heart disease. A fixed elevation in pulmonary vascular resistance may deny them the chance of corrective surgery with the subsequent development of progressive obliterative pulmonary vascular disease and severely reduced life-expectancy. Children with congenital heart disease are frequently cyanotic and have multiple intracardiac shunts, often coexisting with varying degrees of right or left ventricular outflow tract obstruction. Intravenous vasodilators with their attendant risks of hypotension and increased intrapulmonary shunt may be not only hazardous, but yield results that confound analysis of the reactivity of the pulmonary vascular bed.

The Neonate With Congenital Heart Disease

Effects of Cardiopulmonary Bypass

Only a few years ago, it was considered heretical that a child with congenital heart disease should be electively repaired with a single primary pro-

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cedure during the first few days of life using cardiopulmonary bypass. Criticism of this approach focused not only on the technical capabilities of the surgeon, but on the adverse effects of cardiopulmonary bypass on the neonatal myocardium. Furthermore, concerns existed that severe pulmonary hypertension, activated by cardiopulmonary bypass, would compromise postoperative hemodynamic stability. Today, surgical correction of congenital heart disease, in contrast to palliation with shunts or pulmonary artery bands, has been extended to the neonate; surgical correction is emerging as the preferred approach to many defects in most major centers.[7,8] However, perioperative care of the newborn and infant does require an appreciation of the relative intolerance of the immature myocardium to increased afterload. The right ventricle must face the potential challenges of the transitional pulmonary circulation rendered ischemic and reactive by cardiopulmonary bypass, while simultaneously coping with impaired ventricular function caused by the adverse effects of bypass. Aside from the consequences of cardiopulmonary bypass, aortic cross-clamp time, routine use of deep hypothermia and cardioplegia solutions, many congenital heart defects (eg, tetralogy of Fallot, truncus arteriosus, pulmonary atresia) require a right ventriculotomy as part of the repair. Thus, it is imperative that one minimize right ventricular afterload during the early postoperative hours while the ischemic-reperfusion injury transiently depletes myocardial reserve and cardiac output normally declines.[9]

Causes of Pulmonary Hypertension

The neonatal pulmonary vasculature may be extremely labile. Remodeling of the vessel wall, functional maturation of the endothelial cell, differentiation of the smooth muscle cell, release of vasoactive mediators, and vessel recruitment all contribute to the successful transition from fetal to neonatal pulmonary circulation. The child with congenital heart disease and pulmonary hypertension has abnormal postnatal vessel remodeling.[10] Prolonged exposure to high pulmonary blood flow under conditions of high pressure will accelerate the pathological progression to less reversible states. Thus early surgical repair has been advocated to prevent later pulmonary vascular obstructive disease.[11,12] Neonatal cardiac surgical repair achieves earlier and more normal pulmonary vascular maturation. It seems to reduce but not abolish the incidence of problematic postoperative pulmonary hypertension.[12]

Several factors attributable to cardiopulmonary bypass may raise pulmonary vascular resistance: microemboli, platelet aggregation, complement activation, pulmonary leukosequestration, excess thromboxane and endothelin production, atelectasis, and hypoxic pulmonary vasoconstriction among others. Furthermore, prior data would suggest that preoperative conditioning of the pulmonary vascular bed, perioperative vasospastic stimuli, increased postoperative adrenergic tone, along with damage to the pulmonary endothelium likely combine to increase pulmonary vascular resistance after cardiopulmonary bypass. The effect may be insidious, expressed over several hours as low cardiac output and right heart failure, or more acutely as pulmonary hypertensive crises. Pulmonary hypertensive crises are dramatic events that threaten the life of an infant despite a good surgical repair.[13,14] In such situations, the pulmonary artery pressure increases to systemic or suprasystemic levels, the systemic blood pressure falls and the arterial oxygen saturation decreases. In a report of a series from one large center, half of the postoperative cardiac children who had pulmonary hypertensive crises died during their hospitalization.[4]

Inhaled NO: Measuring the Response

The first investigations of pulmonary vasodilation with NO in adults were quickly followed by several clinical reports of inhaled NO aimed at the transitional circulation of the newborn and children with congenital heart disease. Successful clinical trials of inhaled NO have been conducted among patients with persistent pulmonary hypertension of the newborn (PPHN).[15,16] However, direct measurement of pulmonary artery pressure is rarely undertaken in patients with PPHN or in other forms of neonatal respiratory failure. Effects of NO treatment on pulmonary hypertension may be inferred from changes in systemic oxygenation only when hypoxia results from right to left shunting across the ductus arteriosus or foramen ovale. Even then, oxygenation is an indirect and ambiguous measure of the effect of treatment on pulmonary vascular resistance. The analysis is further confounded when severe pulmonary parenchymal disease

coexists with pulmonary hypertension. In this setting, systemic oxygenation may improve with inhaled vasodilators by enhancing ventilation-perfusion matching.[17] Pulmonary artery pressure is often monitored directly in the neonate and infant with congenital heart disease. This population affords us a unique opportunity to directly record the hemodynamic effects of initiation and withdrawal of inhaled NO.

Clinical Studies

We will review the current literature regarding the use of inhaled NO in congenital heart disease, focusing on neonates. We first present studies that used nitric oxide as a means to identify endothelial dysfunction resulting from cardiopulmonary bypass and then suggest how NO may benefit cardiac patients with combined problems of pulmonary hypertension and acute respiratory failure. We will review its therapeutic utility in perioperative patients with pulmonary hypertension, and its use as a diagnostic tool to distinguish between neonates with reactive pulmonary vasoconstriction and those with right ventricular hypertension resulting from anatomic obstruction to pulmonary blood flow. We will also explore its use and limitations in patients with single ventricle physiology and discuss potential adverse effects as pertains to cardiac disease. Finally, we will consider the potential benefits of longer-term administration of NO to facilitate growth and remodeling of the abnormal pulmonary vasculature in unusual forms of idiopathic pulmonary hypertension identified in early infancy.

Age Distribution

By 1997, we had studied the clinical response to inhaled NO in more than 400 patients at a single center. Nearly two-thirds of these patients exhibited pulmonary hypertension associated with congenital heart disease. Thirty-seven percent were younger than 1 month of age and the majority were less than 1 year (Fig 1), reflecting the bias toward early surgical repair of congenital heart defects at Children's Hospital, Boston[7] and the perceived benefit of NO for PPHN.

Endothelial Dysfunction After Cardiopulmonary Bypass

Pulmonary vascular endothelial dysfunction contributes to post-cardiopulmonary bypass pulmonary hypertension. The degree of pulmonary hypertension correlates with the extent of damage to the pulmonary endothelium after cardiopulmonary bypass. Reactivity of the pulmonary vascular bed is related to the presence and degree of preoperative pulmonary hypertension, magnitude of preoperative left to right shunts, and duration of bypass. On cardiopulmonary bypass, pulmonary blood flow is supplied only by the vasovasorum via the bronchial circulation, which may be inadequate to prevent ischemic damage to the endothelium and subsequently compromise endogenous production of nitric oxide. We hypothesized that transient pulmonary vascular endothelial cell dysfunction could be shown in neonates and older children by documenting the loss of endothelium dependent vasodilation during the immediate postoperative period.

We recorded hemodynamic variables after a 2-minute infusion of the endothelium dependent vasodilator, acetylcholine, at a concentration of 10^{-6}M and after inhalation of the endothelium-independent smooth muscle relaxant, NO inhaled at 80 parts per million (ppm).[18] The two agents were compared in patients with pulmonary hypertensive congenital heart disease before and after surgical repair on cardiopulmonary bypass. Plasma levels of cyclic GMP were measured before and after acetylcholine and NO administration. Pulmonary vasodilation to acetylcholine was present preoperatively but attenuated postoperatively, while response to inhaled nitric oxide was present both preoperatively and postoperatively. Baseline mean pulmonary artery pressure decreased 27% ± 4% preoperatively but only 9% ± 2% postoperatively with acetylcholine. However, after the attenuated response to acetylcholine was shown, postoperative inhalation of NO immediately lowered mean pulmonary artery pressure by 26% ± 3% (Fig 2). Similarly, baseline pulmonary vascular resistance decreased 46% ± 5% in preoperative patients, but declined only 11% ± 4% in postoperative patients with acetylcholine. Inhalation of NO after acetylcholine infusion lowered pulmonary vascular resistance postoperatively by 33% ± 4%. This suggested that the functional integrity of the smooth muscle was intact in the presence of endothelial dysfunction resulting from cardiopulmonary bypass. Elevated pulmonary vascular resistance from atelectasis, microemboli, platelet plugging of vessels or other fixed obstructive

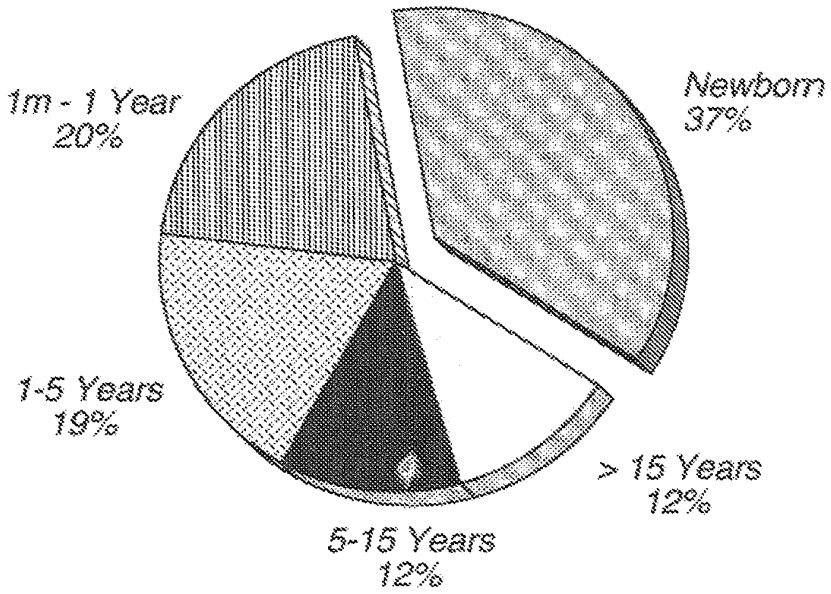

Figure 1. Age analysis of 405 consecutive patients who received inhaled NO at Children's Hospital, Boston.

processes could not be invoked as the cause of the blunted response to acetylcholine because resistance decreased so dramatically with NO. Plasma levels of cGMP in postoperative patients were unchanged after acetylcholine, but increased more than threefold during pulmonary vasodilation with NO. This finding was consistent with the purported role of cGMP as the second messenger effecting smooth muscle relaxation.

This study suggested that cardiopulmonary bypass is responsible for pulmonary endothelial dysfunction. This focused attention on the endothelium as an important organ to address in the management of pulmonary hypertension. It also highlighted the potential importance of maintaining at least some antegrade flow from right ventricle into pulmonary arteries during extracorporeal membrane oxygenation (ECMO).

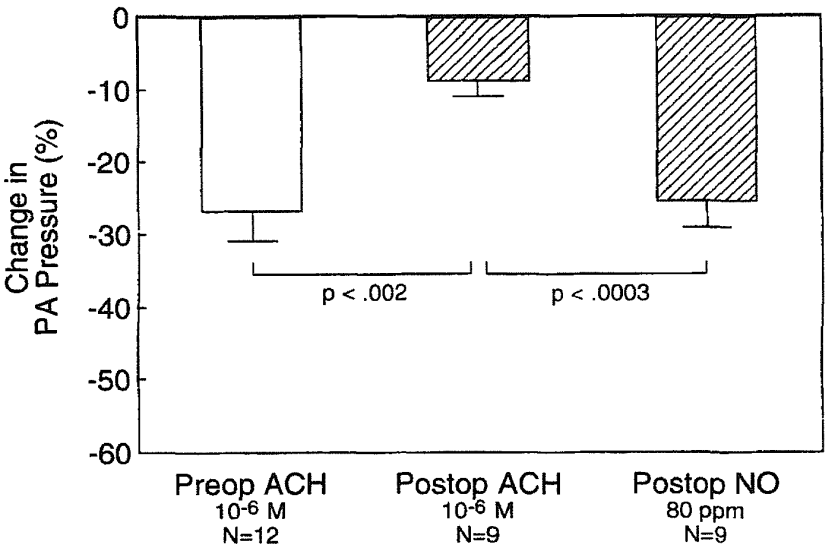

Figure 2. The percentage change in mean pulmonary artery pressure (PA) with acetylcholine (ACH) in preoperative and postoperative patients. The vasodilator response is attenuated with ACH but retained with NO in the postoperative period. (Reprinted with permission from Wessel DL, et al: Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial function after cardiopulmonary bypass. Circulation 88:2128-2138, 1993.[18] Copyright 1993 American Heart Association.)

The heart should be permitted to eject some flow into the pulmonary arteries rather than allowing ECMO to provide total cardiopulmonary bypass for several hours or days. These early findings further suggested an important diagnostic and therapeutic role that inhaled nitric oxide might play as a result of its selective pulmonary vasodilation with minimal systemic side effects in children with congenital heart disease.

Acute Respiratory Failure After Cardiopulmonary Bypass

Pulmonary parenchymal disease may coexist with heart disease in the newborn. It complicates evaluation and treatment of the child. In some instances, structural abnormalities in the heart produce pulmonary venous hypertension, flood the alveoli with pulmonary edema fluid, and induce severe intrapulmonary and extrapulmonary right to left shunting of blood.

Examples of this phenomenon include the child born with transposition of the great arteries and intact ventricular and atrial septa. In this example, inadequate mixing of blood occurs simultaneously with extreme elevation in left atrial pressure. Pulmonary venous oxygen desaturation may critically lower the systemic oxygen levels further in this cyanotic heart disease. Immediate performance of a balloon atrial septostomy is essential, but may not instantly correct the pulmonary parenchymal abnormalities and alveolar hypoxia.[19] Treatment with inhaled NO may address ventilation-perfusion abnormalities in this circumstance as well as lower the still reactive pulmonary artery pressure. Reports have suggested that use of NO may obviate the need for ECMO in some such circumstances by accelerating improvements in gas exchange as well as hemodynamic recovery.[20,21]

Transient acute respiratory failure may occur in other instances after cardiopulmonary bypass, notably after lung transplantation in children. Here the ischemic injury to the endothelium is exaggerated after hours of cold ischemic preservation of the donor lung. The lung parenchyma is injured such that transient graft dysfunction characterized by lung consolidation, decreased lung compliance, hypoxia, and pulmonary hypertension may plague the patient postoperatively. Again in this clinical scenario, the injured lung vasculature is unresponsive to the endothelium-dependent vasodilators but highly responsive to inhaled nitric oxide.[22] Pulmonary artery pressure decreased precipitously with treatment, but more importantly, PaO_2 increased dramatically (Fig 3).

In the presence of increased pulmonary vascular tone, patients with large intrapulmonary shunts respond to inhaled vasodilators with a reduction in intrapulmonary shunt fraction and improved systemic oxygenation. This contrasts with traditional intravenous vasodilators, which are prone to override hypoxic pulmonary vasoconstriction and worsen ventilation/perfusion abnormalities. Evidence now exists that NO can be administered to the donor lung to enhance preservation during storage and transport to the recipient.[23,24] Although neonatal lung transplantation is a rare procedure, other forms of respiratory failure in newborns after cardiopulmonary bypass are more commonly encountered. Overwhelming pneumonia is a devastating complication that may be exacerbated by cardiopulmonary bypass. Mild infectious pneumonitis or bronchiolitis in the young preoperative infant can turn to life-threatening respiratory failure during postoperative recovery. As an inhaled vasodilator, NO therapy addresses both aspects of the disease: pulmonary hypertension and hypoxia. Inhaled NO, by virtue of its antioxidant effects, inhibition of unwanted platelet aggregation and suppression of deleterious inflammatory responses during reperfusion injury, may even have a role in routine prophylactic use for all patients at risk of postbypass respiratory complications.

NO or ECMO After Cardiopulmonary Bypass

ECMO support for severe cardiopulmonary failure after cardiac surgery in newborns and children has been advocated in many centers.[25,26] Because postoperative pulmonary hypertension after reparative cardiac operations is believed to be life-threatening, yet reversible, NO treatment in this condition may diminish the need for ECMO. Certainly, Journois et al have shown the value of NO in the treatment of acute pulmonary hypertensive crises.[27] Goldman et al described 6 of 10 patients who met institutional ECMO criteria, but were managed with NO instead and survived to hospital discharge.[21] This compares favorably with published survival rates in postcardiotomy patients supported by ECMO.[25]

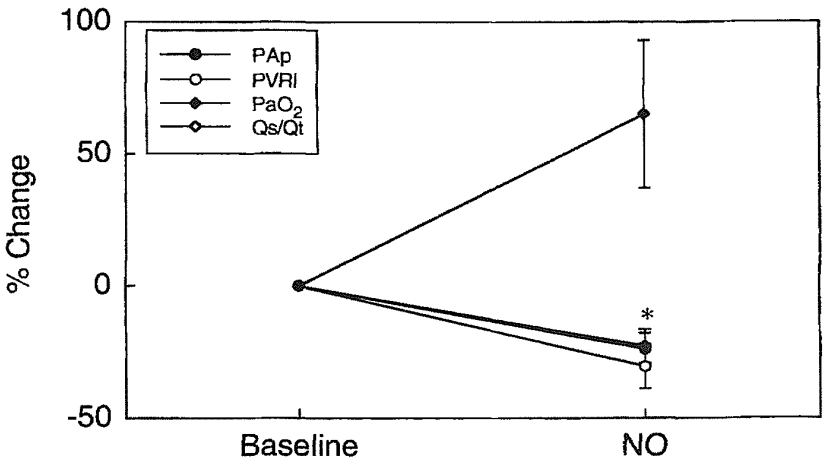

Figure 3. The effect of 80 ppm NO in six patients with transient graft dysfunction after lung transplantation. Pulmonary artery pressure (PAp), pulmonary vascular resistance (PVRI), and intrapulmonary shunt fraction (Qs/Qt) decreased significantly and PaO_2 increased. (Adapted and reprinted with permisssion from Adatia I, Wessel DL: Therapeutic use of inhaled nitric oxide. Curr Op Pediatr 6:583-590, 1994.)

Although there are no randomized trials examining the benefit of NO among cardiac patients, this information suggests that a trial of inhaled NO should be considered in these patients before cannulation for ECMO.

Total Anomalous Pulmonary Venous Connection

Infants with total anomalous pulmonary venous connection (TAPVC) frequently have obstruction of the pulmonary venous pathway as it connects anomalously to the systemic venous circulation. When pulmonary venous return is obstructed preoperatively, pulmonary hypertension is severe and demands urgent surgical relief. Increased neonatal pulmonary vasoreactivity, endothelial injury induced by cardiopulmonary bypass,[18] and intrauterine anatomic changes in the pulmonary vascular bed in this disease[28] contribute to postoperative pulmonary hypertension. We hypothesized that infants with anatomically obstructed TAPVC would have a high occurrence rate of postoperative pulmonary hypertension, and that their pulmonary vascular bed could be selectively dilated with inhaled NO. Our aim was to define the incidence of postoperative pulmonary hypertension in infants with TAPVC and to describe the hemodynamic effects of initiation and withdrawal of inhaled NO in those postoperative patients with pulmonary hypertension. Twenty infants presented with isolated TAPVC over a 3-year period and were monitored for pulmonary hypertension. Nine patients had postoperative pulmonary hypertension treated with a 15-minute trial of inhaled NO at 80 ppm. Five patients received prolonged treatment with NO at 20 ppm or less (median 28 hours, range 12 to 71 hours).

We showed a mean percentage decrease of 42% in pulmonary vascular resistance and 32% in mean pulmonary artery pressure.[29] There was no significant change in heart rate, systemic blood pressure, or vascular resistance. Although not statistically significant, cardiac index increased by 10% (Fig 4).

Congenital Mitral Stenosis

We examined the effect of inhaled NO at 80 ppm for 15 minutes in 15 children with pulmonary hypertension and congenital mitral stenosis to assess the extent of reversible pulmonary vasoconstriction.[30] Mean pulmonary artery pressure decreased from 42 ± 2 to 30 ± 2 ($P < .05$) during NO inhalation. Pulmonary vascular resistance declined from 5.8 ± 0.7 to 2.9 ± 0.4 $U \cdot m^2$ ($P < .05$) (Fig 5). Cardiac index, left and right atrial pressure, mean systemic blood pressure, heart rate, systemic vascular resistance, PaO_2, and calculated intrapulmonary shunt fraction were not changed. Selective pulmonary vasodilation occurred in all patients, proving the presence of a significant reactive component of pulmonary hypertension in this disease. Prolonged therapy with inhaled NO facilitated the management and recovery of 4 patients. It is particularly useful adjunctive therapy during awakening and extubation when pulmonary hypertension worsens and predisposes patients to pulmonary

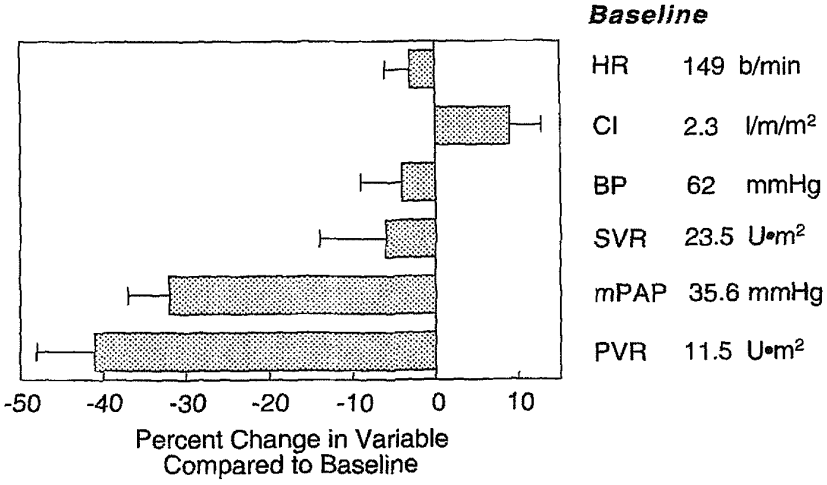

Figure 4. Percentage change in hemodynamic variables from baseline during 15 minutes of NO at 80 ppm in 9 patients with TAPVC. There is marked specificity for the pulmonary circulation.

edema. The vasoreactivity is greater than previously reported in adults with acquired mitral stenosis.[31,32] This may be due to the particular sensitivity of pulmonary veins to inhaled NO when pulmonary venous hypertension has been present since birth.

We have found patients with TAPVC, congenital mitral stenosis, and other pulmonary venous hypertensive disorders to be the most responsive to NO. These infants are born with significantly increased amounts of smooth muscle in their pulmonary veins.[33,34] Histological evidence of muscularized pulmonary veins as well as pulmonary arteries[35] suggest the presence of vascular tone and capacity for change in resistance at both the arterial and venous sites. The increased responsiveness observed in younger patients with pulmonary venous hypertension to NO may result from pulmonary vasorelaxation at a combination of pre and postcapillary vessels.[30,36]

Anatomic Obstruction Versus Pulmonary Vasoconstriction

As we have discussed, even if a neonatal cardiac operation is successfully performed, endothelium-dependent pulmonary vascular relaxation is impaired after cardiopulmonary bypass and the postoperative course may be complicated by

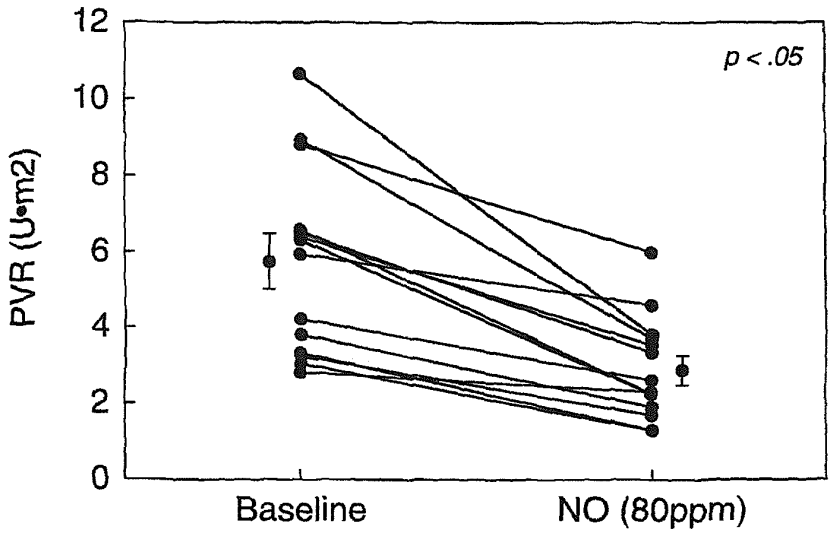

Figure 5. The effect of 80 ppm NO on pulmonary vascular resistance (PVR) in patients with congenital mitral stenosis. PVR decreased from baseline in all patients. (Reprinted with permission of the publisher from Atz AM, et al: Inhaled nitric oxide in children with pulmonary hypertension and congenital mitral stenosis. Am J Cardiol 77:316-319, 1996.[30] Copyright 1996 by Excerpta Medica Inc.)

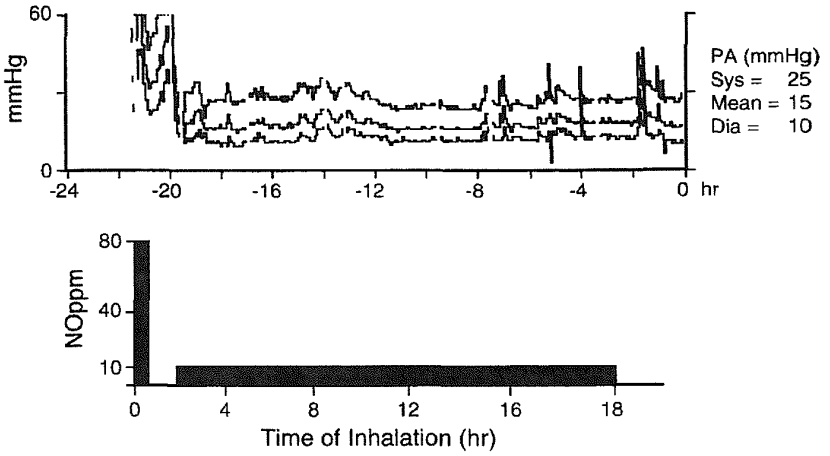

Figure 6. Bedside tracing of pulmonary artery pressure (PA) (systolic, mean, diastolic) with NO dose and duration of therapy on bottom. PA pressure decreased during 80 ppm trial. Vasodilation was sustained with 10 ppm NO for 18 hours of therapy.

transient pulmonary hypertension. As shown previously, pulmonary vasoconstriction in the postoperative newborn is exquisitely responsive to inhaled NO. However, reactive pulmonary vasoconstriction may not be the only cause of elevated pulmonary artery and right ventricular pressures. Differentiation between pulmonary vasoconstriction and anatomic obstruction to pulmonary blood flow may be difficult, especially in neonates. Branch pulmonary artery stenosis, hypoplastic distal pulmonary arteries, or iatrogenic causes of obstruction to pulmonary blood flow may be reflected in elevated pressure in the main pulmonary artery. A definitive diagnosis may require invasive and potentially dangerous investigation of the circulation.

We therefore proposed to use inhaled NO diagnostically in neonates with pulmonary hypertension after cardiac surgery to discern those with reversible vasoconstriction. Nine of 15 patients responded to a 15-minute trial with a reduction in mean pulmonary artery pressure from 35 ± 4 to 26 ± 4 mm Hg and pulmonary vascular resistance from 17 ± 6 to 10 ± 4 U · m^2. There were insignificant changes in systemic hemodynamics. Two patients received prolonged therapy with inhaled NO after the initial trial. In both cases the use of continuous low dose (3 to 10 ppm) NO allowed management of the pulmonary artery pressure, without episodic increases, and optimization of the right ventricular afterload. It was also possible to wean ventilatory support and decrease sedation unpunctuated by increases in pulmonary artery pressure (Fig 6).

Six patients did not respond to inhaled NO with either a decrease in proximal pulmonary artery pressure or an increase in systemic oxygen saturation. In each of these patients subsequent investigation, prompted by the failed response to inhaled NO, showed anatomic obstruction to pulmonary blood flow. Thus, failure of the postoperative newborn with pulmonary hypertension to respond to NO successfully discriminated anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction. Judicious use of a trial of inhaled NO may be of value to rule out pulmonary vasoconstriction and redirect investigation toward reassessment of the surgical result. Failure of the patient to show response to NO should be regarded as strong evidence of anatomic and possibly surgically remediable obstruction.

Other Lesions

Successful use of inhaled NO in a variety of congenital heart defects after cardiac surgery has been reported by several groups.[20,27,37-41] Selective pulmonary vasodilation has been documented after surgical repair of ventricular septal defects, atrioventricular septal defects, transposition of the great arteries, total anomalous pulmonary venous connection, and other structural heart defects. Some studies suggest that there is a correlation between the response to NO and the extent of preoperative pulmonary hypertension.[38,39] Synergistic use of NO with aerosolized or intravenous prostacyclin,[42,43] atrial natriuretic peptide,[44] dipyridamole,[45,46] or specific type V phosphodiesterase inhibitors holds considerable promise for more effective control of pulmonary

hypertension in infants with congenital heart disease.

Single Ventricle

Pulmonary blood flow in the newborn with a single ventricle and no anatomic obstruction of flow to the lungs may become excessive as pulmonary vascular resistance decreases after birth. A pulmonary artery band may be applied to limit pulmonary over circulation while the child grows and the lungs mature. More complex single ventricle anatomy with pulmonary or aortic valve atresia requires that reliable pulmonary blood flow be established surgically with a systemic to pulmonary artery shunt that is sufficiently restrictive to prevent congestive heart failure but adequate to permit oxygenation. Later during infancy, when pulmonary resistance has safely declined, a cavopulmonary anastomosis (ie, a bidirectional Glenn or later, a modified Fontan procedure) can be attempted as a more hemodynamically efficient method of providing pulmonary blood flow. If there is excessive cyanosis in the newborn after placement of a systemic to pulmonary artery shunt (eg, Blalock-Taussig), it is tempting to attribute the hypoxemia to pulmonary vasoconstriction. Indeed we have observed dramatic improvements in oxygenation in some of these newborns when NO is delivered. However, it is far more common for the reduction in pulmonary blood flow to result from a kinked or otherwise obstructed shunt that requires surgical revision[47] (Fig 7).

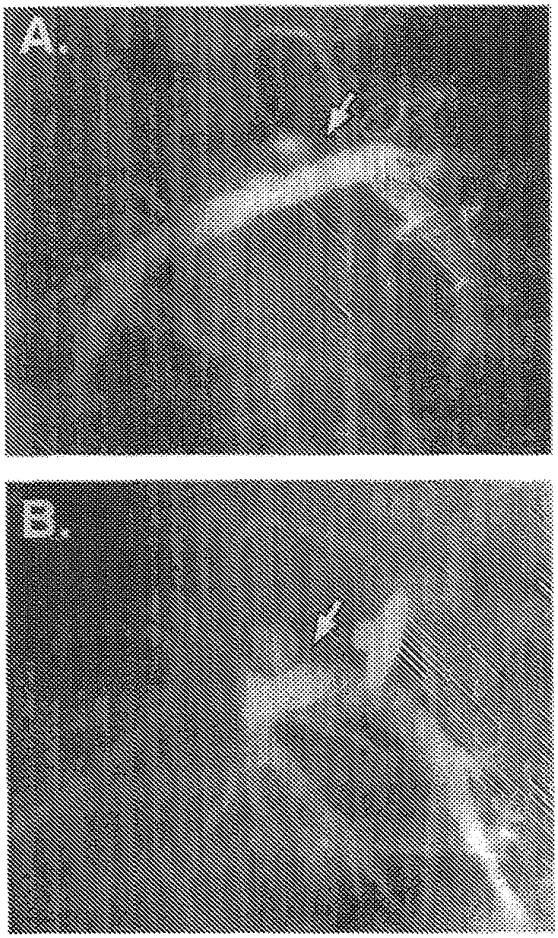

Figure 7. Anterior-posterior (A) and lateral (B) angiograms taken in a neonate with severe cyanosis and shunt-dependent pulmonary blood flow who failed to respond to inhaled NO. The arrow points to a discrete shunt narrowing that required surgical revision.

As a prelude to potential use of the cavopulmonary anastomosis in the newborn, we studied infants (2 to 8 months old) with refractory cyanosis after a bidirectional Glenn anastomosis.[48] Although median baseline oxygen saturation was only 65%, administration of inhaled NO provided minimal improvement in oxygenation. One child with respiratory syncytial virus bronchiolitis showed significant improvement in oxygenation, but NO did not substantially change systemic oxygenation or the transpulmonary pressure gradient in any other patient. Saturations and PaO_2 did not change despite the fact that there was a fivefold increase in plasma cyclic GMP production, suggesting that inadequate NO delivery or failure of guanylate cyclase activation could not explain the lack of therapeutic effect. We have extended these observations to nearly 30 patients. This suggests that the pulmonary vascular bed in the newborn after a bidirectional Glenn will not be limited by pulmonary vasoconstriction, but rather by other regulatory mechanisms. Rather than refractory pulmonary vascular tone, it is likely that the limiting factor is pulmonary vascular cross-sectional area insufficient in the newborn to permit adequate passive blood flow through the lungs. Alternative treatment strategies may combine agents to accelerate postnatal growth of vessels for several days before a planned operation and then use NO postoperatively to avoid reactive pulmonary vasoconstriction.

Although not directly applicable to the newborn, the modified Fontan procedure is the ultimate reconstructive surgery for patients with a single ventricle. The Fontan physiology succeeds only with very low pulmonary vascular resistance, because flow through the lungs is conducted passively without a pumping chamber. NO has been used to considerable advantage by Macrae et al in the postoperative management of these patients.[49]

Chronic NO Use

Although outpatient use of inhaled NO has been reported in a small number of adults, its use in younger patients with heart disease or as a therapeutic bridge to lung or heart lung transplantation is largely unstudied. NO inhibits smooth muscle growth and matrix protein synthesis in the extracellular matrix. It also reduces hypoxic remodeling in the rat lung,[50-53] suggesting that it might have a salutary effect on scarring or pathological remodeling in the human lung. We hypothesized that the antioxidant and antiproliferative effects of NO combined with its antihypertensive action might provide a theoretical basis for prolonged treatment of idiopathic pulmonary hypertension. This might be particularly applicable to infants, who by virtue of their young age, have substantial capacity for smooth muscle regression, alveolar growth, and angiogenesis. We treated three infants younger than 3 months old who had severe unexplained pulmonary hypertension (biopsy-proven and presumed to be fatal) with a 25-day treatment regimen including inhaled NO. At the end of the treatment period, they had significantly lower (nearly normal) pulmonary artery pressures without recurrence of pulmonary hypertension during 3 to 22 months of follow-up. Although no conclusion can be drawn from such limited experience, it has prompted us to reevaluate our notion about presumed irreversibility of "primary" pulmonary hypertension early in life.

Adverse Effects

Rebound Pulmonary Hypertension

We observed in all patients with TAPVC after prolonged treatment with NO that a transient elevation in pulmonary artery pressure routinely occurred when NO was successfully discontinued (Fig 8). Previous reports have described the abrupt return of pulmonary hypertension to systemic levels when NO was temporarily discontinued. When this phenomenon occurs very early in the postoperative course, and is accompanied by systemic hypotension and hypoxia, one is inclined to ascribe the changes to persistence of the underlying pulmonary hypertensive disorder. We described a somewhat different phenomenon. After several hours (12 to 72) of postoperative treatment and recovery NO could be discontinued, but a transient increase in pulmonary artery pressure was always observed. During the first minutes after successful NO withdrawal, pulmonary artery pressure increased moderately (peak effect 7 ± 3 minutes after withdrawal) and then declined to very low levels without impact on systemic hemodynamics. These changes were complete within 1 hour of withdrawal and were not attributable to any change in ventilation or pharmacological support.[29]

Rebound pulmonary hypertension is not unique to inhaled vasodilators, but its causes are unclear. Negative feedback inhibition by exogenous NO has been postulated to account for this observation and shown to exist for inducible[54] and endothelial[55] NO synthase in vitro. NO donor agents inhibit endothelial NO biosynthesis in bovine arterial ring preparations by an apparent negative feedback on endothelial NO synthase. The arterial rings recovered responsiveness to endothelium-dependent relaxing agents within 30 to 40 minutes of withdrawing the NO donor agent, similar in timing to our witnessed rebound.[56] Decreased endogenous production of exhaled NO from smokers could also support a negative feedback theory.[57]

Alternatively inhaled NO may play an unknown role in the modulation of endogenous pulmonary vasoconstrictors. It is reported that after abrupt withdrawal of nitroprusside (an NO donor), a transient rebound phenomenon exists.[58] Accordingly, one could hypothesize that pulmonary vasodilation by NO provoked secondary production or activation of vasoconstrictors. With the short half-life of NO, abrupt discontinuation allowed a brief period of unopposed vasoconstriction until stimulation of endogenous vasodilators or change in the stimulus for vasoconstriction achieved a new balance of vasomotor tone. A third alternative is that exposure

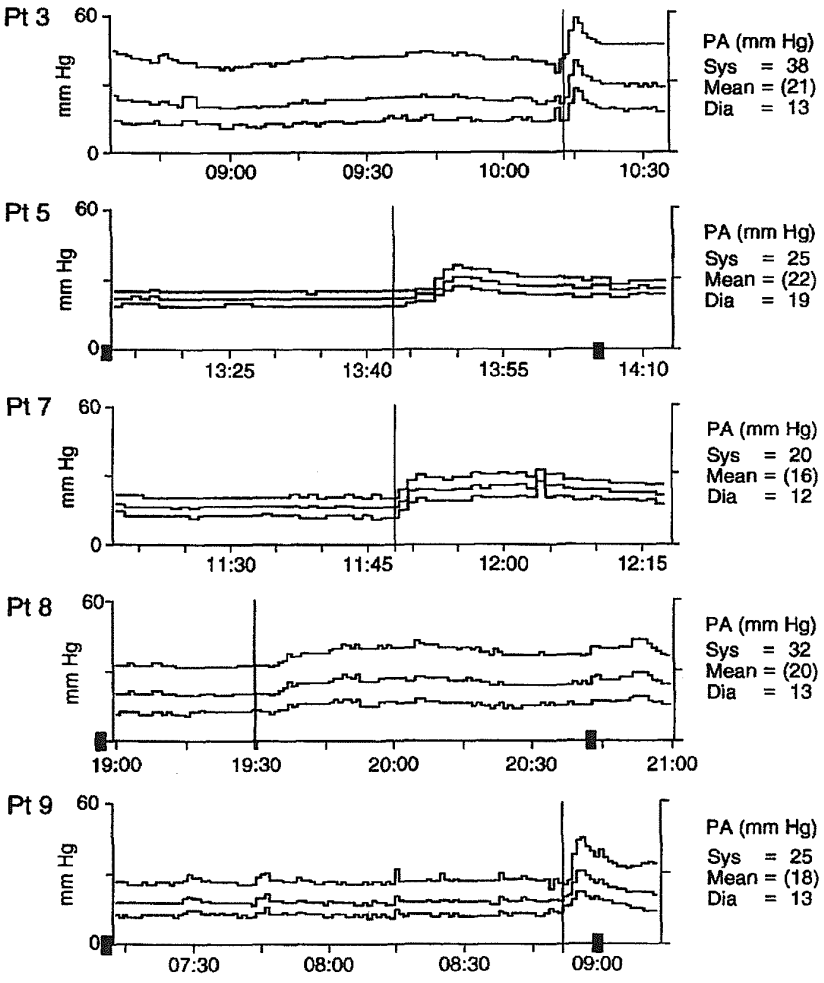

Figure 8. Bedside tracings of pulmonary artery (PA) pressure (systolic, mean, diastolic) for 5 patients (Pt) with TAPVC receiving prolonged NO plotted against time. Cursor represents time of withdrawal of NO; pulmonary artery pressures at time of withdrawal are displayed to the right of each tracing. In each patient a transient increase is observed, which dissipates without reinstitution of NO. (Reprinted with permission from the Society of Thoracic Surgeons [The Annals of Thoracic Surgery, 1996, Vol 62, pp 1759-1764].[29])

to exogenous NO altered membrane receptor conformation in vascular smooth muscle which reconfigured within 30 to 60 minutes after NO was withdrawn.

Rebound hypertension confounds assessment of whether postoperative pulmonary hypertension has resolved. NO therapy may be prolonged unnecessarily if clinicians are unaware that a moderate increase in pulmonary artery pressure on withdrawal may be transient and well tolerated if the underlying pathological process has improved. During weaning of NO, if mild elevations in pulmonary artery pressure are observed, it seems prudent to continue careful observation if the effect is transient and systemic hemodynamic stability is not impaired. Dose response testing for inhaled NO should be undertaken during the initial exposure to NO, because information obtained during weaning may reflect rebound effects and not the true dose-response relationship.

Appreciation of rebound pulmonary hypertension and its transient characteristic may facilitate weaning from NO and has important implications for patients with persistent pulmonary hypertensive disorders when interruption of NO is necessary. If the underlying pulmonary hypertensive process has not resolved, then the tendency for an abrupt increase in pulmonary artery pressure may be hazardous if NO therapy must be withdrawn or interrupted. For example, one should continue to provide a source of NO when suctioning or changing NO tanks because abrupt discontinuation can result in cardiovascular col-

lapse.[59-61] If withdrawal of NO is necessary before resolution of the pathological process, hemodynamic instability may be expected. If a labile patient with pulmonary hypertension is stabilized with NO before transfer to a specialized center for further management, NO should be available during patient transport.

Severe Left Ventricular Dysfunction

Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension. In adults with ischemic cardiomyopathy, sudden pulmonary vasodilation may occasionally unload the right ventricle sufficiently to increase pulmonary blood flow and harmfully augment preload in a compromised left ventricle. The attendant increase in left atrial pressure may produce pulmonary edema.[62] This is not likely to arise from any negative inotropic effect of NO[63] and may be ameliorated with vasodilators or diuretics. A different but related phenomenon may be operative in the newborn with severe left ventricular dysfunction and pulmonary hypertension. In these patients, the systemic circulation may depend in part on the ability of the right ventricle to sustain cardiac output through a right-to-left shunt across the patent ductus arteriosus. Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation. Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively right to left shunting at the ductus arteriosus, NO should be used with extreme caution, if at all. We and others have reported adverse outcomes in this circumstance.[64,65]

NO Dosage and Toxicity

There has been concern over potential NO induced cellular injury during exogenous exposure to the drug, as well as the generation of nitrogen dioxide and methemoglobinemia during the delivery of NO (see article by Dr Darley-Usmar). If the dose of NO is maintained below 40 ppm, there have been few acute problems reported as the result of methemoglobinemia or excessive nitrogen dioxide concentrations. At a dose of 80 ppm, we have reported in a very few infants a transient elevation of methemoglobin.[66] Optimal dosing of NO to maximize pulmonary vascular relaxation without incurring toxic side effects, systemic hypotension, or an increase venous admixture is unclear. Miller showed in 10 infants and children that low and potentially less toxic doses of NO were effective after cardiac surgery, with nearly identical response at 2 ppm compared with 10 and 20 ppm.[39] Day showed little additional value with 60 ppm over 12 ppm in patients with congenital heart disease.[67] However, Roberts et al have shown a dose-response relationship up to 80 ppm in a similar population.[68]

Maximal pulmonary vasodilator response to inhaled NO may occur at higher doses than that which produce optimal ventilation perfusion matching in patients with elevated pulmonary artery pressure and severe pulmonary parenchymal disease. By redistributing pulmonary blood flow away from underventilated alveoli toward normally ventilated areas of lung, inhaled NO in very low concentrations (<1 ppm) may improve intrapulmonary shunt fraction and raise PaO_2. It has been suggested that this effect may be optimized at doses of inhaled NO that are low (1 to 10 ppm), even though maximal pulmonary vasodilation occurred in the same patients at higher NO doses (10 to 100 ppm) among 12 adult patients with ARDS.[69] Improved oxygenation was lost at the higher NO doses in these patients in whom pulmonary vasodilation was maximized. Presumably, this occurred from a "spillover" effect of NO into poorly ventilated lung with loss of preferential delivery to and vasodilation of better ventilated areas. Thus, the desirable dose may depend in part on the severity of the pulmonary artery hypertension versus the severity of intrapulmonary shunting from lung disease. It seems likely that the recommended starting dose of NO for newborns with congenital heart disease will lie between 5 and 40 ppm.

Delivery Considerations

The potential toxicity of NO underscores the importance of developing reliable delivery and monitoring systems. Newborns are typically ventilated with devices designed to operate with continuous fresh gas flows from which all tidal breaths are derived. Stable NO concentrations can be achieved by titrating NO directly from the source tank into the inspiratory side of the continuous gas flow of the ventilator.[70] The resi-

dent times of NO and oxygen are minimized in continuous flow delivery systems because the gases are continuously purged through the ventilator. This system is limited to use in small patients who never require peak inspiratory flow rates greater than 10 to 12 L/min. It uses substantial amounts of NO gas and can be complicated by scavenging systems that interfere with the exhalation valve of the ventilator. NO source tanks are balanced with nitrogen and are available in a variety of concentrations from 100 to 10,000 parts per million (ppm). As NO is titrated into a delivery circuit, nitrogen will dilute the set FiO_2. Using a ventilator gas flow rate of 9 L/min and a NO source tank of 800 ppm, 1 L/min flow of NO gas will be diluted to 80 ppm in inspiratory gas flow with a maximal FiO_2 of .90. Because doses as low as 1 ppm may achieve therapeutic benefit, low-flow meters are needed to obtain a wide range of NO doses. Nitric oxide can be titrated into other continuous flow devices such as high frequency ventilators and continuous positive airway pressure systems.[71]

An ideal delivery system uses medical grade quality gas manufactured by a process approved by the Food and Drug Administration. It minimizes the duration of gas in the delivery circuit, can deliver a wide range of precise NO doses with uniform mixing despite variable flow rates, has on-line analysis of NO, NO_2 and oxygen, incorporates stringent controls for exhaled gases, and has alarms to protect against excessive dosing or inadvertent discontinuation. Because rebound pulmonary hypertension or respiratory collapse after prolonged inhalation of NO in some patients represents an additional hazard of abrupt interruption of NO delivery, an appropriate alarm and back-up supply of NO must be in place. The system should be adaptable to different clinical situations, oxygen and NO concentrations should be independently controlled, and when used in conjunction with mechanical ventilation should not interfere with ventilator functions. Commercial products are just now available that use mass flow-controller technology capable of rapid and precise regulation and mixing of NO, oxygen, and air gas flows.[72] When integrated into a microprocessor-governed, flow-sensing circuit, these devices promise to markedly improve the variability and precision of "homemade" systems, enabling the set NO concentration to remain constant during the dynamic flow of a single breath regardless of flow or ventilatory mode. They may be contained within standard ventilator housing with two separate control panels (oxygen and NO) directing output for the three relevant modules (air, oxygen, NO). Alternatively more flexible systems, similarly controlled, are now available to function in series with the most common mechanical ventilators.

Summary

Inhaled NO has emerged as an important diagnostic and therapeutic agent in the treatment of pulmonary hypertension among newborns with congenital heart disease. It is a selective pulmonary vasodilator with minimal adverse hemodynamic effects when administered and monitored in a judicious fashion. It seems to be more effective in the newborn than the older patient and has a number of advantages compared with intravenous vasodilators. Its hemodynamic benefit has been shown in patients with pulmonary hypertension associated with total anomalous pulmonary venous connection, congenital mitral stenosis, postoperative patients with preexisting left to right shunts, and other lesions. It can be used in the newborn to help discriminate anatomic obstruction to pulmonary blood flow from pulmonary vasoconstriction, and it may be used effectively in the treatment or prevention of pulmonary hypertensive crises after cardiopulmonary bypass. As an inhaled vasodilator, it has special advantage in the treatment of acute respiratory failure that may arise in conjunction with pulmonary hypertension after bypass. There are also potential benefits of chronic, outpatient administration of NO to facilitate growth, and beneficial remodeling of the abnormal pulmonary vasculature in unusual forms of idiopathic pulmonary hypertension identified in early infancy. However, none of the purported benefits of inhaled NO in children with congenital heart disease have been studied in a randomized, placebo-controlled manner with convincing demonstration of improved outcomes. This must be kept in mind when evaluating the risks and potential benefits of this new therapy.

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Combined Effects of Nitric Oxide and Oxygen During Acute Pulmonary Vasodilator Testing

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OBJECTIVES We compared the ability of inhaled nitric oxide (NO), oxygen (O_2) and nitric oxide in oxygen ($NO+O_2$) to identify reactive pulmonary vasculature in pulmonary hypertensive patients during acute vasodilator testing at cardiac catheterization.

BACKGROUND In patients with pulmonary hypertension, decisions regarding suitability for corrective surgery, transplantation and assessment of long-term prognosis are based on results obtained during acute pulmonary vasodilator testing.

METHODS In group 1, 46 patients had hemodynamic measurements in room air (RA), 100% O_2, return to RA and NO (80 parts per million [ppm] in RA). In group 2, 25 additional patients were studied in RA, 100% O_2 and 80 ppm NO in oxygen ($NO+O_2$).

RESULTS In group 1, O_2 decreased pulmonary vascular resistance (PVR) (mean ± SEM) from 17.2 ± 2.1 U·m^2 to 11.1 ± 1.5 U·m^2 ($p < 0.05$). Nitric oxide caused a comparable decrease from 17.8 ± 2.2 U·m^2 to 11.7 ± 1.7 U·m^2 ($p < 0.05$). In group 2, PVR decreased from 20.1 ± 2.6 U·m^2 to 14.3 ± 1.9 U·m^2 in O_2 ($p < 0.05$) and further to 10.5 ± 1.7 U·m^2 in $NO+O_2$ ($p < 0.05$). A response of 20% or more reduction in PVR was seen in 22/25 patients with $NO+O_2$ compared with 16/25 in O_2 alone ($p = 0.01$).

CONCLUSIONS Inhaled NO and O_2 produced a similar degree of selective pulmonary vasodilation. Our data suggest that combination testing with $NO+O_2$ provides additional pulmonary vasodilation in patients with a reactive pulmonary vascular bed in a selective, safe and expeditious fashion during cardiac catheterization. The combination of $NO+O_2$ identifies patients with significant pulmonary vasoreactivity who might not be recognized if O_2 or NO were used separately. (J Am Coll Cardiol 1999;33:813–9) © 1999 by the American College of Cardiology

Elevated pulmonary vascular resistance (PVR) complicates the evaluation, clinical course and outcome of patients with congenital heart disease or end-stage pulmonary disease. It is a crucial factor in determining the timing or type of intervention, and has been invoked as the primary determinant of mortality in many lesions (1,2). Opinion varies on what resistance must be achieved with vasodilator testing to insure safe operability for children with congenital heart disease. An increased or fixed elevation in PVR may deny patients the chance of corrective surgery, leaving them susceptible to the development of progressive obliterative pulmonary vascular disease and reduced life expectancy (3,4). Demonstration of pulmonary vasoreactivity in patients with end-stage pulmonary disease may differentiate patients who would benefit from long-term medical therapy (5,6) from those with high, fixed resistance who should be more urgently considered for lung transplantation (3). Safe and expeditious demonstration of maximal pulmonary vasodilation in patients with a reactive pulmonary bed is therefore an important objective.

Many vasodilators have been utilized for diagnostic testing during cardiac catheterization. Systemic vasodilators with their attendant risks of hypotension and increased intrapulmonary shunt may be hazardous (7), especially in patients with ventricular outflow tract obstruction. Breathing oxygen (O_2) remains a standard means of pulmonary vasodilator testing in pediatric cardiac catheterization laboratories (8,9). However, failure to respond to acute treatment with O_2 has been reported in some patients who did indeed have reactive pulmonary vasculature (3,10).

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator with minimal systemic effects and does not increase intrapulmonary shunting. It can be administered easily with O_2 or room air (RA) during cardiac catheterization by either ventilator or mask. The purpose of this study was to compare the ability of NO and O_2 to identify patients with a reactive pulmonary vascular bed during cardiac catheter-

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Abbreviations and Acronyms

FiO_2	= fraction of inspired oxygen
NO	= nitric oxide
NO_2	= nitrogen dioxide
O_2	= oxygen
$PaCO_2$	= partial pressure of carbon dioxide, arterial
PCO_2	= partial pressure of carbon dioxide
ppm	= parts per million
PVR	= pulmonary vascular resistance
RA	= room air

ization. We further compared the hemodynamic effects of breathing nitric oxide in oxygen ($NO+O_2$) to breathing O_2 alone during acute vasodilator testing.

METHODS

We enrolled patients between January 1992 and December 1996 who had mean pulmonary artery pressure ≥30 mm Hg, PVR >3 U·m^2, and were determined during catheterization to require vasodilator testing. We included for analysis 71 patients who had complete hemodynamic measurements to allow calculation of vascular resistances.

Study groups. The first 46 patients (group 1) were studied under the following four study conditions: A) in RA; B) after breathing 100% O_2 for 15 min; C) after another 15 min in RA, and D) after 15 min breathing NO at 80 parts per million (ppm) in 23% O_2 (NO+RA). As NO is titrated into a delivery circuit, the delivered fraction of inspired O_2 (FiO_2) is decreased. Therefore a small amount of supplemental O_2 (23%) was added to NO to avoid administration of a hypoxic gas mixture. The patients in group 1 had a median age of 6.5 years, range 4 months to 59 years.

Twenty-five additional patients (group 2) were studied in the following three conditions: A) in RA; B) after breathing 100% O_2 for 15 min, and C) after 15 min of inhaling 80 ppm NO in 91% O_2. This was the maximal FiO_2 attainable after dilution with 80 ppm of NO. Patients in group 2 had a median age of 3.5 years, range 5 months to 69 years.

The patients in each group represented a broad spectrum of diagnoses characteristic of a high volume pediatric cardiac catheterization laboratory. Most had unrepaired or previously palliated congenital heart disease, although some had end-stage pulmonary disease (Tables 1 and 2). Four of 46 patients in group 1 and three of 25 patients in group 2 were mechanically ventilated. The remainder in each group were breathing spontaneously. Sedation was given according to a routine, which included intravenous morphine and midazolam. Partial pressure of carbon dioxide (PCO_2) was normal throughout the study in both groups.

Hemodynamic assessment. Hemodynamic measurements included left atrial, right atrial, pulmonary and systemic arterial pressures during each of the conditions described above. Cardiac output was measured by thermodilution in patients without an intracardiac shunt. In those with shunts, O_2 consumption was measured (Waters Inc., model MM20, Rochester, Minnesota), and systemic and pulmonary blood flows were calculated using the Fick equation with inclusion of dissolved O_2. Errors related to sampling site variances were minimized by ensuring that, for each patient, venous samples were collected at the same site during each of the study conditions.

Delivery and monitoring of NO. Detailed descriptions of the technical aspects of our delivery of NO in both ventilated and spontaneously breathing patients have been published previously (11,12). We used NO gas (Scott Specialty Gases, Plumsteadville, Pennsylvania or BOC Gases, Murray Hill, New Jersey) of medical grade quality, which

Table 1. Diagnoses of Patients in Group 1 (n = 46)

Unrepaired Heart Disease (n = 26)	n	Repaired Heart Disease (n = 14)	n	Lung Pathology (n = 6)	n
VSD	5(1)	Complex single ventricle postpalliation	4(1)	Pulmonary emboli	3(2)
CAVC	5	TGA post Senning	3(1)	Restrictive lung disease (lupus)	1
Shone's syndrome	5	TGA/VSD post PAB	2	Primary pulmonary hypertension	1
PDA	2	TGA post Mustard	1	Cystic fibrosis	1
Cardiomyopathy	2	TGA post ASO	1(1)		
VSD with PDA	1	CAVC repair	1		
Truncus arteriosus	1	TOF/PA full repair	1		
ASD primum	1	ASD secundum	1		
ASD secundum with PDA	1				
Supracardiac TAPVC	1				
ASD secundum	1				
TGA/VSD	1				

In parentheses is the number of patients who did not respond to either oxygen or nitric oxide.
ASD = atrial septal defect; ASO = arterial switch operation; CAVC = complete atrioventricular canal; PAB = pulmonary artery band; PDA = patent ductus arteriosus; Shone's syndrome = multiple left-sided obstructive lesions; TAPVC = total anomalous pulmonary venous connection; TGA = transposition of the great arteries; TOF/PA = tetralogy of Fallot with pulmonary atresia; VSD = ventricular septal defect.

Table 2. Diagnoses of Patients in Group 2 (n = 25)

Unrepaired Heart Disease (n = 19)	n	Repaired Heart Disease (n = 3)	n	Lung Pathology (n = 3)	n
VSD	5	PDA	1	COPD	1(1)
CAVC	1	TAPVC with PV stenosis	1(1)	Primary pulmonary hypertension	1
Shone's syndrome	3	TOF/PA	1	Pulmonary emboli	1
PDA	1				
ASD secundum	4(1)				
VSD with mitral stenosis	2				
VSD with coarctation	1				
ASD primum	1				
Cardiomyopathy	1				

In parentheses is the number of patients who did not respond to either oxygen or nitric oxide in oxygen.
COPD = chronic obstructive pulmonary disease; PV = pulmonary vein; other abbreviations as in Table 1.

conformed to Food and Drug Administration standards. In the spontaneously breathing individuals NO was delivered using the titration technique from source tanks with an 800-ppm concentration. Flow rates greater than the patients' minute volumes were delivered through a one-way inspiratory valve to a face mask. The expired gases were scavenged using a reservoir bag and regulated wall suction. In the seven patients who were mechanically ventilated, ventilator settings were kept constant throughout the study. Nitric oxide, nitrogen dioxide (NO_2) and FiO_2 were continuously monitored from a sampling port at the airway (Thermoenvironmental Instruments Chemiluminescence model 42H, Franklin, Massachusetts or NOxBOX Electrochemical Inhaled NO Therapy Monitor, Bedfont Scientific USA, Medford, New Jersey). Peak measured NO_2 concentrations were recorded in all patients during delivery of the drug. Because there were no reports of methemoglobinemia during 15-min diagnostic trials of NO at 80 ppm (11), we eventually ceased to routinely measure methemoglobin levels during brief inhalations. Therefore, methemoglobin levels were obtained by cooximetry (CIBA-Corning model 2500, Medfield, Massachusetts) after 15 min in the first 22 of 46 patients in group 1 and not thereafter. Written informed consent was obtained from the patients or their parents under a protocol approved by the Clinical Investigation Committee of Children's Hospital and submitted to the Food and Drug Administration.

Statistical analysis and calculations. Results are presented as mean values ± SEM. Vascular resistances were calculated using standard equations and were expressed in Wood units corrected for body surface area ($U \cdot m^2$). Groups 1 and 2 were analyzed separately with patients in each group acting as their own controls. Repeated measures analysis of variance was used to look for differences in the measurements over the four study conditions in group 1 and the three conditions in group 2. If differences were found, then the Bonferroni multiple comparisons procedure was used to determine where differences existed. A p value <0.05 was considered significant.

RESULTS

Group 1: comparison of RA, O_2, RA and NO+RA. Pulmonary vascular resistance differed across the four conditions, ($p < 0.0001$) (Table 3). Oxygen decreased PVR from 17.2 ± 2.1 $U \cdot m^2$ to 11.1 ± 1.5 $U \cdot m^2$ ($p < 0.05$). Administration of inhaled NO at 80 ppm in RA caused a comparable decrease from 17.8 ± 2.2 $U \cdot m^2$ to 11.7 ± 1.7 $U \cdot m^2$ ($p < 0.05$) (Fig. 1). Comparison of the mean percentage decreases from RA to O_2 (36.9 ± 3.3%) and RA to NO+RA (35.1 ± 3.5%) revealed no difference by paired *t* test. Changes in pulmonary artery pressures may not reflect pulmonary vasodilation, because there were patients with intracardiac shunts. Nevertheless, the mean pulmonary artery pressure was significantly lower in both O_2 and NO+RA compared with RA despite increases in pulmonary blood flow in 21 of 23 patients with intracardiac shunts during treatment.

Mean systemic arterial pressure, systemic vascular resistance, right atrial pressure, left atrial pressure, heart rate, pH and P_{CO_2} did not change with administration of O_2 or NO. Arterial P_{CO_2} (Pa_{O_2}) increased from 66 ± 3 mm Hg in RA to 278 ± 23 mm Hg with 100% O_2; however, there was no significant difference in Pa_{O_2} between RA and NO+RA (68 ± 4 vs. 73 ± 4 mm Hg).

Using a reduction in PVR of 20% or more as a marker for responsiveness, we compared individual patient results to O_2 and NO+RA (Fig. 2). Oxygen caused a positive response in 36/46 patients. Of the 10 nonresponders, four responded with a 20% or more decrease to NO. Nitric oxide in RA caused a positive response in 32/46. Of the 14 nonresponders to NO+RA, eight responded to O_2. Six patients did not respond to either vasodilator (Table 1).

The peak NO_2 level was recorded in all 46 patients and was 1.3 ± 0.2 ppm. Methemoglobin measured at the conclusion of the 15-min period of NO inhalation in 22/46 patients was 0.8 ± 0.1%.

Group 2: comparison of RA, O_2 and NO+O_2. Pulmonary vascular resistance differed across the three conditions ($p < 0.0001$) (Table 4). Pulmonary vascular resistance

Table 3. Hemodynamic Data for Group 1

Variable (mean ± SEM)	A: RA	B: Oxygen	C: RA	D: NO+RA	ANOVA p Value
PVR (U·m^2)	17.2 ± 2.1	11.1 ± 1.5	17.8 ± 2.2	11.7 ± 1.7	< 0.0001*†
mPAp (mm Hg)	62.7 ± 3.3	54.9 ± 3.1	60.9 ± 3.4	51.2 ± 3.0	< 0.0001*†
LAp (mm Hg)	13.7 ± 0.8	14.6 ± 1.0	14.0 ± 0.9	14.9 ± 1.1	0.05
CI (liters/min/m^2)	3.6 ± 0.3	3.2 ± 0.2	3.5 ± 0.2	3.3 ± 0.2	0.19
RAp (mm Hg)	9.0 ± 0.5	9.1 ± 0.5	8.8 ± 0.5	8.4 ± 0.5	0.08
MAP (mm Hg)	79.2 ± 2.3	81.0 ± 2.3	79.5 ± 2.6	79.4 ± 2.6	0.55
SVR (U·m^2)	24.2 ± 1.8	25.7 ± 1.6	24.2 ± 1.8	24.8 ± 1.7	0.33
pH	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01	7.35 ± 0.01	0.43
P_{CO_2}	41.6 ± 1.1	41.2 ± 1.0	41.8 ± 1.1	43.0 ± 1.2	0.07
P_{O_2}	65.6 ± 2.7	277.6 ± 23.2	68.1 ± 3.6	73.5 ± 3.5	< 0.0001*
Heart rate	108 ± 4	107 ± 4	104 ± 5	105 ± 5	0.24

*Variable in oxygen (B) is different than in room air (A) ($p < 0.05$). †Variable in nitric oxide (D) is different than in room air (C) ($p < 0.05$).

ANOVA = analysis of variance; CI = cardiac index; LAp = left atrial pressure; MAP = mean arterial blood pressure; mPAp = mean pulmonary artery pressure; P_{CO_2} = partial pressure of carbon dioxide; P_{O_2} = partial pressure of oxygen; PVR = pulmonary vascular resistance; RA = room air; RAp = right atrial pressure; SVR = systemic vascular resistance.

decreased from 20.1 ± 2.6 U·m^2 in RA to 14.3 ± 1.9 U·m^2 in O_2 and further to 10.5 ± 1.7 U·m^2 in NO+O_2 (Fig. 3). Pulmonary vascular resistance was significantly lower in O_2 compared to RA ($p < 0.05$). The PVR with combination therapy was statistically lower than that measured in air or in O_2 ($p < 0.05$ for both). Oxygen caused a reduction in PVR from baseline of 20% or more in 16 of 25 patients. Of the remaining nine patients, six responded with a 20% or more decrease when inhaling NO+O_2. Three patients did not have a positive response to either O_2 or the combination of O_2 and NO (see Table 2). Using the McNemar's test, if responsiveness differed between the two treatments, patients were more likely to respond to NO+O_2 than to O_2 alone ($p = 0.01$). Ten of the 25 patients underwent complete surgical repair of their cardiac defects within 1 month of their catheterization. Those 10 patients had a baseline PVR in RA of 12.9 ± 1.9 U·m^2 that decreased to 7.1 ± 1.9 U·m^2 in O_2 and to 4.1 ± 1.9 U·m^2 in NO+O_2. Each patient undergoing surgical repair had a baseline PVR in RA >6 U·m^2. Five of 10 had PVR >6 U·m^2 in O_2, but only one had PVR >6 U·m^2 in NO+O_2. All 10 patients survived and were discharged home on median postoperative day 5.5, range 4 to 29.

Mean pulmonary artery pressure decreased from 63.4 ± 3.7 mm Hg in RA to 57.7 ± 3.5 mm Hg in O_2 to 50.6 ± 3.5 mm Hg in NO+O_2. This occurred despite an increase in pulmonary blood flow in 13 of 15 patients with shunts. The pulmonary artery pressure with NO+O_2 was significantly lower than that measured in air or in O_2 ($p < 0.05$ for both). There was no difference between left atrial pressure in RA and in O_2. Left atrial pressure was significantly higher in NO+O_2 (15.5 ± 1.3 mm Hg) than in RA (13.1 ± 1.1 mm Hg) or O_2 (12.7 ± 1.0 mm Hg).

Mean systemic blood pressure increased over the three study conditions, from 76.8 ± 2.9 mm Hg in RA to 80.6 ± 2.5 mm Hg in O_2 to 83.4 ± 2.6 mm Hg in NO+O_2. Blood pressure was significantly higher in NO+O_2 than in RA, but not statistically different from blood pressure in O_2. Cardiac index, systemic vascular resistance, right atrial pressure, heart rate, pH and P_{CO_2} did not change. Arterial

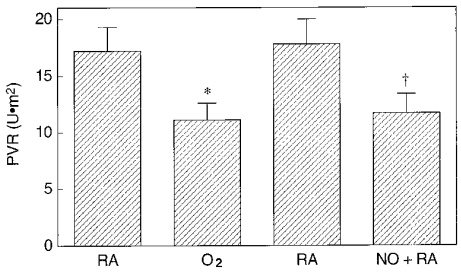

Figure 1. Pulmonary vascular resistance (PVR) (mean ± SE) differed across the four study conditions in group 1 ($p < 0.0001$); PVR was lower in oxygen (O_2) compared with room air (RA) (*) and was lower in nitric oxide in RA (NO+RA) compared with RA (†) ($p < 0.05$ for both).

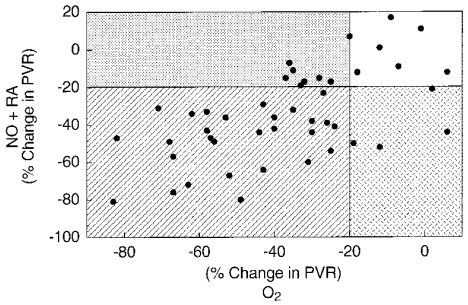

Figure 2. Individual patients' percentage change in PVR with O_2 is plotted against percentage change in PVR with NO+RA. Using a 20% decrease in PVR as a marker for responsiveness, some patients responded to one drug only. Neither O_2 nor NO+RA identified all patients with pulmonary vasoreactivity. Abbreviations as in Figure 1.

Table 4. Hemodynamic Data for Group 2

Variable (mean ± SEM)	A: RA	B: Oxygen	C: NO+O_2	ANOVA p Value
PVR (U·m^2)	20.1 ± 2.6	14.3 ± 1.9	10.5 ± 1.7	< 0.0001*†‡
mPAp (mm Hg)	63.4 ± 3.7	57.7 ± 3.5	50.6 ± 3.5	0.0002†‡
LAp (mm Hg)	13.1 ± 1.1	12.7 ± 1.0	15.5 ± 1.3	0.002†‡
CI (liter/min/m^2)	3.1 ± 0.3	3.2 ± 0.3	3.2 ± 0.3	0.93
RAp (mm Hg)	8.0 ± 0.7	8.3 ± 0.8	8.4 ± 0.7	0.78
MAP (mm Hg)	76.8 ± 2.9	80.6 ± 2.5	83.4 ± 2.6	0.004‡
SVR (U·m^2)	26.8 ± 2.7	28.1 ± 2.6	29.8 ± 3.0	0.34
pH	7.38 ± 0.01	7.36 ± 0.01	7.36 ± 0.01	0.08
P_{CO_2}	38.8 ± 1.2	39.7 ± 1.5	40.5 ± 1.7	0.27
P_{O_2}	67.3 ± 3.9	277.6 ± 30.4	302.8 ± 27.9	< 0.0001*‡
Heart rate	108 ± 4	107 ± 4	105 ± 5	0.58

*Variable in oxygen (B) is different than in room air (A) ($p < 0.05$). †Variable in NO+O_2 (C) is different than in oxygen (B) ($p < 0.05$). ‡Variable in NO+O_2 (C) is different than in room air (A) ($p < 0.05$). Abbreviations as in Table 3.

partial pressure of O_2 was significantly higher both in O_2 and in NO+O_2 as compared with RA. Arterial partial pressure of O_2 was not different in NO+O_2 compared with O_2 (302.8 ± 27.9 vs. 277.6 ± 30.4 mm Hg). The peak NO_2 level during NO delivery was 2.3 ± 0.3 ppm.

DISCUSSION

We compared the inhaled vasodilators O_2 and NO in 71 patients during acute vasodilator testing at cardiac catheterization. In 46 patients, 100% O_2 and inhaled NO at 80 ppm in air produced comparable and selective decreases in mean pulmonary artery pressure and PVR. However, O_2 or NO used separately failed to identify all patients with a significant capacity for pulmonary vasodilation. The combination of NO (80 ppm) with 91% O_2 in an additional group of 25 patients produced significantly more pulmonary vasorelaxation compared with O_2 used alone. In 22/25 patients there was a positive pulmonary vasodilator response during combination therapy compared to only 16/25 when breathing O_2 alone. None of the 71 patients studied showed any evidence of toxicity from either drug during the brief period of this diagnostic trial. Our data suggest that combination testing with NO in O_2 provides additional pulmonary vasodilation, can be safely and accurately delivered to patients during diagnostic cardiac catheterization and can rapidly identify patients with pulmonary vasoreactivity. The combination of agents appears to identify patients with significant pulmonary vasoreactivity who might not be recognized if O_2 or NO were used separately.

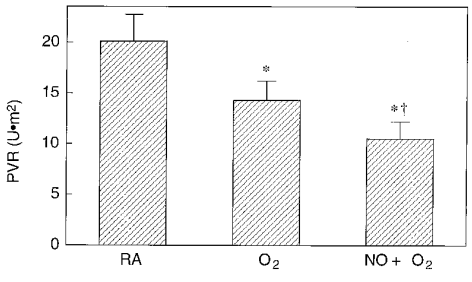

Figure 3. Pulmonary vascular resistance (mean ± SE) differed across the three study conditions in group 2 ($p < 0.0001$); PVR was lower in O_2 compared with RA (*) and was lower in NO+O_2 compared with RA (*) and O_2 (†) ($p < 0.05$ for all comparisons). Abbreviations as in Figure 1.

Importance of vasodilator testing. The precise stage when pulmonary vascular disease has progressed to a point where surgical repair of congenital heart lesions cannot be safely performed is unknown. Morphologic criteria (2) and pulmonary hemodynamics (13) are useful, but imprecise. Pulmonary vascular resistance calculated to be more than 6 to 8 U·m^2 has been shown to be associated with poor operative outcome regardless of lung histology (1,4,14). In contrast, patients who respond to vasodilators with a PVR less than 6 to 8 U·m^2 do well postoperatively (13). Demonstration of a reactive pulmonary bed in patients being evaluated for transplantation has enabled patients to be offered a single organ heart instead of heart–lung block with successful results (15). Patients with elevated resistance but reactive pulmonary vasculature may need more intensive postoperative care and presumably would be excellent candidates for NO therapy in the postoperative period should pulmonary hypertension emerge. Response to acute vasodilator testing in patients with primary pulmonary hypertension is an important marker for survival (3) and may identify patients who would benefit from chronic medical therapy (5,6).

Comparison with other studies. Prior research in children with pulmonary hypertension has shown that O_2 failed to unmask all reversible pulmonary vasoconstriction (3,10). Prostacyclin administration in patients with pulmonary hypertension breathing O_2 caused further pulmonary vasodilation. However, prostacyclin can cause systemic side effects including tachycardia and hypotension (16). Previous studies of vasoreactivity in children during cardiac catheterization found variable responsiveness to NO that seemed to

parallel the progression of established vascular disease (17). Studies examining the efficacy of NO in O_2, including recent work by Allman and colleagues, have suggested differences between the responses to NO, O_2 and/or the combination of agents (18–20). Each prior study, however, has had insufficient power to establish a significant difference in PVR.

Nitric oxide causes vasorelaxation through a cyclic guanosine monophosphate–mediated pathway. The mechanism of vasorelaxation caused by O_2 is not clearly known (21). The fact that some patients responded to one agent with significant vasodilation but not the other, and that the majority of patients experienced increased vasodilation with combination therapy compared with O_2 alone, suggests that the mechanisms may not be identical.

Potential toxicities. The major recognized toxicities associated with inhaling NO are cytotoxic effects in the lung due to exposure to excess NO_2 and methemoglobinemia due to the intravascular binding to hemoglobin. Nitrogen dioxide will develop in delivery systems at a rate that is proportional to NO and O_2 concentrations and contact times between the two gases. When NO was delivered with maximal amounts of O_2 in this study, NO_2 levels averaged 2.3 ± 0.3 ppm, below the accepted environmental exposure level of 5 ppm (22). Nitrogen dioxide should be continuously monitored, especially in patients mechanically ventilated with circuits that do not use continuous gas flows. If patients receive prolonged treatment with NO in high concentrations of O_2, we recommend reduction in the NO dose to diminish potential dose-related toxicity. There have been no reports of clinically significant methemoglobinemia during brief exposure to NO at doses as high as 80 ppm. Methemoglobin measured at the conclusion of the 15-min period of NO inhalation in 22/46 patients was 0.8 ± 0.1%. This along with previously published results (11) supports the contention that routine measurement of methemoglobin may be unnecessary during brief diagnostic trials of NO.

It is notable that the combination of NO in O_2 resulted in an increase in left atrial pressure compared with RA or O_2 alone. Reports have suggested that O_2 (23) or NO (24) may have deleterious effects to patients with heart failure. In this study no patient demonstrated clinically important pulmonary edema, hemodynamically significant systemic vasoconstriction or decreased cardiac index during the brief administration of O_2 or NO in O_2. Nevertheless, we believe that NO, especially when used with O_2, should be carefully monitored in patients with elevated left atrial pressures due to the potential induction of pulmonary edema.

Study limitations. The patient population studied was quite heterogeneous. However, this accurately reflects the typical spectrum of patients presenting for vasodilator testing during cardiac catheterization. Subgroup analysis of patients with congenital heart disease showed no differences in response compared to the group as a whole. Patients with lung pathology analyzed separately showed similar results, but numbers were too small to form conclusions. Subgroup analysis of patients with left to right shunts did not reveal any difference in response compared to those without shunts. The definition of responder and nonresponder is arbitrary, but a 20% change is often used in drug testing as a marker of responsiveness. There was no apparent predictive marker in patients who responded to one agent but not the other. It may be that repeated exposure to O_2 or NO would minimize differences between responders and nonresponders. Nonetheless, a single exposure to a drug is the common catheterization protocol. Limited information exists concerning optimal dosing of NO, with some investigators showing maximal vasodilation at doses as low as 2 ppm (19), and others demonstrating a dose–response relationship up to 80 ppm in a similar population (18). This study was designed as a brief diagnostic trial in a catheterization laboratory to determine the most effective and inclusive method of identifying patients with pulmonary vasoreactivity. Accordingly, 80 ppm was used during this brief testing with the appreciation that, if delivered for prolonged periods, it may be associated with dose-related increased toxicity. This study was not designed to demonstrate differences in long-term patient outcomes or clinical value of vasodilator testing. Maximal vasodilatory capacity may be of limited clinical value in some patients. Nevertheless, as a result of information acquired during combination therapy, some patients were offered surgery who did not respond to NO or O_2 alone; all patients survived.

Summary. Individually, NO and O_2 produced significant and comparable selective pulmonary vasodilation in a heterogeneous group of patients presenting to cardiac catheterization for pulmonary vasodilator testing. However, neither agent used separately identified all patients with the capacity to relax their pulmonary vascular bed. The combination of NO+O_2 caused significantly greater pulmonary vasodilation compared to O_2 and identified patients who had pulmonary vasoreactivity that was not appreciated during O_2 breathing alone. This study suggests that combination testing with NO+O_2 provides additional pulmonary vasodilation in patients with a reactive pulmonary vascular bed in a specific, safe and expeditious fashion during cardiac catheterization. Nitric oxide in O_2 distinguishes patients with significant pulmonary vasoreactivity who might not be identified using either agent separately.

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Cardiovascular Effects of Inhaled Nitric Oxide in Patients With Left Ventricular Dysfunction

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Background Pulmonary vascular resistance (PVR) is frequently elevated in patients with advanced heart failure. Nitric oxide (NO), which contributes to the activity of endothelium-derived relaxing factor, causes relaxation of pulmonary arteries and veins in vitro. Inhalation of NO gas causes pulmonary vasodilation in patients with primary and secondary forms of pulmonary hypertension.

Methods and Results To test the hypothesis that inhalation of NO gas lowers PVR in patients with heart failure, we studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with New York Heart Association class III (n=5) and class IV (n=14) heart failure due to left ventricular (LV) dysfunction. Although inhalation of NO had no effect on pulmonary artery pressures, the PVR decreased by 31±7% ($P<.001$) due to a 23±7% increase ($P<.001$) in pulmonary artery wedge pressure and despite a 4±2% ($P<.05$) decrease in cardiac index. The magnitude of the decrease in PVR with inhaled NO was inversely related ($r=-.713$; $P<.001$) to the baseline PVR. Inhaled NO had no effect on heart rate, systemic arterial pressure, systemic vascular resistance, or LV peak +dP/dt or −dP/dt.

Conclusions In patients with heart failure due to LV dysfunction, inhalation of NO causes a decrease in the PVR associated with an increase in LV filling pressure. These findings predict that inhaled NO, if used alone at this dose (80 ppm), may have adverse effects in patients with LV failure. (*Circulation*. 1994;90:2780-2785.)

Key words • nitric oxide • lung • heart failure • endothelium-derived factors

The endothelium plays an essential role in the dynamic regulation of vascular tone by synthesizing and releasing a variety of substances, one of which, endothelium-derived relaxing factor (EDRF), has the physicochemical properties of nitric oxide (NO) or a closely related substance.[1,2] Endogenous NO produced by endothelial cells diffuses into neighboring vascular smooth muscle cells, where it binds to the heme component of guanylyl cyclase, thereby activating the enzyme, resulting in increased cyclic GMP production and relaxation.[3,4] Arterial and venous endothelial cells in the pulmonary vasculature produce NO constitutively and in response to a variety of stimuli.[5-8] NO appears to be involved both in the regulation of basal pulmonary vascular resistance (PVR)[9,10] and in counterregulating the effects of vasoconstrictor substances.[11-15]

PVR is frequently increased in patients with advanced heart failure. The underlying mechanism for increased PVR in heart failure is not known, but it almost certainly involves activation of vasoconstrictor pathways by the sympathetic nervous system, the renin-angiotensin system, and/or endothelin.[15,17] Although there is evidence that endothelium-dependent vasodilation is impaired in the systemic vasculature of both animal models[18] and patients with heart failure,[19-22] it is not known whether this mechanism contributes to increased PVR.

Inhalation of NO gas causes pulmonary vasodilation in patients with primary pulmonary hypertension[23] and pulmonary hypertension secondary to congenital heart disease[24] and to adult respiratory distress syndrome.[25] These observations suggest that inhaled NO might ameliorate pulmonary vasoconstriction, and they led to our hypothesis that inhalation of NO would lower PVR in patients with heart failure. To test this hypothesis, we studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with moderate to severe heart failure secondary to LV dysfunction from idiopathic or ischemic dilated cardiomyopathy.

Methods

Study Population

Nineteen patients with New York Heart Association functional class III (n=5) or IV (n=14) heart failure were studied. All patients were receiving digitalis, diuretics, and angiotensin-converting enzyme inhibitors. There were 15 men and 4 women, with a mean age of 52±3 years. The cause of heart failure was ischemic cardiomyopathy in 10 patients and idiopathic dilated cardiomyopathy in 9. The peak VO_2 averaged 9.9±1.6 $mL \cdot kg^{-1} \cdot min^{-1}$. The study protocol was approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women's Hospital, and written informed consent was obtained in all cases.

Hemodynamic Measurements

Vasodilators, converting enzyme inhibitors, digitalis, and diuretics were withheld on the morning of the catheterization. A 7F Swan-Ganz catheter (Arrow International, Inc) was placed in the pulmonary artery. Femoral artery pressure was monitored via an 8F side-arm sheath (Cordis Laboratories). In 10 patients, a 7F micromanometer-tipped pigtail catheter

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Table 1. Hemodynamic Effects of Inhaled NO in Patients With Congestive Heart Failure (n=19)

	Room Air	NO	P
HR, bpm	90±3	93±3	NS
MAP, mm Hg	79±3	81±3	NS
SVR, dyne·s·cm^{-5}	1102±104	1041±97	NS
PA, mm Hg	35±4	37±4	NS
PAWP, mm Hg	25±3	31±4	<.001
LVEDP, mm Hg; n=10	28±4	34±5	.02
PVR, dyne·s·cm^{-5}	228±30	119±13	<.001
PA−PAWP, mm Hg	11±1	6±0.5	<.001
SVI, mL/m^2	26±2	24±2	.03
CI, L·min^{-1}·m^{-2}	2.3±0.2	2.1±0.2	.03

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery measure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index; and CI, cardiac index.

(Millar Industries) was placed in the left ventricle (LV), allowing for simultaneous dP/dt and right heart pressure measurements. The ECG, femoral artery pressure, pulmonary artery pressure, and LV pressure were recorded on a strip chart recorder (Electronics for Medicine, PPG Biomedical Systems Division). Cardiac output was determined by the Fick method, based on the measured oxygen uptake (model MRM 2B, Waters Instruments, Inc) and oxygen content in the pulmonary and femoral arteries.[25] Oxygen content was calculated from the blood hemoglobin and oxygen saturation by standard methods.[26] Blood oxygen saturation was determined in duplicate samples on a Ciba-Corning model 270 Co-oximeter. LV peak +dP/dt (+dP/dt) and peak −dP/dt (−dP/dt) were computed on-line by an Electronics for Medicine amplifier (model 220A). Values for heart rate, arterial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure, LV systolic pressure, LV end-diastolic pressure

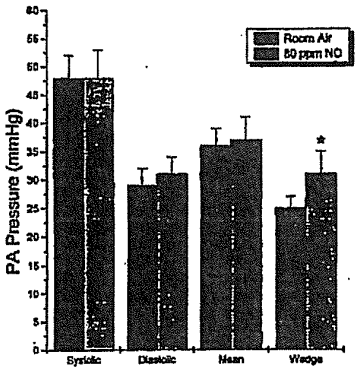

Fig 1. Bar graph showing effect of inhalation of NO gas (80 ppm, 10 minutes) on pulmonary artery (PA) pressures in 19 patients with heart failure secondary to left ventricular dysfunction. Measurements were made after the patients inhaled room air (shaded bars) or NO (solid bars) from a face mask for 10 minutes. *P<.001 vs room air.

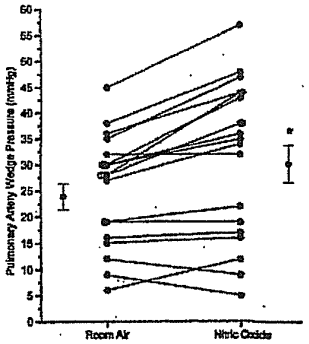

Fig 2. Graph showing pulmonary artery wedge pressure before and after a 10-minute inhalation of room air or NO. *P<.001 vs room air.

(LVEDP), and LV +dP/dt and −dP/dt were calculated by averaging at least 50 consecutive beats under each experimental condition.

Inhalation of Nitric Oxide

NO gas (800 ppm) and N_2 (Airco) were mixed by use of a standard low-flow blender (Low Flow MicroBlender, Bird Products Corp) before introduction into the inspiratory limb of a closed breathing circuit attached to a face mask. The inhaled concentrations of NO and oxygen were regulated separately. The inhaled O_2 concentration was measured directly with an on-line oximeter (Ohmeda Oximeter). The inhaled concentrations of NO, nitrogen dioxide (NO_2), and the higher oxides of nitrogen (NO_x) were measured continuously by a chemiluminescence technique (Chemiluminescent NO_x-NO_2 Analyzer, Thermo Environmental Instruments, Inc). The exhaled gases were scavenged by a vacuum system.

To establish baseline conditions, patients inhaled room air (F_{IO_2}, 21%; N_2, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (F_{IO_2}, 21%; N_2, 79%) via

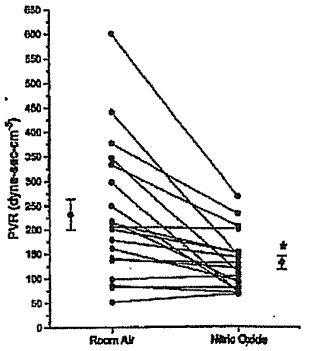

Fig 3. Graph showing effect of NO inhalation on pulmonary vascular resistance (PVR). *P<.001 vs room air.

face mask for 10 minutes, and hemodynamic measurements were repeated.

Statistical Methods

All data are presented as the mean±SEM. Differences between two observations for one variable within the same group were determined by two-tailed paired *t* test. Differences between groups were determined by two-tailed unpaired *t* test. Differences were considered significant if the null hypothesis could be rejected at the .05 probability level.

Results

Hemodynamic Effect of Inhaled NO

Baseline measurements during inhalation of room air revealed moderate LV failure with elevation of the LVEDP and mean pulmonary artery wedge pressure, and reduced stroke volume and cardiac indexes (Table 1). There was moderate reactive pulmonary hypertension, with an average PVR of 226±30 dyne · sec · cm^{-5}.

Inhalation of NO caused no change in heart rate, mean systemic arterial pressure, systemic vascular resistance, or pulmonary artery pressure (systolic, diastolic, or mean) but caused a 23±7% increase in the mean pulmonary artery wedge pressure (Table 1, Figs 1 and 2) associated with 4±2% and 7±2% decreases in cardiac index and stroke volume index, respectively (Table 1). The mean transpulmonary pressure gradient decreased by 35±7% (Table 1), and the PVR decreased by 31±7% (Table 1 and Fig 3).

The decrease in PVR was due to the increase in pulmonary artery wedge pressure, as shown by the correlation (r=−.848, P=.0001) between the changes in PVR and pulmonary artery wedge pressure (Fig 4A) and lack of correlation with changes in pulmonary artery pressure (Fig 4B; r=.13) or cardiac index (Fig 4C; r=.04). The increase in mean pulmonary artery wedge pressure was due to an increase in LV filling pressure, as shown by the correlation (r=.939, P<.0001) between the changes in LV end-diastolic pressure and pulmonary artery wedge pressure with inhaled NO (Fig 5).

TABLE 2. Hemodynamic Characteristics of Patients With a Change in Pulmonary Artery Wedge Pressure Above or Below the Median With Inhalation of NO

	% PAWP <0.26 (n=9)	% PAWP >0.26 (n=10)	P
HR, bpm	87±4	94±3	NS
MAP, mm Hg	75±3	84±3	.02
SVR, dyne · s · cm^{-5}	987±153	1218±148	NS
PA, mm Hg	29±5	42±5	.02
PAWP, mm Hg	21±4	28±4	.02
SVI, mL/m^2	30±2	21±2	.004
CI, L · min^{-1} · m^{-2}	2.6±0.2	1.9±0.2	.01
PVR, dyne · s · cm^{-5}	138±23	295±40	.002
LVEDD, cm	6.2±0.4	7.1±0.3	.04
$\dot{V}O_2$	9.6±0.1	11.7±0.8	NS

LVEDD indicates left ventricular end-diastolic dimension; $\dot{V}O_2$, peak oxygen consumption. Other abbreviations as in Table 1. n=19 for all parameters except EDD (n=16) and $\dot{V}O_2$ (n=17).

Hemodynamic Determinants of an Increase in Pulmonary Artery Wedge Pressure With Inhaled NO

The most prominent hemodynamic effect of NO inhalation was the increase in pulmonary artery wedge pressure (median increase, 26%). In the 10 patients with an increase in pulmonary artery wedge pressure of ≥26% (mean increase, 33±7%), the baseline pulmonary artery pressure, pulmonary vascular resistance, and LV end-diastolic dimension (by M-mode echocardiography; n=16) were higher and the cardiac index and stroke volume index were lower than in the 9 patients with an increase of <26% (Table 2). Thus, more severe LV dysfunction (as evidenced by higher left heart filling pressures, lower stroke volume, and larger LV cavity size) was present in the patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO.

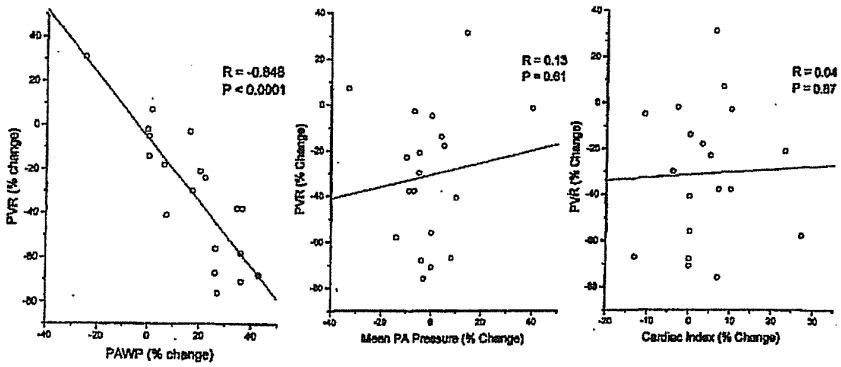

FIG 4. Scatterplots of regression analyses depicting the relation between the change in pulmonary vascular resistance (PVR) with NO (vs room air) and the change in pulmonary artery wedge pressure (PAWP) (left), mean PA pressure (middle), or cardiac index (right) in 19 patients.

The baseline PVR was more than twofold higher in the group that had the largest increases in pulmonary artery wedge pressure with inhaled NO (Table 2), suggesting that resting PVR might be a determinant or predictor of the response to inhaled NO. Consistent with this view, there was a strong correlation (r=−.713, P<.001) between the baseline PVR and the decrease in PVR with inhaled NO (Fig 6).

As an alternative approach to this issue, we identified a subgroup of 5 patients who had "compensated" LV failure, as defined by a pulmonary artery wedge pressure ≤18 mm Hg (mean, 12±2 mm Hg) and a cardiac index ≥2.5 $L \cdot min^{-1} \cdot m^{-2}$ (mean, 2.8±0.3 $L \cdot min^{-1} \cdot m^{-2}$). In these patients, inhalation of NO has no effect on pulmonary artery wedge pressure (+7±3%) or PVR (+5±13%). In the remaining 14 patients with "decompensated" LV failure (mean pulmonary artery wedge pressure, 30±2 mm Hg; mean cardiac index, 1.9±0.1 $L \cdot min^{-1} \cdot m^{-2}$), inhalation of NO increased the pulmonary artery wedge pressure by 27±3% (P<.001) and decreased the PVR by 43±7% (P<.001).

Effects of Inhaled NO on LV Function

Since it has been suggested that NO can depress the contractile function of isolated cardiac myocytes,[27] we considered the possibility that inhaled NO exerted a negative inotropic effect on the LV. A negative inotropic effect of inhaled NO was suggested by a decrease in stroke volume index despite an increase in pulmonary artery wedge pressure (Fig 7A). However, in the 10 patients in whom it was measured, inhaled NO had no effect on LV peak +dP/dt, despite increasing LVEDP by 8±1 mm Hg (Fig 7B). LV peak −dP/dt, which reflects isovolumic relaxation in the absence of changes in loading conditions or heart rate,[28,29] was also not affected by inhaled NO (baseline, 807±140 mm Hg/s; NO, 800±139 mm Hg/s; P=NS; n=10).

Discussion

The major finding of this study is that in patients with reactive pulmonary arterial hypertension secondary to LV failure, inhalation of NO causes reciprocal changes in the PVR (decrease) and LV filling pressure (increase). In patients with primary pulmonary hypertension, inhalation of NO causes a decrease in pulmonary artery pressure.[23] In contrast, in patients with LV failure, we found that inhalation of NO is associated not with a decrease in pulmonary artery pressure, but rather, with an increase in LV filling pressure that accounts for the decrease in PVR. Preliminary reports from two other groups[30,31] also indicate a similar effect of inhaled NO on LV filling pressure in patients with LV failure.

The observed decrease in transpulmonary artery pressure gradient, particularly in the setting of no change or a small decrease in cardiac output, indicates that inhaled NO caused pulmonary vasodilation. NO diffuses readily through tissues, and therefore inhalation of NO may increase the concentration of NO in the vicinity of vascular smooth muscle cells in pulmonary resistance vessels, thereby exerting a direct vasodilator effect.

We believe that the NO-induced increase in LV filling pressure is due to a small increase in LV volume that occurred secondary to an increase in pulmonary venous return to the LV. For a given pulmonary artery pressure, a decrease in PVR will result in an increase in the net driving force for LV filling. Although an increase in LV volume would result in increases in ejection fraction and stroke volume in a normal LV, in our patients LV function was severely depressed and may have been on the flat portion of the Starling relation. In addition, an NO-induced increase in LV volume may have increased the magnitude of functional mitral regurgitation that is present in the majority of such hearts.[32,33] Thus, an NO-induced redistribution of blood from the right ventricle to the LV may occur with no increase, or even a small decrease, in stroke volume. Since the failing LV often operates on the steep portion of the diastolic pressure/volume relation, a substantial increase in LV filling pressure might reflect only a small NO-induced increase in LV volume.

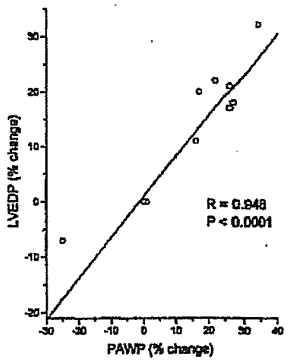

Fig 5. Scatterplot showing relation between the percent changes in pulmonary artery wedge pressure (PAWP) and left ventricular end-diastolic pressure (LVEDP) with inhaled NO in 10 patients.

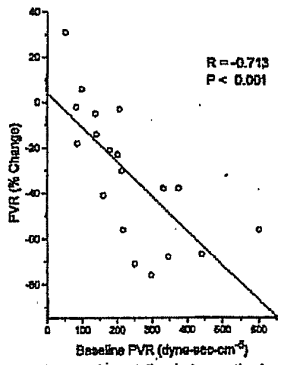

Fig 6. Scatterplot showing relation between the baseline pulmonary vascular resistance (PVR) and the percent change in PVR after inhalation of NO in 19 patients.

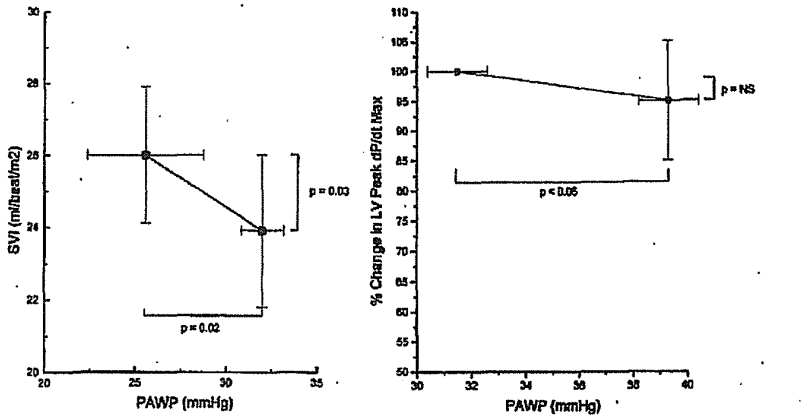

FIG 7. Graphs showing (left) effect of inhaled NO on the relation between stroke volume index (SVI) and mean pulmonary artery wedge pressure (PAWP) and (right) effect of inhaled NO on the relation between left ventricular (LV) peak +dP/dt and PAWP.

The NO-induced changes in LV filling pressure and PVR correlated with both the baseline PVR (see Fig 6) and the severity of hemodynamic compromise (see Table 2). It was previously observed that inhaled NO has no hemodynamic effects in control subjects who have a normal PVR.[34] Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO. To examine this prediction further, we compared the effects of inhaled NO in a subset of 5 patients with relatively compensated hemodynamics ("compensated group," defined by a pulmonary artery wedge pressure ≤18 mm Hg and a cardiac index ≥2.5 $L \cdot m^{-1} \cdot m^{-2}$) and those of the remaining 14 patients ("decompensated group," defined by a pulmonary artery wedge pressure ≥18 mm Hg and/or a cardiac index <2.5 $L \cdot m^{-1} \cdot m^{-2}$). Although the LV ejection fractions were comparable in the two groups, the baseline PVR was higher in the decompensated group (Table 2). As predicted by our hypothesis, the NO-induced fall in PVR (43% versus 7%) and increase in LV filling pressure (27% versus 0%) were larger in the decompensated group. Taken together, these observations suggest that the greater effect of inhaled NO in patients with decompensated LV failure is due to the greater degree of reactive pulmonary hypertension present in such patients.

A second potential explanation for the decrease in transpulmonary gradient is that inhaled NO exerts a direct negative inotropic effect on the LV, resulting in a primary increase in LV filling pressure. In this scenario, passive pulmonary vasodilation might occur because of recruitment of precapillary vessels, an effect that has been demonstrated in animals.[35] However, we feel that a direct negative inotropic effect of inhaled NO is less likely, for several reasons. First, NO is rapidly inactivated by hemoglobin[1] and might not be expected to reach the coronary circulation under these conditions. Second, we observed no decrease in LV +dP/dt, a highly sensitive measure of changes in contractile state. Third, it has been shown that in humans, the intracoronary infusion of nitroprusside, to donate NO to the myocardium, has no effect on +dP/dt and, contrary to our findings with inhaled NO, caused a decrease in LV filling pressure apparently due to an increase in ventricular distensibility.[36]

An interesting corollary of these observations is that selective pulmonary vasodilation, in the absence of systemic vasodilation, may not be desirable in patients with severe LV failure. Clearly, inhaled NO, administered alone at the dose used in this study (80 ppm), may have adverse effects in such patients. Nevertheless, the ability of inhaled NO to reduce PVR selectively (ie, without causing systemic vasodilation), resulted in a unique physiological situation and thus provided the basis for these novel observations. Finally, on the basis of these observations, it is intriguing to speculate that an elevation in PVR may play an important adaptive role in patients with LV failure by limiting LV filling and thereby "protecting" the LV from excessive dilation, albeit at the expense of increased right ventricular work.

Acknowledgments

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Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial

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Summary

Background Inhaled nitric oxide improves oxygenation and lessens the need for extracorporeal-membrane oxygenation in full-term neonates with hypoxaemic respiratory failure and persistent pulmonary hypertension, but potential adverse effects are intracranial haemorrhage and chronic lung disease. We investigated whether low-dose inhaled nitric oxide would improve survival in premature neonates with unresponsive severe hypoxaemic respiratory failure, and would not increase the frequency or severity of intracranial haemorrhage or chronic lung disease.

Methods We did a double-blind, randomised controlled trial in 12 perinatal centres that provide tertiary care. 80 premature neonates (gestational age ≤34 weeks) with severe hypoxaemic respiratory failure were randomly assigned inhaled nitric oxide (n=48) or no nitric oxide (n=32, controls). Our primary outcome was survival to discharge. Analysis was by intention to treat. We studied also the rate and severity of intracranial haemorrhage, pulmonary haemorrhage, duration of ventilation, and chronic lung disease at 36 weeks' postconceptional age.

Findings The two groups did not differ for baseline characteristics or severity of disease. Inhaled nitric oxide improved oxygenation after 60 min (p=0·03). Survival at discharge was 52% in the inhaled-nitric-oxide group and 47% in controls (p=0·65). Causes of death were mainly related to extreme prematurity and were similar in the two groups. The two groups did not differ for adverse events or outcomes (intracranial haemorrhage grade 2–4, 28% inhaled nitric oxide and 33% control; pulmonary haemorrhage 13% and 9%; chronic lung disease 60% and 80%).

Interpretation Low-dose inhaled nitric oxide improved oxygenation but did not improve survival in severely hypoxaemic premature neonates. Low-dose nitric oxide in the most critically ill premature neonates does not increase the risk of intracranial haemorrhage, and may decrease risk of chronic lung injury.

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Introduction

Early reports of inhaled nitric oxide in full-term neonates with persistent pulmonary hypertension showed sustained improvement in oxygenation.[1,2] Subsequently, randomised controlled trials of inhaled nitric oxide confirmed that this selective pulmonary vasodilator improves oxygenation and lessens the need for extracorporeal-membrane oxygenation in such neonates.[3–5] Inhaled nitric oxide did not, however, improve morbidity or survival.[4] In full-term neonates, survival is unlikely to be altered by innovative therapies for persistent pulmonary hypertension because extracorporeal-membrane oxygenation is widely available and can be started quickly when more conservative therapies fail. The role of inhaled nitric oxide in premature neonates with hypoxaemic respiratory failure is, however, more controversial in terms of efficacy and safety.[6] In addition, extracorporeal-membrane oxygenation is not generally offered to premature neonates because of the risks of intracranial haemorrhage associated wth heparinisation, internal-jugular and common-carotid-vessel ligation, and mechanical cardiopulmonary bypass.[7]

Laboratory studies have shown that low-dose inhaled nitric oxide (5–20 parts per million [ppm]) leads to pulmonary vasodilation and improves gas exchange in premature lambs with respiratory-distress syndrome,[8–10] and previous clinical studies have suggested that inhaled nitric oxide acutely improves oxygenation in premature neonates.[11–14] Effects on morbidity and survival in premature neonates have not, however, been tested in a controlled trial. Premature neonates are uniquely susceptible to oxidant lung injury, which could increase the risk of chronic lung disease, but the effects of inhaled nitric oxide on chronic lung disease have not been studied. Laboratory and clinical studies suggest that high doses of inhaled nitric oxide can increase bleeding time,[15–17] and two case reports have suggested a high rate of intracranial haemorrhage in premature neonates treated with inhaled nitric oxide.[18,19] These case reports did not include control groups to find out the actual risk of intracranial haemorrhage, and there is no evidence from controlled trials that inhaled nitric oxide increases the risk of clinical bleeding complications in full-term neonates.

We tested the hypothesis in a double-blind, randomised, controlled trial that the use of low-dose inhaled nitric oxide (5 ppm) would improve survival in premature neonates with severe hypoxaemic respiratory failure unresponsive to conventional therapies, and would not increase the incidence or severity of bleeding complications. Because of the uncertainty about the safety of exposure to inhaled nitric oxide in premature neonates, we limited the study population to selected premature neonates with severe hypoxaemic respiratory failure despite maximum therapeutic intervention and a high predicted mortality rate.

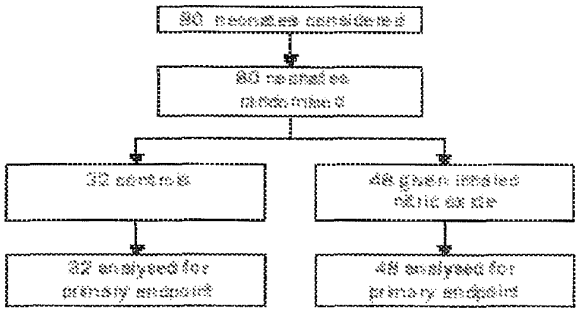

Figure 1: **Trial profile**

Methods

Patients

12 tertiary perinatal centres with clinical experience in inhaled-nitric-oxide therapy participated in the trial. The study was approved by the Institutional Review Board at each centre, and by the US Food and Drug Administration under an investigator-initiated investigational new drug exemption. Criteria for enrolment were: delivery at gestational age 34 weeks or less; age 7 days or younger: severe hypoxaemia (arterial/alveolar oxygen ratio <0·10 on two sequential arterial-blood-gas measurements) despite mechanical ventilation and surfactant treatment (Survanta, Abbott Laboratories, Columbus, OH, USA, 4 mL/kg) when indicated (based on a predicted mortality rate of 50%).[20] Exclusion criteria were fatal congenital anomalies or congenital heart disease (except atrial and ventricular septal defects). We enrolled neonates after informed consent was obtained from parents.

Study design

Treatment assignment was designated by the central coordinating centre according to sequentially numbered randomisation cards, provided in sealed opaque envelopes with the order varied among hospitals. Randomisation was stratified by centre and gestational age (≤28 weeks or >28 weeks), balanced in blocks of ten in each stratum, based on an expected total enrolment of 210 patients. Cranial ultrasound examinations were done before enrolment to find out the baseline incidence and severity of intracranial haemorrhage (Papile standards).[21]

After randomisation, the ventilator circuit was configured to allow delivery of nitric oxide at 5 ppm, as described previously.[3] In patients assigned nitric oxide (n=48) the delivery system was activated. No supplemental gas was delivered to patients in the control group (n=32). Caregivers were unaware of whether nitric oxide was delivered. Delivery systems were monitored routinely (sham monitoring in the control group). Delivered nitric oxide and nitrogen dioxide concentrations were monitored by chemiluminescence or electrochemical sensors.[3] After 7 days' administration, a period of no administration of study gas was tried. We limited the frequency of these periods to keep the risk of unmasking treatment assignment to a minimum. A threshold of 15% or more increase in oxygenation index (fraction of inspired oxygen [FiO_2]×mean airway pressure×100/arterial partial pressure of oxygen [PaO_2]) was used to warrant restarting study gas. If study gas was restarted, periods without gas were kept to every 2 days for a maximum treatment duration of 14 days. We used oxygenation index for periods off gas because the calculation is straightforward for immediate bedside assessments, but after we had done analyses, we believed that PaO_2/FiO_2 would be a more clinically useful comparison and present results in this way.

Patients were mechanically ventilated with standard neonatal, time-cycled, pressure-limited ventilators or with high-frequency devices (Sensormedics 3100A High Frequency Oscillator, Sensormedics Inc, Yorba Linda, CA, USA, or Infant Star HFV, Infrasonics Inc, San Diego, CA). The consensus among centres was that a high-volume strategy would be used during high-frequency oscillatory ventilation. The only ventilator prohibited was the Life Pulse High Frequency Ventilator (Bunnell Inc, Salt Lake City, UT, USA), because of limited information of the accurate measurement of delivered concentrations of inhaled nitric oxide. We did not allow changes in ventilator device or ventilator settings for the first 60 min of the trial to enable recording of acute responses to treatment.

Characteristic	Inhaled nitric oxide (n=48)	Control (n=32)
Mean (SD) weight (g)	1040 (461)	988 (387)
Mean (SD) gestational age (weeks)	27·1 (2·5)	26·8 (2·5)
Sex (female/ male)	20/28	12/20
Median (range) 1 min Apgar score	4 (1–8)	4 (1–9)
Median (range) 5 min Apgar score	7 (2–9)	6 (1–9)
No intracranial haemorrhage	35 (73%)	19 (59%)
Intracranial haemorrhage (grade 2–4)	7 (15%)	6 (19%)
Mean (SD) age at enrolment (h)	30 (38)	27 (37)
Mean (SD) PaO_2/FiO_2 (kPa)	5·6 (2·4)	5·6 (2·1)
Mean (SD) pH	7·33 (0·12)	7·32 (0·10)
Mean (SD) $PaCO_2$ (kPa)	5·7 (1·9)	6·0 (2·1)

$PaCO_2$=arterial partial pressure of carbon dioxide.

Table 1: **Baseline characteristics**

Statistical analysis

We based sample-size estimates on a predicted 50% mortality in the control group.[21] We estimated that 80% power to detect a 30% decrease in mortality with inhaled nitric oxide required 105 neonates in each treatment group. Safety analyses of mortality and rates of intracranial haemorrhage were done by an indepedent data, safety, and monitoring committee after enrolment of 20, 40, and 60 neonates, to find out whether the rate of adverse events warranted ending the trial. No such need was seen.

A planned interim analysis after enrolment of 80 neonates, based on a randomisation-date cut off (study duration 2·5 years) showed that no signficant difference was detectable for the main outcome measure (survival to discharge) and that at the current enrolment rate, projections suggested detection of differences was unlikely in a reasonable time frame (based upon stochastic curtailment procedures). Interim analyses were done by the coordinating centre and the investigators were unaware of results. We did planned secondary analyses (eg, chronic lung disease and intracranial haemorrhage) of differences between treatment groups after the end of study.

For the primary and secondary outcome measures, we did analyses by intention to treat. For acute changes in respiratory variables, the results for seven neonates (four on inhaled nitric oxide, three controls) were censored because of protocol violations in the first 60 min of the trial (changes in ventilator devices or settings). Data from these neonates were, however, included for other study endpoints.

We analysed binomial data with χ^2 or Fisher's exact tests where appropriate. We compared normally distributed continuous data with Student's *t* test. Continuous data that were

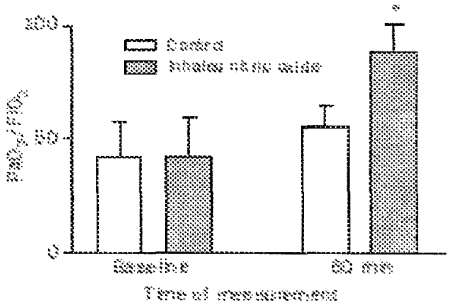

Figure 2: **PaO_2/FiO_2 results at baseline and 60 min after treatment**

*p<0·05 *vs* control.

not normally distributed were compared with the Mann-Whitney *U* test. We set the significance level at $p<0.05$.

Results

Complete data were available for 80 neonates during the planned interim analysis (figure 1). The unequal distribution of neonates was because of the stratification scheme, which was based on our anticipated enrolment of 20 neonates in each centre (ten of 12 centres enrolled fewer than ten neonates). Centres did not differ significantly in randomisation ($p=0.92$). No randomisation violations were reported to the coordinating centre.

There were no differences between groups in baseline characteristics (table 1). 79 (99%) neonates were treated with surfactant. Distribution of ethnic origin, antenatal corticosteroid treatment or treatment, with high-frequency oscillatory ventilation at enrolment were similar in the inhaled-nitric-oxide and control groups.

In the inhaled-nitric-oxide group, there was an acute improvement in PaO_2 after 60 min compared with the control group ($p=0.03$, figure 2). Arterial pH (7·32 [0·18] inhaled nitric oxide *vs* 7·32 [0·16] control) or arterial partial pressure of carbon dioxide (5·7 [2·9] *vs* 5·5 [2·4] kPa) did not differ between groups after 60 min. Methaemoglobin concentrations were also similar in the two groups (1·1% [0·72], inhaled nitric oxide 0·96 [0·60] control). Arterial-blood-gas measurements did not differ between groups after 60 min. In the first period off study gas after 7 days of treatment, treatment had to be restarted in three neonates (treatment was discontinued successfully on day 9 for one neonate and day 11 for two). Days on ventilators in survivors were significantly fewer in the inhaled-nitric-oxide group than in the control group ($p=0.046$).

Survival to discharge or chronic lung disease (table 2) and days spent in hospital (median 86·5 [range 31–395] inhaled nitric oxide *vs* 79·0 [14–106] control) were similar in the two groups. Groups did not differ for incidence of pulmonary haemorrhage (13 *vs* 9%) or symptomatic patent ductus arteriosus (21 *vs* 19%). Periventricular leucomalacia occurred in two (8%) of 25 neonates receiving inhaled nitric oxide and in two (13%) of 15 controls ($p=0.62$). Four neonates had retinopathy of prematurity that required treatment (one in the inhaled-nitric-oxide group, three in the control group, $p=0.10$).

The rate and severity of intracranial haemorrhage at study entry was similar in the two groups (table 3). For intracranial-haemorrhage outcomes, the highest grade recorded (right or left) at age 7 days or 36 weeks postconceptional age was chosen to reflect intracranial-haemorrhage severity. The rate of intracranial haemorrhage for each group did not differ in survivors (table 2).

We did cranial ultrasound scans at study entry and at age 7 days, because most intracranial haemorrhages occur in this time.[22] Therefore, to find out whether intracranial haemorrhage occurred in neonates who died before age 7 days, we did a separate analysis that included results of cranial ultrasound scans done before 7 days as well as the results of necropsy. No intracranial-haemorrhage results were available for 11 of the 80 neonates who died suddenly before age 7 days and who did not undergo necropsy (five in the inhaled nitric oxide group, six in the control group). 13 neonates had cranial ultrasound scans

Outcome	Inhaled nitric oxide	Control	Relative risk (95%CI)	p
Survival	25/48 (52%)	15/32 (47%)	1·11 (0·70–1·8)	0·65
Chronic lung disease (oxygen at 36 weeks)	15/25 (60%)	12/15 (80%)	0·75 (0·5–1·13)	0·30
Death, chronic lung disease, or both	37/48 (77%)	29/32 (91%)	0·85 (0·7–1·03)	0·14
Discharged on oxygen	13/25 (54%)	12/15 (80%)	0·65 (0·41–1·02)	0·10
Median (range) ventilator days for survivors	26 (3–69)	37 (8–395)	..	0·046

Table 2: **Relative risks of outcomes**

after enrolment and before death before age 7 days, and additional intracranial-haemorrhage results were available from necropsies done in seven neonates. Therefore, results for intracranial haemorrhage were available for 43 (90%) of 48 neonates in the inhaled-nitric-oxide group and 26 (81%) of 32 controls (table 3). To find out whether inhaled nitric oxide increased the likelihood of new or worsened intracranial haemorrhage, we analysed the change in intracranial-haemorrhage grade from baseline between the two groups. A higher grade of intracranial haemorrhage after enrolment occurred in 19 (44%) of 43 neonates in the inhaled-nitric-oxide group and 11 (42%) of 26 controls ($p=0.88$). The groups did not differ for the incidence of intracranial haemorrhage within the stratum 28 weeks or less estimated gestational age (ie, at highest risk for intracranial haemorrhage). The rate of intracranial haemorrhage (grades 1–4) was 56% (18 of 32) for the inhaled-nitric-oxide group and 59% (ten of 17) for the control group. The rate of the grade 4 intracranial haemorrhage was 19% for the inhaled-nitric-oxide group and 29% for the control group. 11 (46%) of the 24 neonates on inhaled nitric oxide and four (50%) of eight controls in this stratum who did not have intracranial haemorrhage at baseline subsequently developed intracranial haemorrhage.

Because the rate of intracranial haemorrhage in premature neonates is important to subsequent trials, we also did an analysis based on worst case scenario. We calculated the incidence of intracranial haemorrhage based on the premise that neonates in the inhaled-nitric-oxide group who died before age 7 days with unknown intracranial-haemorrhage status (n=5) actually had grade 4 intracranial haemorrhage and all neonates in the control group who died before age 7 days with unknown intracranial-haemorrhage status (n=6) actually had no intracranial haemorrhage. This analysis yielded a maximum potential rate for grade 4 intracranial haemorrhage of 29% for the inhaled-nitric-oxide group and 27% for the control group. With the prediction for the worst case scenario, a clinical trial designed to prove a significant increase in risk for grade 4 intracranial

	Inhaled nitric oxide (n=48)	Control (n=32)	p
Total unknown ICH status	5/48 (10%)	6/32 (19%)	0·29
Alive without ICH	15/25 (60%)	10/15 (67%)	0·67
Alive with ICH <grade 1	18/25 (72%)	10/15 (67%)	0·72
Alive with ICH grade 2–4	7/25 (28%)	5/15 (33%)	0·72
Died without ICH (<grade 1)	6/18 (33%)	3/11 (27%)	0·73
Died with ICH grade 2–4	12/18 (67%)	8/11 (73%)	0·73
Total known ICH incidence (survivors plus non-survivors)			
Grade 1–4	22/43 (51%)	13/26 (50%)	0·93
Grade 2–4	19/43 (44%)	13/26 (50%)	0·56
Grade 3–4	16/43 (37%)	10/26 (40%)	0·92
Grade 4	7/43 (16%)	7/26 (27%)	0·29

ICH=intracranial haemorrhage.

Table 3: **Outcomes for intracranial haemorrhage**

	Inhaled nitric oxide (n=23)	Control (n=17)	p
Support withdrawn for severe ICH	6 (26%)	4 (24%)	0·85
Extreme prematurity (<25 weeks) and MSOF	6 (26%)	4 (24%)	0·85
PIE/ refractory respiratory failure	3 (13%)	3 (18%)	0·49
Bacterial sepsis	3 (13%)	2 (12%)	0·90
Renal failure	2 (9%)	2 (12%)	0·75
Pulmonary hypoplasia (non-CHD)	1 (4%)	2 (12%)	0·56
Congenital diaphragmatic hernia	2 (9%)	0	0·50

ICH=intracranial haemorrhage; MSOF=multisystem organ failure; PIE=pulmonary interstitial emphysema; CHD=coronary heart-disease.

Table 4: **Cause of death and associated disorders**

haemorrhage in neonates treated with inhaled nitric oxide (80% power, α=0·05) would require a minimum of 15 000 neonates (with illness similar to those in this study). Causes of death and major associated disorders were similar in the two groups (table 4).

Discussion

Low-dose inhaled nitric oxide did not affect survival, but this study population had a high rate of mortality associated with complications of prematurity such as multisystem organ failure and intracranial haemorrhage. Because the potential adverse effects of inhaled nitric oxide on platelet adhesion and the attendant risks of intracranial haemorrhage are severe consequences of prematurity, we included only neonates with the most severe respiratory failure.

One of our most important findings was that low-dose inhaled nitric oxide (5 ppm) did not affect the rate of severity of intracranial haemorrhage, in contrast to observational reports.[18,19] However, no increased incidence of intracranial haemorrhage was found in a small, unblinded trial that tested the effects of inhaled nitric oxide and dexamethasone.[23] In our trial, we found that intracranial haemorrhage occurred with similar frequency in the inhaled-nitric-oxide and control groups. By obtaining all available ultrasound and necropsy findings, it is unlikely that we missed any hidden morbidity of intracranial haemorrhage. This observation is important to future studies of inhaled nitric oxide in premature neonates. Less severely ill premature neonates may be safely treated with low-dose inhaled nitric oxide without the risk of a bleeding diathesis. We did, however, use a constant low dose of inhaled nitric oxide for a minimum of 7 days. We based the use of low-dose inhaled nitric oxide on the results of previous laboratory and clinical studies, which showed optimum beneficial vasoactive and anti-inflammatory effects and low potential adverse effects on platelet adhesion. There is little information about the safety and efficacy of higher doses of inhaled nitric oxide in premature neonates. We did not use laboratory-based assessments of bleeding tendency because, in premature neonates, such laboratory measurements are imprecise, variable, and would not replace the clinically relevant endpoints we reported.

Low-dose inhaled nitric oxide improved oxygenation and decreased the need for mechanical ventilation. Moreover, inhaled nitric oxide substantially lowered the frequency of chronic lung disease. We did not design this trial to test whether inhaled nitric oxide would have this effect on chronic lung disease. However, the possibility that inhaled nitric oxide may have preventive effects on lung injury is important, because, in addition to its effects on pulmonary haemodynamics and gas exchange during inhalation, this treatment may affect neutrophil adhesion in the microcirculation.[24] In premature lambs at 78% of term, inhaled nitric oxide increased pulmonary blood flow and improved gas exchange without increasing pulmonary oedema[14,15] and decreased lung neutrophil accumulation.[16] The effects of low-dose inhaled nitric oxide on early neutrophil accumulation may have important clinical implications because neutrophils play an important part in the inflammatory cascade that contributes to lung injury and the evolution of the most important sequel of respiratory-distress syndrome, chronic lung disease.[25–28] Sequestration of neutrophils in the lung is an early step in a complex inflammatory response mediated through the elaboration of oxyradicals, proteases, phospholipases, and lipid compounds.[29] Therapies that lower neutrophil accumulation in the lung in respiratory-distress syndrome could potentially modify the early inflammatory process that amplifies acute lung injury and contribute to the development of chronic lung disease.[30]

We did not study long-term effects of inhaled nitric oxide in premature neonates. We are continuing follow-up studies on premature infants treated with inhaled nitric oxide and controls after 1 year, 2 years, and 6 years to assess neurodevelopmental outcomes.

Low-dose inhaled nitric oxide may be effective as a lung-specific anti-inflammatory therapy to lessen lung neutrophil accumulation and the attendant inflammatory injury that contributes to the evolution of chronic lung disease. Sufficient evidence may now be available to warrant a controlled trial of low-dose inhaled nitric oxide in premature neonates with less severe disease.

Contributors

John Kinsella and Steven Abman designed the study. Gary Cutter and Monika Baier did the statistical analysis. John Kinsella, William Walsh, Carl Bose, Dale Gerstmann, J Labella, Smeeta Sardesai, Michele Walsh-Sukys, Martin McCaffrey, David Cornfield, Vinod Bhutani, Gary Cutter, Monika Baier, and Steven Abman all contributed to the writing of the paper.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1613
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JAMES S. BALDASSARRE, M.D.
UNDER 37 C.F.R. § 1.132

I, James S. Baldassarre, declare the following:

1. I currently hold the position of Vice President of Clinical Research at Ikaria, Inc. ("Ikaria"), the assignee of U.S. Patent Application No. 12/820,866. My *curriculum vitae* is attached as Exhibit 1.

2. I have over 20 years of experience as a physician, and over fifteen years of experience directing clinical research in the pharmaceutical industry.

3. Ikaria markets pharmaceutical grade nitric oxide (NO) gas under the brand name INOMAX® (nitric oxide) for inhalation. INOMAX® was approved by the U.S. Food and Drug Administration ("FDA") in December 1999, for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure (HRF) associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO).

4. In May 2004, INO Therapeutics LLC[1] initiated a clinical trial, entitled "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing", and designated the INOT22 trial, to compare the utility and side effects of oxygen (O_2), nitric oxide (iNO) and a combination of iNO and O_2 for determining pulmonary reactivity.

5. The INOT22 study was to be an open, prospective, randomized, multi-center, controlled diagnostic trial, with an expected total enrollment of a minimum of 150 patients, in approximately 18 study sites over approximately 2 years.

6. The expected patient population for enrollment into the INOT22 trial were subjects between the ages of four (4) weeks and eighteen (18) years undergoing diagnostic right heart catheterization scheduled to include acute pulmonary vasodilation testing to assess pulmonary vasoreactivity. The expected population were subjects with idiopathic pulmonary arterial hypertension, congenital heart disease (with or without intravascular shunt) with pulmonary hypertension and cardiomyopathies.

7. The INOT22 study was established and designed by the study sponsor, INO Therapeutics LLC (INO), and a Steering Committee comprising internationally recognized experts in the field of pediatric heart and lung disease, whose members would assist INO to develop the INOT22 protocol, monitor the progress of the trial, and provide recommendations to INO on changes in the procedures and conduct of the trial.

8. The Steering Committee consisted of:

a. David L. Wessel, MD, presently Division Chief, Pediatric Critical Care Medicine at Children's National Medical Center, Washington, DC (co-author of Atz., et al., Seminars in Perinatology);[2]

[1] INO Therapeutics LLC is a wholly owned subsidiary of Ikaria, Inc., and holder of the NDA for INOMAX.
[2] Cited in pending Office Action.

b. Robyn J. Barst, MD, presently Professor Emeritus of Pediatrics and Medicine, Columbia University College of Physicians and Surgeons, New York; and

c. Duncan J. Macrae, MD, presently Director, Pediatric Intensive Care, Royal Brompton Hospital, London, U.K. (lead author of Macrae, et al., Intensive Care Medicine, 2004)[3]

9. The original INOT22 protocol designed by INO and the Steering Committee contained the following inclusion and exclusion criteria:

Inclusion Criteria

The patient must meet the following criteria:

1. Have any one of the three disease categories:

a. Idiopathic Pulmonary Arterial Hypertension

i. PAPm >25mmHg at rest, PCWP ≤ 15mmHg, and PVRI >3 u· m^2 or diagnosed clinically with no previous catheterization.

b. CHD with pulmonary hypertension repaired and unrepaired,

i. PAPm >25mmHg at rest, and PVRI >3 u· m^2 or diagnosed clinically with no previous catheterization

c. Cardiomyopathy

i. PAPm >25mmHg at rest, and PVRI >3 u•m^2 or diagnosed clinically with no previous catheterization.

2. Scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

3. Males or females, ages 4 weeks to 18 years, inclusive.

[3] Cited in pending Office Action.

4. Signed IRB/IEC approved informed consent (and assent if applicable).

Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.

2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.

3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.

4. Pregnant (urine HCG +).

10. The INOT22 investigational plan and study protocol was further reviewed, and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the participating study institutions, including review by the principal investigator within each study institution.

11. At no time did any member of the Steering Committee, nor any member of an IRB, IEC, or individual principal investigator, appreciate, recognize or otherwise suggest that the exclusion criteria be amended to exclude study subjects with pre-existing left ventricular dysfunction (LVD), due to an anticipated or predicted risk of adverse events or serious adverse events arising from the use of iNO in patients with pre-existing LVD, and/or elevated pulmonary capillary wedge pressure. Nor was it, in my expert opinion, common sense to any expert in this field of medicine to exclude neonates, near-term neonates or children diagnosed with pre-existing LVD to be excluded from having iNO administered for diagnostic or treatment purposes.

12. After initiation and enrollment of the first 24 subjects in INOT22, there were 5 serious adverse events (SAEs) – a rate much higher than expected by INO and

the Steering Committee based on prior clinical experience. These were all cardiovascular events, and included pulmonary edema, cardiac arrest and hypotension (low blood pressure).

13. Thereafter, in February 2005, INO and the Steering Committee convened to review the unexpected SAEs described above, and upon review and discussion, expressed concern that the unexpected SAEs may be due to the administration of iNO in subjects having pre-existing LVD . Accordingly, based upon a review of the cases, the exclusion criteria of the INOT22 protocol was amended to thereafter exclude subjects with pre-existing LVD. For the purpose of the study, the exclusion criteria was amended to exclude subjects from enrollment if the subjects demonstrated an elevated pulmonary capillary wedge pressure (PCWP), defined within the study as subjects having a PCWP greater than 20 mmHg. All study sites were notified immediately. The amended exclusion criteria (see point 5.) was as follows:

Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. *Focal pulmonary infiltrates on chest radiograph.*
2. *Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.*
3. *Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.*
4. *Pregnant (urine HCG +)*
5. *Baseline PCWP > 20 mmHg*

14. Upon conclusion of the INOT22 study and completion of the final study report, INO noted that subsequent to excluding patients with pre-existing LVD, the rate of serious adverse events (including serious adverse events associated with heart failure) was significantly reduced. There were 5 SAEs amongst the first 24 subjects

prior to the additional exclusion criteria, but only 2 SAEs amongst the last 80 subjects in the study after the additional exclusion. Furthermore, there were 2 SAEs amongst the 4 subjects with evidence of pre-existing left ventricular dysfunction, but only 5 SAEs amongst the 120 subjects without evidence of left ventricular dysfunction.

15. Based upon this unexpected finding, on February, 25, 2009, INO submitted a labeling supplement to the FDA seeking to amend the prescribing information for INOMAX to include a warning statement for physicians such that the use of iNO in patients with pre-existing LVD could cause serious adverse events, such as pulmonary edema.

16. On August 28, 2009, the FDA approved the INO labeling supplement and included (i) a statement in the Warnings and Precautions section of the INOMAX prescribing information that states "Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema", and (ii) new section 5.4 of the INOMAX prescribing information that states "Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema)."

17. Based upon my review of the medical literature of record in this patent application and pending Office Action, none of the prior art suggests, appreciates or otherwise recognizes that exclusion of neonates, near-term neonates or children with LV dysfunction from administration of iNO for diagnostic or treatment purposes would reduce the risk of adverse events and/or serious adverse events, as such terminology is well understood in the medical arts.

18. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from this patent application.

Dated: Sept 29 2010

James S. Baldassarre, M.D.

CURRICULUM VITAE

James S. Baldassarre, MD

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PERSONAL: Married (Susan Cohen-Baldassarre)
Children Alyssa (18), Julia (16) and Andrew (10)
Citizenship: USA

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EDUCATION:

S.U.N.Y. Downstate Medical Center
Brooklyn, NY
1986 - M.D.

S.U.N.Y., Binghamton, NY
1982 - Biology, B.S.

EMPLOYMENT:

2007- present **Ikaria (INO Therapeutics)**
VP, Clinical Research
2009-present Project Team Leader: IK 5001
2008-2010 Project Team Leader: INOmax®

2003- 2007 **INO Therapeutics**
Senior Director, Clinical Research

2003 **Johnson & Johnson Pharmaceutical Research and Development LLC**
Compound Development Team Leader/Clinical Leader-REGRANEX®

2001-2003 **Johnson & Johnson Pharmaceutical Research and Development LLC**
Senior Director, Operations Team Management

1999-2001 **Janssen Research Foundation**
Director of Clinical Research Italy/Greece

1997 -1999 **Janssen-Cilag Limited, UK**
Head of Clinical Research and Senior Medical Advisor

1993 - 1997 **R.W. Johnson Pharmaceutical Research Institute**
Spring House, PA
1995-1997 Associate Director, Clinical Research
1993-1995 Assistant Director, Clinical Research

1992 - 1993 **Presbyterian Medical Center**
Philadelphia, PA
Attending Physician, Division of Infectious Diseases

1986 - 1993 **Medical College of Pennsylvania**
Philadelphia, PA
1990-1993 Fellow, Division of Infectious Diseases
1989-1990 Medical Director (half time)

1986-1989 Internship/Residency Internal Medicine

1989 - 1990 **Philadelphia Department of Health**
Philadelphia, PA
Medical Director, Sexually Transmitted Diseases Clinic (half time)

ACADEMIC APPOINTMENT :

John Radcliffe Hospital, Oxford, UK

1999-2000 Honorary SHO, Dept of Clinical Pharmacology

Medical College of Pennsylvania, Philadelphia, USA

1994 - Clinical Assistant Professor, Department of Medicine

1991 - 1993 Instructor in Medicine

CERTIFICATION:

Diplomat, A.B.I.M.
Internal Medicine, 1989
Infectious Diseases, 1992
Limited GMC registration, 1999

EMPLOYMENT-RELATED ACTIVITIES/COMMITTEES:

RWJ-PRI Continuous Process Improvement Committee	1995-1996
Johnson & Johnson Signature of Quality submission	1997 and 1999
JJ PRD New Product Development Committee Implementation Team	2002-2003
Ikaria Opportunity Review Team	2007-present

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2. Baldassarre J S and Abrutyn E: Antibiotic-Resistant Streptococcus pneumoniae. Infectious Disease Practice 1993; 17 (9).

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Baldassarre J S and Kaye D: Principles and Overview of Antibiotic Use in Infective Endocarditis. In: Kaye D (ed) *Infective Endocarditis* 2nd ed. New York: Raven Press, 1992; 169-190.

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1. Baldassarre J S and Stull T L: Cytosol-Mediated Ulcerogenesis in Haemophilus ducreyi. 1993 Annual Meeting of the Infectious Diseases Society of America, Abst #19, Oct. 16 and 17, 1993.

2. Sutherland J and Baldassarre JS : Mediastinal Adenopathy in a Patient with AIDS. American College of Physicians Regional Scientific Meetings, October 2, 1992.

3. Baldassarre J S and Stull T L: Characterization of Aminopeptidase (AP) Activity in Haemophilus ducreyi. American College of Physicians Regional Scientific Meetings, October 3, 1992.

4. Fontinella E. Dorfman M, Baldassarre J, Kaye D and Murasko D: Immune Response to Influenza Immunization in an Elderly Community Dwelling Africa American Population. FASEB J 1991 5: A1373 Abst 5814.

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8. RJ Barst, G Agnoletti, A Fraisse, J Baldassarre, DL Wessel. Nitric Oxide in Combination with Oxygen Versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study. Pediatric Academic Societies Scientific Meeting, Baltimore Md; May 2009 [3861.195]

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Assist Device Placement: Results of a Prospective, Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial. American Heart Association Scientific Sessions Orlando, Fl; Nov 2009 [3663]

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12820866
Filing Date	2010-06-22
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V Arnold
Attorney Docket Number	I001-0002USC1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

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	1							☐

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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

	1	Cuthbertson et al., "UK guidelines for thee use of inhaled nitric oxide therapy in adults ICUs*", Intensive Care Med (1997), 23, Springer-Verlag, 1997, pp#1212-pp#1218	☐
	2	Ivy, et al., "Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease", J Thorac Cardiovasc Surg 1998; 115:875-882.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christopher P. Rogers/	Date (YYYY-MM-DD)	2010-10-01
Name/Print	Christopher P. Rogers	Registration Number	36,334

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	12820866
Filing Date:	22-Jun-2010
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Daniel Leo Hayes/Anna Goforth
Attorney Docket Number:	I001-0002USC1

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	8544668
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Daniel Leo Hayes/Anna Goforth
Filer Authorized By:	Daniel Leo Hayes
Attorney Docket Number:	I001-0002USC1
Receipt Date:	01-OCT-2010
Filing Date:	22-JUN-2010
Time Stamp:	14:43:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	638
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		O10343.PDF	291639 92f1e4bdb149172154de3c1f5718492af60f40a3	yes	28

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Accelerated Exam - Transmittal amendment/reply	1	1
	Claims	2	5
	Applicant Arguments/Remarks Made in an Amendment	6	27
	Miscellaneous Incoming Letter	28	28

Warnings:					
Information:					
2	Oath or Declaration filed	O10404.PDF	17158212 7747cca95f83131e6e3d7e34ef6c8c1d31824a2e	no	181
Warnings:					
Information:					
3	Oath or Declaration filed	O10410.PDF	1701683 68bb24613c7eb381be457d7e989e8be49ec355ef	no	11
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	O10367.PDF	187769 8ed452887bc4235e37710cf3799852caac194af7	no	3
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
5	NPL Documents	Ivy.pdf	176390 0dd50795fee9d23bc1e794af9c662a0bf36bc529	no	10
Warnings:					
Information:					
6	NPL Documents	Cuthbertson.pdf	1532031 d23d88b2286c697f7135825f349e208b8d6c5701	no	7
Warnings:					
Information:					
7	Fee Worksheet (PTO-875)	fee-info.pdf	30308 3627367a7c54c6a2805173e940e9dae471a88f31	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	21078032

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/820,866	06/22/2010	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/01/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/EVELYN G. NIMMONS/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/820,866	06/22/2010	James S. Baldassarre	I001-0002USC1	2913

49584 7590 11/02/2010

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1613	

MAIL DATE	DELIVERY MODE
11/02/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/820,866	BALDASSARRE ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending and under examination.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/1/10 was filed after the mailing date of the Office Action on 9/23/10. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn rejections:

Applicant's amendments and arguments filed 10/1/10 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 1-19 were rejected under 35 U.S.C. 112, second paragraph. Applicant has shown that the art recognizes 'adverse events' and 'serious adverse events' as two separate 'events'. The terminology is now clear on the record and the rejection is withdrawn. Claims 11-19 were rejected under 35 U.S.C. 112, first paragraph. Applicant's have amended the claims to overcome this rejection. Accordingly, the rejection is withdrawn. Claims 3, 6, 11 and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, May 2000, 13 pages). Applicant has amended the claims and changed the claim dependency and the rejection over these claims is withdrawn. Claims 1, 3, 5, 6, 11, 13 and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Kinsella et al.

(The Lancet 1999, 354, 1061-1065). Applicant has argued and amended the claims and changed the claim dependency and the rejection over these claims is withdrawn. Claims 3, 5, 6, 11, 13 and 15 were rejected under 35 U.S.C. 102(b) as being anticipated by Atz et al. (Seminars in Perinatology 1997, 21(5), pp 441-455). Applicant has amended the claims and changed the claim dependency and the rejection over these claims is withdrawn.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, May 2000, 13 pages).

The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, May 2000, 13 pages) discloses that administration of NO has been approved for use in the treatment of term or near term neonates and that that inhaled NO therapy is relative contraindicated for patients with severe left ventricular failure and to beware of increased left ventricular filling associated with rapid changes in pulmonary pressures

(pages 2-3 of 13). A contraindication means literally contra- (against) an indication, against something that is indicated as advisable or necessary and a relative contraindication is a condition which makes a particular treatment or procedure inadvisable but does not rule it out. Therefore, in reading the guidelines set forth by the NIH one of ordinary skill in the art would practice the instant method by identifying a patient eligible for iNO treatment and then diagnosing/evaluating/screening/determining for a pre-existing left ventricular dysfunction in the patient and if present exclude the neonate from treatment to avoid/reduce the risk of the adverse events/hazards/complications but administer the treatment if the patient is not contraindicated. Claim 1 is therefore anticipated.

Response to arguments:

Applicant asserts that the Magnuson Clinical Center does not have a neonatal intensive care unit. This is irrelevant. The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy) teaches that neonates are the target population for iNO treatment. "NO has been approved for use in the treatment of term or near term (> 34 weeks) neonates…" (page 2 of 13; 3.1 Administration of NO in the MICU).

Applicant asserts that the NIH reference does not teach elevated PCWP or PCWP > 20 mmHg. This is irrelevant. Claim 1 does not recite this limitation either.

Applicant notes, as did the Examiner, that iNO is a relative contraindication for severe left ventricular failure. Applicant erroneously concludes that this does not apply to children because the hospital does not have a neonatal ICU. The Examiner cannot agree because the NIH manual states that neonates are the approved patient population as discussed above.

Applicant asserts the reference is nonenabling and does not exclude children from receiving iNO where such children have LVD, elevated PCWP or PCWP > 20 mmHg and it fails to mention reducing the risk of adverse events or serious adverse events. Respectfully, the Examiner cannot agree. The PCWP is not a limitation of claim 1. The manual clearly sets forth iNO as a relative contraindication with the consequence of adverse events form its use. That is what **HAZARDS/COMPLICATIONS** means (see page 3 of 13). Applicant argues that one would not add NaCL to water unless the reference teaches the act of adding NaCl to water. Somehow this applies to the NIH reference allegedly not stating *ipsis verbis* excluding children with pre-existing LVD. As explained by the Examiner, a relative contraindication makes the treatment inadvisable but does not rule it out. If something is inadvisable then the practitioner can exclude the treatment. This is inherent in the term. As stated above, the ordinary practitioner in reading the guidelines set forth by the NIH one of ordinary skill in the art would practice the instant method by identifying a patient eligible for iNO treatment and then diagnosing/evaluating/screening/determining for a pre-existing left ventricular dysfunction in the patient and if present exclude the neonate from treatment to avoid/reduce the risk of the adverse events/hazards/complications but administer the treatment if the patient is not contraindicated. This is inherent in the disclosure of the NIH.

Applicant's arguments are not persuasive and the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Atz et al. (Seminars in Perinatology 1997, 21(5), pp 441-455).

Atz et al. disclose methods using inhaled nitric oxide in the neonate with cardiac disease (title and Abstract pages 441-453). Atz et al. disclose that: "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension." (page 452, left column). Atz et al. continues with: "Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively right to left shunting at the ductus arteriosus, ***NO should be used with extreme caution, if at all***. We and others have reported ***adverse outcomes*** in this circumstance." (page 452, left column) (Examiner added emphasis). Thus, Atz et al. fairly teaches excluding patients with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment and consequently any adverse events are reduced. The left ventricular dysfunction is inherently pre-existing and therefore instant claim 1 is anticipated.

Response to arguments:

Applicant asserts that "extreme caution" is not the same as 'excluding' and the recitation of "if at all" is at odds with the data provided. The Examiner has stated clearly

how the Examiner interpreted 'if at all' to mean no treatment and hence exclusion from treatment and consequently any adverse events are reduced. The rejection over claims reciting elevated PCWP or PCWP > 20 mmg Hg have been withdrawn. However, claim 1 does not recite these limitations and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-19 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Atz et al. (Seminars in Perinatology 1997, 21(5), pp 441-455) and Kinsella et al. (The Lancet 1999, 354, 1061-1065) and Bolooki (Clinical Application of the Intra-Aortic Balloon Pump 1998, 3rd Ed. Pp 252-253) and Loh et al. (Circulation 1994, 90, 2780-2785) and The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, May 2000, 13 pages).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant claim, for example:

1. (Presently Amended) A method of reducing the risk of one or more adverse events or serious adverse events in an intended patient population comprising neonates or near-term neonates in need of being treated with inhalation of nitric oxide comprising excluding from such treatment anyone in the intended patient population having pre-existing left ventricular dysfunction.

2. (Presently Amended) ~~The method of claim 1,~~ A method of reducing the risk of one or more adverse events or serious adverse events in an intended patient population comprising neonates or near-term neonates in need of being treated with inhalation of nitric oxide comprising excluding from such treatment anyone in the intended patient population having pre-existing left ventricular dysfunction, wherein anyone in the intended patient population further has a pulmonary capillary wedge pressure greater than 20 mm Hg.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Atz et al. teach methods using inhaled nitric oxide in the neonate with cardiac disease (title and Abstract). Atz et al. teach that: "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension." (page 452, left column). Atz et al. continues with: "Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively right to left shunting at the ductus arteriosus, ***NO should be used with extreme caution, if at all***. We and others have reported ***adverse outcomes*** in this circumstance." (page 452, left column) (Examiner added emphasis). Thus, Atz et al. fairly teaches excluding patients with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. The left ventricular dysfunction is intrinsically pre-existing. The methods disclosed by Atz et al. are interpreted to mean identifying a patient eligible for NO treatment; diagnosing if the patient has left ventricular dysfunction; excluding that patient with left ventricular dysfunction from treatment with NO but treating the patient with NO for other conditions discussed by Atz et al. with inhalation of NO thereby reducing the risk of adverse events associated with the medical treatment. Atz et al. teach neonates with pulmonary hypertension (Abstract and page 442, left column to right column).

Bolooki teaches using intra-aortic balloon pump as well as nitroglycerin and calcium channel blockers in the treatment of left ventricular dysfunction (pages 252-253).

The NIH (Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, May 2000, 13 pages) establishes that inhaled NO therapy is relative contraindicated for patients with severe left ventricular failure and to beware of increased

left ventricular filling associated with rapid changes in pulmonary pressures (pages 2-3 of 13). Thus, it is a medical mainstream concept that inhaled NO therapy is relative contraindicated for patients with left ventricular dysfunction.

Kinsella et al. teach excluding patients (premature neonates) from inhaled nitric oxide treatment if they have fatal congenital anomalies or congenital heart disease (Abstract and page 1062, Methods). Since left ventricular dysfunction is a congenital heart disease, as acknowledged by Applicant, (see specification [0028]), and it would be pre-existing, then the methods of Kinsella et al. inherently exclude this patient population from the method. The patients also had pulmonary hypertension which would be associated with the cardiac function (Abstract). Thus, one or more adverse events are reduced in the neonates excluded from the method. The neonate must breathe oxygen to survive. Furthermore, if the patients are already excluded then any further limitations on the treatment are truly irrelevant. The intended patient population is inherently at risk of one or more adverse events. Patients are inherently identified for nitric oxide inhalation treatment, diagnosed for congenital heart disease which inherently includes left ventricular dysfunction, and if the patient meets the criteria than treatment with NO is performed thereby reducing the risk of adverse events associated with the treatment. The neonate must breathe oxygen to survive.

Loh et al. teach that inhaled nitric oxide in patients with left ventricular dysfunction may have adverse effects in patients with LV failure (Title and Abstract).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Atz et al. is that Atz et al. do not expressly teach a method of excluding patients from treatment with a pulmonary capillary wedge pressure greater than 20 mm Hg or using a ventilator for the treatment or idiopathic pulmonary arterial hypertension/congenital heart disease/cardiomyopathy or catheterization characterized by different means. This deficiency in Atz et al. is cured by the teachings of Kinsella et al., Loh et al., The NIH and common sense.

2. The difference between the instant application and Atz et al. is that Atz et al. do not expressly teach: reducing the left ventricular afterload with nitroglycerin, calcium channel blocker or intra-aortic balloon pump such that pulmonary edema is reduced/minimized. This deficiency in Atz et al. is cured by the teachings of Bolooki.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of Atz et al. and exclude patients with left ventricular dysfunction wherein the intended patient population is excluded that has a pulmonary capillary wedge pressure greater than 20 mm Hg or using a ventilator for the treatment or idiopathic pulmonary arterial hypertension/congenital heart disease/cardiomyopathy or catheterization characterized by different means, as suggested by Loh et al., the NIH and Kinsella et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Atz et al. clearly teach using extreme caution or not using NO at all in the treatment of

patients with left ventricular dysfunction and the art of Kinsella et al. establishes excluding certain patients from treatment. Furthermore, the NIH teaches that inhaled NO therapy is relative contraindicated for patients with left ventricular dysfunction. ***In other words, the art is already well aware and informed that inhaled NO is contraindicated for patients with left ventricular dysfunction, and consequently it is not inventive to exclude that patient population from treatment when the art already suggests it!*** Thus it is no stretch of the imagination to exclude patients with left ventricular dysfunction with or without the myriad number of other conditions characterized by various medical parameters claimed by Applicant from inhaled nitric oxide therapy in order to avoid adverse outcomes as taught by Atz et al. which intrinsically include all the adverse events recited by Applicant. The ordinary artisan would err on the side of caution for the benefit of the patient. Such patients intrinsically have a pulmonary capillary wedge pressure of greater than 20 mm Hg. In other words, the teachings of Atz et al. include the patients with left ventricular dysfunction intrinsically that have a pulmonary capillary wedge pressure of greater than 20 mm Hg. Inhaled NO increased the wedge pressure as taught by Loh et al. (see entire document) Furthermore, it is merely a design choice by the ordinary artisan to select a ventilator to administer the gas. This is just common sense. Furthermore, with respect to instant claims 3 and 4, if the patients are already excluded from treatment then any further limitations on the treatment are truly irrelevant.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to reducing the left ventricular afterload with nitroglycerin, calcium channel blocker or intra-aortic balloon pump such that pulmonary edema is reduced/minimized, as suggested by Bolooki, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because administration of nitroglycerin, calcium channel blocker or intra-aortic balloon pump to treat left ventricular dysfunction is a common technique in the art as taught by Bolooki and intrinsically reduces the left ventricular afterload and reduces pulmonary edema.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Please note that the Declarations of Smith and Baldassarre will be addressed with the arguments below.

Applicant first discusses the INOT22 study designed by international experts in the field of pediatric heart and lung disease. The original NOT22 protocol did not exclude patients with pre-existing LVD. Applicant states that at no time did any member appreciate, recognize or otherwise suggest that the exclusion criteria be amended to exclude study subjects with pre-existing LVD due to an anticipated or predicted risk of adverse events or serious adverse events arising from the use of iNO in patients with pre-existing LVD and/or elevated capillary wedge pressure. This is really irrelevant because: 1) the Examiner is not citing INOT22 study as prior art and therefore whatever the panel

of experts failed to appreciate or recognize is moot; and 2) the preponderance of art cited by the Examiner (in the 103 rejection here as well the art made of record), especially Atz et al., fairly teaches excluding patients with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. Applicant acts surprised that patients with pre-existing LVD were at risk of adverse or serious adverse events from iNO therapy but he art has already established such knowledge. Applicant states that Dr. Baldassarre did not anticipate or predict that patients with pre-existing LVD would be at risk of adverse events or serious adverse events arising from treatment with iNO and that one of skill in the art at the time of the invention would not have predicted or anticipated that patients with pre-existing LVD would be at risk of adverse events or serious adverse events arising from treatment with iNO. This is simply ignoring the art as a whole. This position by Applicant is especially problematic when the art, Loh et al., clearly teaches that patients with pulmonary artery wedge pressure, which is synonymous with the instantly claimed pulmonary capillary wedge pressure, ***of greater than or equal to 18 mm Hg*** had a greater effect of inhaled NO due to the greater degree of reactive pulmonary hypertension present in such patients (page 2784, left column). Loh et al. state: "*Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO*." Loh et al. examined this prediction further and verified it (page 2784, left column). Therefore, contrary toApplicant's assertion that "one of skill in the art at the time of the invention would not have predicted or anticipated that patients with pre-existing LVD

would be at risk of adverse events or serious adverse events arising from treatment with iNO" the art in 1994 already **anticipated** and **predicted** adverse effects in patients with LV failure from inhaled NO (p 2780, Abstract).

Applicant then argues that Loh et al. is directed to adults and not children. This is correct. Applicant and Smith asserts that iNO clinical studies in adults cannot be extrapolated to children, neonates or near-term neonates. Applicant and Smith concludes that the teachings of Loh et al. are irrelevant to the instantly claimed invention. Respectfully, the Examiner cannot agree. The art is not examined in a vacuum but rather as a whole. The Lipshultz article is a review of current issues in clinical research and teaches that children are not small adults. Applicant and Smith construe this article to mean that iNO clinical studies involving adults cannot be extrapolated to children, neonates or near-term neonates. This is an invalid conclusion. Nowhere in Lipshultz does it say never to extrapolate iNO clinical studies on adults to children with LVD. However, these arguments are moot because the art has already performed iNO therapy on neonates as discussed above and observed adverse effects. In other words, the Examiner gives no weight to the reference of Lipshultz given the preponderance of art as a whole.

Applicant argues that none of the references mentions or recognizes using pre-existing LVD, elevated LVD or PCWP>20 mmHg as exclusionary criteria. Respectfully, the examiner cannot agree because at least Loh et al. teach predicting adverse effects in patients with pulmonary capillary wedge pressure, ***of greater than or equal to 18 mm Hg*** as discussed above. It stands to reason that adults with pulmonary capillary wedge pressure of greater than or equal to 18 mm Hg have adverse effects from iNO and that neonates are subject to adverse effects from iNO then neonates with pulmonary capillary

wedge pressure of greater than or equal to 18 mm Hg are also prone to adverse effects with iNO. It is simply not inventive to exclude those patients at increased risk from iNO therapy when the art already teaches that they are at risk of adverse events. This is not surprising or unexpected given the art as a whole.

Applicant continues to argue that if experts did not recognize or anticipate adverse events associated with the use of iNO in patients with pre-existing LVD then the level of skill is presumptively extraordinary skill and it is that much more surprising and supportive of the non-obviousness of the claims. Respectfully, the Examiner cannot agree given the art as a whole as explained above. The Examiner cannot control what the 'experts' read and apply to their studies but the art clearly teaches adverse effects in neonates from iNO therapy was public knowledge. At most what Applicant has done is practice/confirm what was already known in the art.

Respectfully, after consultation with supervisory patent examiner Brain Kwon and quality assurance specialist Jean Vollano, we are in agreement that these arguments, Declarations and amendments are not persuasive to overcome the rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the

reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 of copending Application No. 12/820980. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach near-term neonates or neonates.

However the copending broadly teaches children patient population which would include neonates and near-term neonates as clearly neonates are children. The instant specification defines 'children' as being 4 weeks old [0023] which would be newborn and hence neonatal.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/821020. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach the intended population as having one or more conditions.

However the copending application is drawn to the same patient population which intrinsically has one or more conditions as instantly claimed.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/821041. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach the intended population as having one or more conditions.

However the copending application is drawn to the same patient population which intrinsically has one or more conditions as instantly claimed.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to arguments:

Applicant will file a terminal disclaimer upon allowance of the instant application. Until that time the claims remain rejected.

Conclusion

No claims are allowed.

Applicant is reminded that for any amendments to the claims (including any new claim) that is not encompassed by the preexamination search and accelerated examination support documents previously filed, applicant is required to provide updated preexamination search and accelerated examination support documents that encompass the amended or new claims at the time of filing the amendment. Failure to provide such updated preexamination search and accelerated examination support documents at the time of filing the amendment will cause the amendment to be treated as not fully responsive and not to be entered. See MPEP § 708.02(a) subsection VIII.D. for more information.

If the reply is not fully responsive, the final disposition of the application may occur later than twelve months from the filing of the application.

Any reply or other papers must be filed electronically via EFS-Web so that the papers will be expeditiously processed and considered. If the papers are not filed electronically via EFS-Web, the final disposition of the application may occur later than twelve months from the filing of the application.

Any reply to this communication filed via EFS-Web must include a document that is filed using the document description of "Accelerated Exam - Transmittal amendment/reply." Applicant is reminded to use proper indexing for documents to avoid any delay in processing of follow on papers. Currently document indexing is not automated in EFS-Web and applicant must select a particular document description for

each attached file. An incorrect document description for a particular file may potentially delay processing of the application. A complete listing of all document codes currently supported in EFS-Web is available at http://www.uspto.gov/ebc/portal/efs/efsweb_document_descriptions.xls.

Any payment of fees via EFS-Web must be accompanied by selection of a proper fee code. An improper fee code may potentially delay processing of the application. Instructions on payment of fees via EFS-Web are available at http://www.uspto.gov/ebc/portal/efs/quick-start.pdf.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12820866	BALDASSARRE ET AL.
	Examiner	Art Unit
	ERNST V ARNOLD	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
inventor name EAST/PALM	8/10/10	eva
EAST 424/718 text limited all databases	8/10/10	eva
google	8/10/10	eva
consultation Brian Kwon SPE 1613 and Jean Vollano QAS	10/24/10	eva

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

U.S.PATENTS						
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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U.S.PATENT APPLICATION PUBLICATIONS						
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS								
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

/E.A./	1	Cuthbertson et al., "UK guidelines for thee use of inhaled nitric oxide therapy in adults ICUs*", Intensive Care Med (1997), 23, Springer-Verlag, 1997, pp#1212-pp#1218	☐
/E.A./	2	Ivy, et al., "Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease", J Thorac Cardiovasc Surg 1998; 115:875-882.	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	10/25/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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BIB DATA SHEET

CONFIRMATION NO. 2913

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/820,866	06/22/2010 **RULE**	514	1613	I001-0002USC1

APPLICANTS

James S. Baldassarre, Doylestown, PA;
Ralf Rosskamp, Chester, NJ;

**** CONTINUING DATA ***************************

This application is a CON of 12/494,598 06/30/2009 ABN

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
06/24/2010

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ERNST V ARNOLD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	0	19	2

ADDRESS

LEE & HAYES, PLLC
601 W. RIVERSIDE AVENUE
SUITE 1400
SPOKANE, WA 99201
UNITED STATES

TITLE

METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

FILING FEE RECEIVED		
462	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Number	12820866
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Attorney Docket Number	I001-0002USC1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

	1	Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/ NCT00626028/2009_01_12 January 12, 2009	☐
	2	INO Therapeutics, LLC, "INOflo for Inhalation 800ppm", package leaflet, 2010, 2	☐
	3	Notification of Reason for Rejection, mailed 7/30/2010, from Japanese Patent Application No. 2009-157623 (cites foreign references).	☐
	4	Yoshida, Kiyoshi, " Well-illustrated Diagnostics and Treatment of Heart Failure" Professor of Kawasaki Medical University, cardiovascular internal medicine CIRCULATION Up-to-Date Vol. 2, No. 4, 2007(343), pp. 23-28	☐

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EXAMINER SIGNATURE

Examiner Signature	/Christopher P. Rogers, Reg. No. 36,334/	Date Considered	2010-11-03

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☒ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2010-11-03
Name/Print	Christopher P. Rogers	Registration Number	36,334

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	8764697
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Daniel Leo Hayes
Filer Authorized By:	
Attorney Docket Number:	I001-0002USC1
Receipt Date:	03-NOV-2010
Filing Date:	22-JUN-2010
Time Stamp:	18:34:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed (SB/08)	IDS.pdf	38279 68f2053eaf4ef35bb8c7f02db0053557be360abb	no	4

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Warnings:					
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3	NPL Documents	O86037.pdf	369742 4a332bdd82d6f9a661ba2a15ce0e7b15d484387f	no	5
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Information:					
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Warnings:					
Information:					
			Total Files Size (in bytes):	1490143	

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/820,866	06/22/2010	James S. Baldassarre	I001-0002USC1

CONFIRMATION NO. 2913

49584
LEE & HAYES, PLLC
601 W. RIVERSIDE AVENUE
SUITE 1400
SPOKANE, WA 99201

PUBLICATION NOTICE

OC00000004521147

Title:METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

Publication No.US-2010-0330206-A1
Publication Date:12/30/2010

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/84 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

AUTHORIZATION TO ACT IN A REPRESENTATIVE CAPACITY

In re Application of: James S. Baldassarre et al.	
Application No. 12/820,866	
Filed: 06/22/2010	
Title: METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION	
Attorney Docket No. I001-0002USC1	Art Unit: 1613

The practitioner named below is authorized to conduct interviews and has the authority to bind the principal concerned. (Note: pursuant to 37 CFR 10.57(c), a practitioner cannot authorize other registered practitioners to conduct interviews without consent of the client after full disclosure.) Furthermore, the practitioner is authorized to file correspondence in the above-identified application pursuant to 37 CFR 1.34:

Name	Registration Number
Jonathan N. Provoost	44,292
Henry C. Lebowitz	36,196

This is not a Power of Attorney to the above-named practitioner. Accordingly, the practitioner named above does **not** have authority to sign a request to change the correspondence address, a request for an express abandonment, a disclaimer, a power of attorney, or other document requiring the signature of the applicant, assignee of the entire interest or an attorney of record. If appropriate, a separate Power of Attorney to the above-named practitioner should be executed and filed in the United States Patent and Trademark Office.

SIGNATURE of Practitioner of Record

Signature	/Christopher P. Rogers, Reg. No. 36,334/	Date January 5, 2011
Name	Christopher P. Rogers	Registration No., if applicable 36,334
Telephone	509-944-4785	

Electronic Acknowledgement Receipt

EFS ID:	9170342
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
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Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

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Alexandria, VA 22313-1450

REPLY AFTER FINAL (37 CFR 1.116)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Final Office Action mailed November 2, 2010, setting a shortened statutory period for reply of 3 months.

Applicant respectfully requests entry of this Reply After Final, reconsideration of the pending rejections, and allowance of the application. A listing of the claims and amendments thereof is shown starting at page 2.

Applicant further asserts that this Reply After Final has been diligently filed and that the application is in compliance with MPEP 708.02(a)(IV) After-Final and Appeal Procedures, thus maintaining the application's status as an accelerated application.

Remarks to the pending Office Action begin at page 4.

Amendments to the Claims

Please cancel claims 1-10 and 12-19. In addition, amend claim 11 and add new claims 20-22.

1-10. Canceled.

11. (Twice Amended) A method of reducing the risk of the occurrence, in a patient under the age of 18 ~~being a neonate or near-term neonate~~, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

(a) identifying a patient under the age of 18 who is eligible ~~for inhalation of~~ to receive inhaled nitric oxide treatment according to FDA–approved prescribing information;

(b) determining if said eligible patient has pre-existing left ventricular dysfunction ~~evidenced by an elevated pulmonary capillary wedge pressure; and,~~

(c) administering said inhaled nitric oxide ~~medical~~ treatment to said eligible patient if said eligible patient does not have pre-existing left ventricular dysfunction~~,~~ ~~wherein said patient is excluded from being administered said medical treatment if said patient has pre-existing left ventricular dysfunction~~; and

(d) not administering said inhaled nitric oxide to said eligible patient if said eligible patient has pre-existing left ventricular dysfunction in order to reduce ~~thereby reducing~~ the risk of the occurrence of the adverse event or serious adverse event associated with said inhaled nitric oxide ~~medical~~ treatment.

12-19. Canceled.

20. (New) A method of reducing the risk of one or more adverse events or serious adverse events associated with the use of inhaled nitric oxide in patients under the age of 18, said method comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider;

b. informing the medical provider that inhaled nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood;

c. providing an additional warning to the medical provider, independent of the contraindication for neonates known to be dependent on right-to-left shunting of blood, that inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema in patients under the age of 18 with pre-existing left ventricular dysfunction.

21. (New) The method of claim 20, further providing an additional warning to the medical provider that independent of the contraindication for right-to-left shunt, patients under the age of 18 who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events.

22. (New) A method of reducing the risk of one or more adverse events or serious adverse events in patients under the age of 18 in need of treatment with inhaled nitric oxide comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider; and

b. informing the medical provider that inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema in patients with pre-existing left ventricular dysfunction that are eligible to receive inhaled nitric oxide treatment.

23. (New) The method of claim 22, wherein patients eligible to receive inhaled nitric oxide treatment excludes neonates known to be dependent on right-to-left shunting of blood.

REMARKS

Applicant would like to thank Examiner Kwon and Examiner Arnold for providing Applicant an opportunity to discuss the subject matter of the present application during the interview of January 10, 2011, conducted in connection with Applicant's related, co-pending patent applications 12/821,020 and 12/821,041.

Claims 11 and 20-22 are pending in the application. The application contains three independent claims (claims 11, 20 and 22), five total claims, and no multiple dependent claims. As such, the application continues to comply with the 3/20 claim limitation for accelerated applications.

Claim 11 has been amended, and new claims 20-23 have been added to more particularly point out and distinctly claim the subject matter applicant regards as the invention and to address matters discussed during the interview of January 10, 2011. The claims have been amended without prejudice. Each of these claims is believed allowable over the prior art of record for at least the reasons described below.

As discussed at the interview, the prior art cited by the Examiner is addressed to two patient populations that are not the subject of the claimed invention. In particular, some of the disclosures in the cited prior art (e.g., the "NIH reference," and Loh et al., as cited in the Office Action mailed November 2, 2010) are directed to potential effects of inhaled nitric oxide on adults with left ventricular dysfunction due primarily to ischemic cardiomyopathy.

Other disclosures in the cited prior art are directed to potential effects of inhaled nitric oxide on a second class of patients - neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus (Atz et al., page 452). At the time of the instant invention, it was widely recognized by those of skill in the art that this class of patients should not be given inhaled NO therapy. In fact, this contraindication has been present on the prescribing label for nitric oxide since its introduction into the

marketplace. Consequently, patients with this specific condition were, of course, excluded from the INOT22 study that resulted in the discovery that is the subject of the presently claimed invention.

In contrast to the prior art references cited by the Examiner, the claimed invention relates to an important discovery in a third patient population - pediatric patients with pre-existing left ventricular dysfunction who are eligible to receive inhaled nitric oxide treatment (i.e., those not dependent on a right-to-left shunting of blood). As explained during the interview, those of ordinary skill in the art, prior to the instant invention, would not have found it obvious to withhold inhaled NO treatment from this class of patients based on the prior art cited by the Examiner in the Office Action mailed November 2, 2010, because the etiology and pathophysiology of the left ventricular dysfunction present in these three patient populations is markedly different. In fact, the members of the INOT22 Screening Committee who designed the study and the approximately 18 Institutional Review Boards and 4 national Health Authorities who reviewed and approved the study prior to its initiation – failed to predict that any untoward effects would be caused by the administration of inhaled NO in this third patient population.

Turning now to the specific language of the claims, amended claim 11 and new claims 20-23 are each limited to patients under the age of 18 and accordingly are not anticipated or rendered obvious by the prior art cited by the Examiner in the Office Action mailed November 2, 2010.

In addition, claim 11 is limited to patients eligible to receive inhaled nitric oxide treatment. To those skilled in the art, this patient population does not include neonates dependent on right-to-left shunt, since it was and is well known that inhaled nitric oxide is contraindicated for such patients. This is demonstrated not only by Atz et al. cited by the Examiner (see, e.g., Atz at 452: "We and others have reported adverse outcomes in this circumstance), but also by the contraindication clearly stated on the FDA-approved label for inhaled nitric oxide (see label section 4: "Contraindications"). Thus,

claim 11 does not include within its scope the neonate patients described by Atz et al. in column 452 of their paper who are not, to begin with, eligible to receive inhaled nitric oxide.

Similarly, new claim 20 expressly calls out this distinction between the patient population addressed by Atz et al., as to which the potential dangers of inhaled nitric oxide were well known in the prior art, and the distinct patient population that is the subject of the claimed invention. In particular, part (b) of the claim refers to the contraindication contained within the prescribing label for inhaled nitric oxide (see section 4, Contraindications). As noted above, this part of the claim embodies the disclosure of Atz et al., with respect to the treatment of neonates known to be dependent on right-to-left shunting of blood through a patent ductus arteriosus. Conversely, part (c) of claim 20 pertains to the novel and non-obvious finding that resulted from the INOT22 study, i.e., the new warning added to the Warnings and Precautions section of the prescribing label for inhaled nitric oxide (see page 1, right column). Claim 20(c) expressly states that the warning is independent from the known contraindication pertaining to neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus. Accordingly, the warning claimed in part (c) of claim 20 is <u>not directed</u> to the neonates described by Atz et al., as to whom the treatment is already contraindicated. Relatedly, claim 21 includes specific reference to the other warning added to the prescribing label for inhaled nitric oxide in Section 5.4 (see page 2, right hand column) arising from the INOT22 Study.

Support for the amendments and new claims is found in the specification of the application, as filed, including the original claims as filed and paragraphs [0007], [0020], and [0023] of the specification. Notably, the reference in claims 11 and 22 to patients "eligible to receive inhaled nitric oxide treatment" is original language in claim 11 as filed and is also found in paragraph [0007] of the application as filed. In addition, with respect to claim 20, both the contraindication for neonates dependent on right to left shunting of blood recited in part (b) of the claim and the warning recited in part (c) of the

claim are expressly found in the prescribing label for inhaled nitric oxide incorporated by reference in the specification at paragraph [0020] (copy attached as Appendix A).

In light of the above, Applicant respectfully submits that the application as amended is in condition for allowance and respectfully requests the same. Examiner Arnold is invited to contact Chief Patent Counsel for the patent owner, Jonathan Provoost (Reg. No. 44, 292) at 908-238-6392 to discuss any of the amendments or remarks set forth above.

No fees are believed to be due with this submission. Please apply any necessary charges or credits to deposit account **12-0769**, referencing Attorney Docket No. I001-0002USC1.

Respectfully submitted,

/Jonathan N. Provoost, Reg. No. 44,292/ Dated: January 14, 2011

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APPENDIX A

INOmax® (nitric oxide) for inhalation

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INOmax safely and effectively. See full prescribing information for INOmax.

INOmax (nitric oxide) for inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions, Heart Failure (5.4) 9/2009

INDICATIONS AND USAGE

INOmax is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (1.1).

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration (1.1).

Utilize additional therapies to maximize oxygen delivery (1.1).

DOSAGE AND ADMINISTRATION

Dosage: The recommended dose of INOmax is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).

Administration:

- INOmax must be delivered via a system which does not cause generation of excessive inhaled nitrogen dioxide (2.2).
- Do not discontinue INOmax abruptly (2.2).

DOSAGE FORMS AND STRENGTHS

INOmax (nitric oxide) is a gas available in 100 ppm and 800 ppm concentrations.

CONTRAINDICATIONS

Neonates known to be dependent on right-to-left shunting of blood (4).

WARNINGS AND PRECAUTIONS

Rebound: Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).

Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).

Elevated NO_2 Levels: NO_2 levels should be monitored (5.3).

Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

ADVERSE REACTIONS

Methemoglobinemia and elevated NO_2 levels are dose dependent adverse events. Worsening oxygenation and increasing pulmonary artery pressure occur if INOmax is discontinued abruptly. Other adverse reactions that occurred in more than 5% of patients receiving INOmax in the CINRGI study were: thrombocytopenia, hypokalemia, bilirubinemia, atelectasis, and hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and http://www.inomax.com/ or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nitric oxide donor agents: Nitric oxide donor compounds, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical formulations, may have an additive effect with INOmax on the risk of developing methemoglobinemia (7).

Revised: August 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Hypoxic Respiratory Failure

INOmax® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies *[see Clinical Studies (14)]*.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but those patients did not then improve on the higher dose. As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm, doses above this level ordinarily should not be used.

2.2 Administration

The nitric oxide delivery systems used in the clinical trials provided operator-determined concentrations of nitric oxide in the breathing gas, and the concentration was constant throughout the respiratory cycle. INOmax must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. The INOvent® system and other systems meeting these criteria were used in the clinical trials. In the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms. The system should be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide, such as INOcal®. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. Oxygen levels should also be measured.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

Do not discontinue INOmax abruptly, as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax. Discontinue/wean cautiously.

3 DOSAGE FORMS AND STRENGTHS

Nitric oxide is a gas available in 100 ppm and 800 ppm concentrations.

4 CONTRAINDICATIONS

INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound

Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

5.2 Methemoglobinemia

Methemoglobinemia increases with the dose of nitric oxide. In clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 48 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide, the methemoglobin levels returned to baseline over a period of hours.

5.3 Elevated NO_2 Levels

In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

5.4 Heart Failure

Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Clinical Trials Experience

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax in the CINRGI study with event rates >5% and greater than placebo event rates. None of the differences in these adverse reactions were statistically significant when inhaled nitric oxide patients were compared to patients receiving placebo.

Table 1:
Adverse Reactions in the CINRGI Study

Adverse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 (10%)	13 (13%)
Withdrawal	9 (10%)	12 (12%)
Atelectasis	8 (9%)	9 (9%)
Hematuria	5 (6%)	8 (8%)
Hyperglycemia	6 (7%)	8 (8%)
Sepsis	2 (2%)	7 (7%)
Infection	3 (3%)	6 (6%)
Stridor	3 (3%)	5 (5%)
Cellulitis	0 (0%)	5 (5%)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of INOmax. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

7 DRUG INTERACTIONS

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

8.2 Labor and Delivery

The effect of INOmax on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

8.4 Pediatric Use

Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). No information about its effectiveness in other age populations is available.

8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

10 OVERDOSAGE

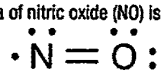
Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

11 DESCRIPTION

INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

12.2 Pharmacodynamics

Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

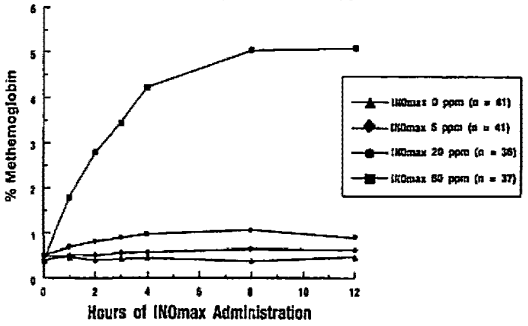
12.4 Pharmacokinetics: Uptake and Distribution

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

12.5 Pharmacokinetics: Metabolism

Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1:
Methemoglobin Concentration – Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients, but one patient did not exceed 7% until 40 hours.

12.6 Pharmacokinetics: Elimination

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

14 CLINICAL STUDIES

14.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O × fraction of inspired oxygen concentration [FiO_2]× 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 *[see Clinical Pharmacology (12.1)]*.

NINOS Study

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2:
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*,†	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups *[see Adverse Reactions (6.1)]*. Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI Study

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 3.

Table 3:
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO*,†	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

* Extracorporeal membrane oxygenation
† ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups *[see Adverse Reactions (6.1)]*.

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

ARDS Study

In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FiO_2 <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation. Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

16 HOW SUPPLIED/STORAGE AND HANDLING

INOmax (nitric oxide) is available in the following sizes:

Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)
Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

Electronic Acknowledgement Receipt

EFS ID:	9237230
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Kayla D. Brant/Anna Goforth
Filer Authorized By:	Kayla D. Brant
Attorney Docket Number:	I001-0002USC1
Receipt Date:	14-JAN-2011
Filing Date:	22-JUN-2010
Time Stamp:	16:06:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		P80022.PDF	1941125 3f41b64b443e4984f706349a238fb102b127cbcd	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Accelerated Exam - Transmittal amendment/reply	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	12
Warnings:			
Information:			
	Total Files Size (in bytes):	1941125	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/820,866	06/22/2010	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	82		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	82		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 01/14/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 4	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/820,866	06/22/2010	James S. Baldassarre	I001-0002USC1	2913

49584 7590 02/23/2011

LEE & HAYES, PLLC
601 W. RIVERSIDE AVENUE
SUITE 1400
SPOKANE, WA 99201

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1613	

NOTIFICATION DATE	DELIVERY MODE
02/23/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

lhpto@leehayes.com

Notice of References Cited	Application/Control No. 12/820,866	Applicant(s)/Patent Under Reexamination BALDASSARRE ET AL.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Figure from Dr. Green's presentation given 1/10/11; 1 page.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/820,866	**Applicant(s)** BALDASSARRE ET AL.	
	Examiner ERNST V. ARNOLD	**Art Unit** 1613	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 January 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-19*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 11/3/10
13. ☒ Other: PTO 892.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

Continuation of 3. NOTE: Applicant has changed the scope of the patient population from neonate or near term noenate to under the age of 18. This is a new patient population that requires further search and consideration. One of Applicant's arguments has been that treatment of mature adults cannot be directly correlated to treatment for children but by amending the claims to include a patient 17.99 years of age, which is essentially a mature adult, then the claims need to be re-evaluated in consideration of this new patient population. Atz clearly teaches that pulmonary edema can occur in adults with left ventricular dysfunction who are administered NO (page 452, left column of Atz). Thus, at least the reference of Atz needs to be reconsidered with respect to the new limitations. Also, parts (b) and (c) of claim 20 are directed to neonates but the patients are under the age of 18 which include 17.99 year olds and by Applicant's own arguments, what applies to neonates is different than what applies to mature individuals, which a 17.99 year old person is. What does a warning about neoates have to do with a 17.99 year old mature individual? It appears to be incongruous to the Examiner and possibly a 35 USC 112 second paragraph problem. Furthermore, iNO is already known to increase the capillary wedge pressure as taught by Loh. So, new claim 20 does not appear to be in condition for allowance. Amdended claim 11 also has the patient under the age of 18 and is not allowable. Applicant directed the Examiner to [0020] which incorporates by reference the label on iNOmax. The label states that the neonates known to be dependent on right to left shunting of blood are contraindicated and this appears to be a proper incorporation by reference and not new matter.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant's proposed amendments create numerous problems including requiring further search and consideration as discussed above. Applicant asserts that Atz teaches right to left shunting of blood which is part (b) of the claim 20. Applicant asserts that part (c) of claim 20 is not directed to the neonates described by Atz et al. but a new patient population discovered by Applicant. Respectfully, this is not distinguishing. As discussed during the interview of 1/10/11, Dr. Greene discussed that the Atz is directed to right to left shunting of blood in patent ductus arteriosus (See attached Figure provided during the interview). The instant claims are directed to increases in pulmonary wedge pressure which is already known in the art as taught by Loh and discussed above. Furthermore, Atz also teaches left to right shunting at the foramen ovale in newborns with left ventricular dysfunction and that iNO should be used with extreme caution, if at all with these patients (page 452, left column Atz). Thus, Atz is not limited to right to left shunting as found in ductus arteriosus. Consequently, it remains obvious to exclude patients with left ventricular dysfuction from iNO therapy because of the inherent risk of adverse and serious adverse effects. Respectfully, the Examiner consulted with his supervisor and has tried to find language to be copacetic with our informative discussion during the interview but cannot at this time find adequate language supported in the specification as filed. Respectfully, the claims remain rejected for the reasons of record and those provided above.

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	12820866
Filing Date	2010-06-22
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V Arnold
Attorney Docket Number	I001-0002USC1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V Arnold
	Attorney Docket Number	I001-0002USC1

/E.A./	1	Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/ NCT00626028/2009_01_12 January 12, 2009	☐
/E.A./	2	INO Therapeutics, LLC, "INOflo for Inhalation 800ppm", package leaflet, 2010, 2	☐
/E.A./	3	Notification of Reason for Rejection, mailed 7/30/2010, from Japanese Patent Application No. 2009-157623 (cites foreign references).	☐
/E.A./	4	Yoshida, Kiyoshi, " Well-illustrated Diagnostics and Treatment of Heart Failure" Professor of Kawasaki Medical University, cardiovascular internal medicine CIRCULATION Up-to-Date Vol. 2, No. 4, 2007(343), pp. 23-28	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature	/Christopher P. Rogers, Reg. No. 36,334/	Date Considered	2010-11-03

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

/Ernst Arnold/ 02/14/2011

Do Not Enter
/EA/
2/14/11

Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop After Final Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY AFTER FINAL (37 CFR 1.116)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Final Office Action mailed November 2, 2010, setting a shortened statutory period for reply of 3 months.

Applicant respectfully requests entry of this Reply After Final, reconsideration of the pending rejections, and allowance of the application. A listing of the claims and amendments thereof is shown starting at page 2.

Applicant further asserts that this Reply After Final has been diligently filed and that the application is in compliance with MPEP 708.02(a)(IV) After-Final and Appeal Procedures, thus maintaining the application's status as an accelerated application.

Remarks to the pending Office Action begin at page 4.

Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop After Final Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY AFTER FINAL (37 CFR 1.116)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Advisory Action mailed Feb. 23, 2011 and the Final Office Action mailed November 2, 2010, setting a shortened statutory period for reply of 3 months.

Applicant respectfully requests entry of this 2nd Reply After Final, reconsideration of the pending rejections, and allowance of the application. A listing of the claims and amendments thereof is shown starting at page 2.

Applicant further asserts that this 2nd Reply After Final has been diligently filed and that the application is in compliance with MPEP 708.02(a)(IV) After-Final and Appeal Procedures, thus maintaining the application's status as an accelerated application.

Remarks to the pending Office Action begin at page 3.

Amendments to the Claims

Please cancel claims 1-10 and 12-19.

1-10. Canceled.

11. (Twice Amended) A method of reducing the risk of the occurrence, in ~~a patient a~~ nenonate or near-term neonate patients, of one or more ~~adverse events or~~ adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

(a) identifying a neonate or near-term neonate patient eligible to receive inhaled nitric oxide treatment according to FDA–approved prescribing information, wherein said neonate or near-term neonate patient is not eligible to receive inhaled nitric oxide treatment if he or she is dependent on right-to-left shunting of blood at the patent ductus arteriosus;

(b) determining if said eligible patient has pre-existing left ventricular dysfunction ~~evidenced by an elevated pulmonary capillary wedge pressure~~; ~~and,~~

(c) administering said inhaled nitric oxide ~~medical~~ treatment to said eligible patient if said eligible patient does not have pre-existing left ventricular dysfunction~~,~~ ~~wherein said patient is excluded from being administered said medical treatment if said patient has pre-existing left ventricular dysfunction~~; and

(d) not administering said inhaled nitric oxide to said eligible patient if said eligible patient has pre-existing left ventricular dysfunction in order to reduce ~~thereby reducing~~ the risk of the occurrence of ~~the~~ a serious adverse event associated with said inhaled nitric oxide ~~medical~~ treatment.

12-19. Canceled.

REMARKS

Claims 1-10 and 12-19 have been cancelled. Claim 11 has been amended. Allowance of the present application in light of the above amendments and the following remarks is respectfully requested.

Applicants would like to thank Examiner Arnold for the comments and discussion provided in the Advisory Action of February 23, 2011, and Examiner Kwon and Examiner Arnold for providing Applicant an opportunity to discuss the subject matter of the present application during the interview of January 10, 2011, conducted in connection with Applicants' related, co-pending patent applications 12/821,020 and 12/821,041.

Following the interview, Applicants submitted a response to the Final Office Action in which they sought to amend and add claims that highlighted the distinctions between the present invention and the prior art discussed at the January 10 interview. In response, the Examiner issued an Advisory Action indicating that those amendments did not put the application in condition for allowance and would require additional searching of the prior art. Accordingly, Applicants' January 14th Amendment was not entered.

It was certainly not Applicants intention to expand the scope of the claimed subject matter in a way that would require additional searching, but rather simply to present claims that reflected Applicants' understanding of the discussion at the interview. Applicants remain hopeful that there remains agreement with respect to the underlying fact that the INO22 study resulted in a significant medical invention not taught in the prior art and that the question presented is how appropriately to claim that invention. With this as background, Applicant respectfully submits this second after final response in an attempt to address the specific points made by the Examiner in the Advisory Action.

Applicant sought to establish three points during the January 10, 2011 Interview:

1. That the present invention is not directed to neonates reliant on right-to-left shunting of blood at the patent ductus arteriosus because it was already well known in the art at the time of the INO22 study that such patients were ineligible to receive inhaled nitric oxide treatment. This is demonstrated by the Atz et al. article cited by the Examiner and the original FDA label for inhaled nitric oxide issued by the FDA which specifically states that inhaled nitric oxide is contraindicated for this patient population. Rather, the invention claimed in the present application is directed to pediatric patients with pre-existing left ventricular dysfunction that are not reliant on such right-to-left shunting.

2. That the risk of increased adverse events and serious adverse events from administering inhaled nitric oxide to pediatric patients that are not reliant on right-to-left shunting, represented a highly surprising result to those skilled in the art, as demonstrated, e.g., by the fact that it was not recognized or considered by any of the 18 independent review boards (IRBs) at medical institutions in the United States and abroad as a risk to be considered in the original protocol for the INO22 study.

3. That the references cited by the Examiner are directed solely either (a) to neonates reliant on right-to-left shunting (e.g., Atz et al.); or (b) to adults suffering from an entirely different category of left ventricular dysfunction than the type that affects children. Adults with LVD suffer from diastolic dysfunction (stiff, non-compliant heart that cannot fill properly) caused by ischemic cardiomyopathy (heart failure due to coronary artery disease and resultant partial cardiac muscle death) and idiopathic dilated cardiomyopathy. By contrast, children with LVD suffer from systolic dysfunction (soft flabby heart that cannot push blood out) caused by congenital (structural) defects or cardiomyopathies (muscle diseases). For this reason, there were no existing concerns about left ventricular dysfunction in children or neonates until the INOT 22 study was analyzed and understood despite the known teachings of Loh and others with respect to adults.

It is respectfully submitted that if the above three points are agreed, the only barrier to allowance of the present application is identifying claim language that both the Examiner and Applicant agree captures the distinction between the claimed invention and the prior art and would not require an additional search of the prior art. The claim amendments above are an attempt to present such language and, for the reasons described below, are believed to address the concerns raised by the Examiner in the Advisory Action.

The Examiner raises two concerns in the Advisory Action. First, the Examiner states that amending the claims from neonates to patients under the age of 18 raises new obviousness issues and would require additional search. In particular, the Examiner contends that a pediatric patient just under 18 years of age will be medically equivalent to an adult just over 18 years of age. Consequently, the Examiner concludes, a prior art reference such as Loh relating to adult patients may render obvious a claim that covers patients who are just short of their 18th birthday.

Applicants respectfully disagree with the Examiner's arguments on this point. The adults at issue in the Loh reference had an average age of 52 +/- 3 years and suffered from ischemic cardiomyopathy (heart failure due to coronary artery disease and resultant partial cardiac muscle death) and idiopathic dilated cardiomyopathy, which resulted in systolic left ventricular failure. These are symptoms of older adults, and Loh's teachings would not be understood as referring to an "adult" of age 18, and certainly not to a pediatric patient.

Nevertheless, to facilitate the present prosecution, the claims presented in this second after-Final amendment are directed to neonates, and (without prejudice to Applicants' right to submit further amendments in the future in this or related applications), Applicant has not attempted in this response to amend the claims to cover patients under the age of 18.

Second, the Examiner contends that Atz et al. is not limited to patients with right-to-left shunting of blood at the patent ductus arteriosus but also allegedly refers to patients with extreme left-to-right shunting at the foramen ovale in newborns with left ventricular dysfunction. It is respectfully submitted that the Examiner is simply incorrect in his reading of Atz et al. on this point.

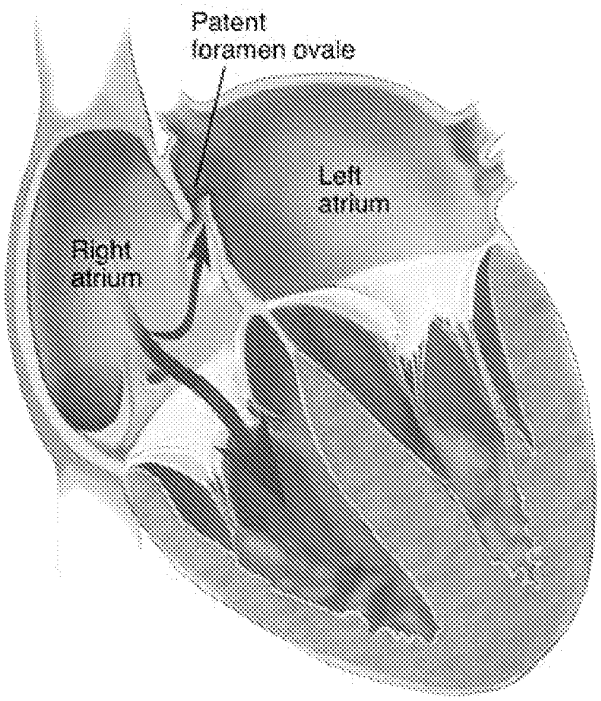
Atz et al., page 452, states in pertinent part:

> *"A different, but related phenomenon may be operative in the newborn with severe left ventricular dysfunction and pulmonary hypertension. In these patients, the systemic circulation may depend in part on the ability of the right ventricle to sustain cardiac output through a right-to-left shunt across the patent ductus arteriosus. Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation. Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale* ***and*** *exclusively right to left shunting at the ductus arteriosus, NO should be used with extreme caution. (emphasis added)"*

With all due respect, the operative key word is "***and***." The Examiner seems to be interpreting Atz et al. as describing two separate conditions, "predominantly left to right shunting at the foramen ovale" and "exclusively right to left shunting at the ductus arteriosus." That is simply not a correct reading of Atz et al. Atz et al. is referring to a single condition, one in which patients exhibit a right to left shunt across the patent ductus arteriosus and a left-to-right shunt at the foramen ovale.

Left-to-right shunt at the foramen ovale is not, in and of itself, a form of LVD. Indeed, a foramen ovale is not even located or associated with a left or right ventricle. Rather, as shown in Figure 1 below, a foramen ovale is an unintended opening between the right and left atrium.

Figure 1



In particular, prior to birth, the fetal heart utilizes the foramen ovale as a means for blood to pass from the right atrium directly into the left atrium. This "bypass" allows fetal blood to circumvent the nonfunctional fetal lungs, while the fetus obtains its oxygen from the placenta. A layer of tissue called the septum primum acts as a valve over the foramen ovale during fetal development. After birth, the pressure in the pulmonary circulatory system drops, thus causing the foramen ovale to close entirely. In certain instances, the foramen ovale may not entirely seal after birth. In this case, elevation of pressure in the pulmonary circulatory system (i.e., pulmonary hypertension due to various causes) can cause the foramen ovale to remain open. This is known as a patent foramen ovale. Indeed, the use of inhaled nitric oxide to decrease pulmonary hypertension is known to be a successful treatment for right-to-left shunting through a

patent foramen ovale (see *Right-to-Left shunting through a patent foramen ovale in right ventricular infarction: improvement of hypoxemic and hemodynamics with inhaled nitric oxide*; Fessler MB et al, J Clin Anesth. 2003 Aug; 15(5): 371-4).

By contrast, it has long been known that the use of inhaled nitric oxide is contraindicated in patients dependent on right-to-left shunt across the patent ductus arteriosus. Atz implies that the risk may be even greater if the newborn patient has **both** a dependency on right-to-left shunt across the patent ductus arteriosus **combined with** left to right shunt at the foramen ovale. In other words, Atz et al. is describing neonates with predominantly left-to-right shunting at the foramen ovale **and** exclusively right-to-left shunting at the ductus arteriosus, which is a subset of the well-known broader contraindication for the use of iNO in neonates (i.e., newborns) dependent on right-to-left shunt across the patent ductus arteriosus. But Atz et al. teaches nothing about patients with left-to-right shunt at the foramen ovale, in and of itself. This condition is neither a contraindication for inhaled nitric oxide (rather inhaled nitric oxide is used to treat it in specific instances), nor is it considered to be representative of "left ventricular dysfunction" (rather it is a defect of the atrium, not a ventricle).

Support for the amendments and new claims is found in the specification of the application, as filed, including the original claims as filed and paragraphs [0007], [0020], [0023] and [0052] of the specification. Notably, the reference in claim 22 to patients "eligible to receive inhaled nitric oxide treatment" is original language in claim 11 as filed and is also found in paragraph [0007] of the application as filed. In addition, with respect to claim 20, both the contraindication for neonates dependent on right to left shunting of blood recited in part (b) of the claim and the warning recited in part (c) of the claim are expressly found in the prescribing label for inhaled nitric oxide incorporated by reference in the specification at paragraph [0020] (copy attached as Appendix A).

In light of the above, Applicant respectfully submits that the application as amended is in condition for allowance and respectfully requests the same. Examiner Arnold is invited to contact Chief Patent Counsel for the patent owner, Jonathan

Provoost (Reg. No. 44,292) at 908-238-6392 to discuss any of the amendments or remarks set forth above.

The application as amended contains one independent claim, one total claim, and no multiple dependent claims. As such, the application continues to comply with the 3/20 claim limitation for accelerated applications.

No fees are believed to be due with this submission. Please apply any necessary charges or credits to deposit account **12-0769**, referencing Attorney Docket No. I001-0002USC1.

Respectfully submitted,

/Jonathan N. Provoost, Reg. No. 44,292/ Dated: March 1st, 2011

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Electronic Patent Application Fee Transmittal

Application Number:	12820866
Filing Date:	22-Jun-2010
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Beatrice L. Koempel-Thomas/Anna Goforth
Attorney Docket Number:	I001-0002USC1

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	65	65

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

Electronic Acknowledgement Receipt	
EFS ID:	9563947
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Beatrice L. Koempel-Thomas/Anna Goforth
Filer Authorized By:	Beatrice L. Koempel-Thomas
Attorney Docket Number:	I001-0002USC1
Receipt Date:	01-MAR-2011
Filing Date:	22-JUN-2010
Time Stamp:	18:04:48
Application Type:	Utility under 35 USC 111(a)

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Payment Type	Credit Card
Payment was successfully received in RAM	$65
RAM confirmation Number	5066
Deposit Account	
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		PO3587.PDF	125298 dd3db582f0bd1e70889bcacc648a65106578cae2	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Accelerated Exam - Transmittal amendment/reply	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	9

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	30641 0245d31d5ea766d2292cf53f81b6883c87b1b0b8	no	2

Warnings:

Information:

Total Files Size (in bytes):	155939

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop After Final Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY AFTER FINAL (37 CFR 1.116)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Examiner Interview of March 3, 2011, and the Advisory Action mailed Feb. 23, 2011.

Applicant respectfully requests entry of this 3nd Reply After Final, reconsideration of the pending rejections, and allowance of the application. A listing of the claims and amendments thereof is shown starting at page 2.

Applicant further asserts that this 3nd Reply After Final has been diligently filed and that the application is in compliance with MPEP 708.02(a)(IV) After-Final and Appeal Procedures, thus maintaining the application's status as an accelerated application.

Remarks to the pending Office Action begin at page 3.

Amendments to the Claims

Please cancel claims 1-10 and 12-19.

1-10. Canceled.

11. (Twice Amended) A method of reducing the risk of the occurrence, in ~~a patient a~~ neonate or near-term neonate patients, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

(a) identifying a patient ~~eligible for~~ in need of inhaled nitric oxide treatment; ~~,~~

(b) ~~determining~~ identifying if said patient has a first condition, said first condition being ~~has pre-existing left ventricular dysfunction evidenced by an elevated pulmonary capillary wedge pressure~~ dependency on right-to-left shunting of blood at the patent ductus arteriosus; ~~and,~~

(c) further identifying if said patient has a second condition, said second condition being pre-existing left ventricular dysfunction, independent and separate from whether said patient has right-to-left shunting of blood at the patent ductus arteriosus; and

(d) administering said inhaled nitric oxide ~~medical~~ treatment to said patient if said patient does not have the first condition or the second condition. ~~pre-existing left ventricular dysfunction, wherein said patient is excluded from being administered said medical treatment if said patient has pre-existing left ventricular dysfunction;~~

~~thereby reducing the risk of the occurrence of the a serious adverse event associated with said medical treatment.~~

12-19. Canceled.

REMARKS

Claims 1-10 and 12-19 have been cancelled. Claim 11 has been amended. Allowance of the present application in light of the above amendments and the following remarks is respectfully requested.

Applicants would like to thank Examiner Arnold for the comments and discussion provided in the Examiner interview of March 3, 2011.

Based on the discussion during the interview, Applicants have attempted to amend claim 11 to reflect the agreement reached during the interview. In sum, amended claim 11 more clearly distinguishes between the step of identifying patients depending on right-to-left shunting of blood at the patent ductus arteriosus, and with respect to the present invention, further identifying patients with pre-existing left ventricular dysfunction, independent of whether such patients have right-to-left shunting of blood at the patent ductus arteriosus.

To reiterate, the prior art (Atz et al., page 452) discloses the well known contraindication (also found on the prescribing information of INOMAX®, submitted with prior communications) that neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus should not be administered inhaled nitric oxide. Indeed, at the time of the invention, it was widely recognized by those of skill in the art that this class of patients should not be given inhaled NO therapy. In contrast to the prior art and the contraindication, the claimed invention relates to an important discovery of an elevated risk for the use of inhaled NO within a newly identified and separate patient population - pediatric patients with pre-existing left ventricular dysfunction, independent and separate from those dependent on a right-to-left shunting of blood.

Turning to the specific language of amended claim 11, step (b) relates to identifying patients who are dependent on right-to-left shunting of blood at the patent ductus arteriosus – i.e., the prior art. Conversely, step (c) separately and independently from (b), relates to the nature of the invention – i.e., further identifying patients with pre-existing left ventricular dysfunction, independently of those captured in step (b). Finally, as discovered during INOT22, step (d) relates to excluding from treatment with inhaled nitric oxide, those patients found to have either (b) or (c).

Support for the amendments and new claims is found in the specification of the application, as filed, including the original claims as filed and paragraphs [0007], [0020], [0023] and [0052] of the specification.

In light of the above, Applicant respectfully submits that the application as amended is in condition for allowance and respectfully requests the same. Examiner Arnold is invited to contact Chief Patent Counsel for the patent owner, Jonathan Provoost (Reg. No. 44,292) at 908-238-6392 to discuss any of the amendments or remarks set forth above.

The application as amended contains one independent claim, one total claim, and no multiple dependent claims. As such, the application continues to comply with the 3/20 claim limitation for accelerated applications.

No fees are believed to be due with this submission. Please apply any necessary charges or credits to deposit account **12-0769**, referencing Attorney Docket No. I001-0002USC1.

Respectfully submitted,

/Jonathan N. Provoost, Reg. No. 44,292/ Dated: March 3, 2011

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Electronic Acknowledgement Receipt

EFS ID:	9583338
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Beatrice L. Koempel-Thomas/Anna Goforth
Filer Authorized By:	Beatrice L. Koempel-Thomas
Attorney Docket Number:	I001-0002USC1
Receipt Date:	03-MAR-2011
Filing Date:	22-JUN-2010
Time Stamp:	18:40:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		PP6196.PDF	73564 23a96980f3cb2b0425b65d6b7a69a6769cfe10dd	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	2
	Applicant Arguments/Remarks Made in an Amendment	3	5
Warnings:			
Information:			
	Total Files Size (in bytes):	73564	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/820,866	06/22/2010	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 03/03/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 1	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/MARISSA R. BLYTHER/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/820,866	06/22/2010	James S. Baldassarre	I001-0002USC1	2913

49584 7590 03/25/2011

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SPOKANE, WA 99201

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1613	

NOTIFICATION DATE	DELIVERY MODE
03/25/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

lhpto@leehayes.com

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 12/820,866	**Applicant(s)** BALDASSARRE ET AL.	
	Examiner ERNST ARNOLD	**Art Unit** 1613	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 March 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-19*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

Continuation of 3. NOTE: The term 'patent ductus arteriosus' is not in the speciation as filed and appears to be new matter.

Continuation of 11. does NOT place the application in condition for allowance because: After consultation with a quality assurance specialsit, it has been determined that: 1) the amendment raise issues of proper incorporation by reference of essential subject matter; 2) raises the issue of a need for applicant to UPDATE both their search and examination support documents; 3) requires additional search by the Examiner; 4) requires modification of existing rejections; 5) does not simplify issues for appeal; and 6) does not place the case in immediate condition for allowance.

Do Not Enter
/EA/
3/14/11

Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop After Final Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY AFTER FINAL (37 CFR 1.116)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Examiner Interview of March 3, 2011, and the Advisory Action mailed Feb. 23, 2011.

Applicant respectfully requests entry of this 3nd Reply After Final, reconsideration of the pending rejections, and allowance of the application. A listing of the claims and amendments thereof is shown starting at page 2.

Applicant further asserts that this 3nd Reply After Final has been diligently filed and that the application is in compliance with MPEP 708.02(a)(IV) After-Final and Appeal Procedures, thus maintaining the application's status as an accelerated application.

Remarks to the pending Office Action begin at page 3.

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Request for Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	12/820,866
Filing Date	6/22/2010
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Ernst V. Arnold
Attorney Docket Number	I001 - 0002USC1

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 CFR 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

   a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

      i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

      ii. ☐ Other _____

   b. ☑ Enclosed

      i. ☑ Amendment/Reply

      ii. ☐ Affidavit(s)/ Declaration(s)

      iii. ☑ Information Disclosure Statement (IDS)

      iv. ☑ Other Accelerated exam support docs

2. Miscellaneous

   a. ☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

   b. ☐ Other _____

3. Fees The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

   a. ☑ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 12-0769.

      i. ☑ RCE fee required under 37 CFR 1.17(e)

      ii. ☑ Extension of time fee (37 CFR 1.136 and 1.17)

      iii. ☐ Other _____

   b. ☐ Check in the amount of $ _____ enclosed

   c. ☑ Payment by credit card (~~Form PTO-2038 enclosed~~) Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Christopher P. Rogers, RegNo 36334/	Date	May 2, 2011
Name (Print/Type)	Christopher P. Rogers	Registration No.	36,334

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature	Filed via EFS WEB		
Name (Print/Type)		Date	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1613
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

UPDATED ACCELERATED EXAMINATION SUPPORT DOCUMENT

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

This Updated Accelerated Examination Support Document (AESD) is submitted in support of the Petition for Accelerated Examination filed herewith.

Pending claims 20-27 are shown starting at page 2 herein.

Consideration and grant of the Petition to Accelerate Examination is respectfully requested.

CLAIMS

20. A method of reducing the risk of the occurrence, in a neonate or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

(a) identifying a patient in need of inhaled nitric oxide treatment;

(b) identifying if said patient has a first condition, said first condition being where the patient is known to be dependent on right-to-left shunting of blood;

(c) further identifying if said patient has a second condition, said second condition being pre-existing left ventricular dysfunction, independent and separate from whether said patient is dependent on right-to-left shunting of blood; and

(d) administering said inhaled nitric oxide treatment to said patient if said patient does not have the first condition or the second condition.

21. A method of reducing the risk of one or more adverse events or serious adverse events associated with the use of inhaled nitric oxide in term or near-term neonate patients, said method comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider;

b. informing the medical provider of a first risk factor, said first risk factor being that nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood; and,

c. informing the medical provider of a second risk factor, said second risk factor being independent and separate from said first risk factor, said second risk factor being that in patients with elevated pulmonary capillary wedge pressure, inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema.

22. The method of claim 20 wherein the patients have an elevated pulmonary capillary wedge pressure greater than or equal to 20 mg Hg.

23. The method of claim 20 wherein the neonate patients are receiving inhaled nitric oxide for the treatment of hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

24. The method of claim 20 wherein the source of inhaled nitric oxide is a pressurized cylinder containing nitric oxide and one or more inert gases.

25. A method of reducing the risk of one or more adverse events or serious adverse events associated with the use of inhaled nitric oxide in term or near-term neonates, said method comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider;

b. informing the medical provider of a first risk factor, said first risk factor being that nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood; and,

c. informing the medical provider of a second risk factor, said second risk factor being independent and separate from first risk factor, wherein said second risk factor being that in children with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema.

26. The method of claim 25 wherein children with pre-existing left ventricular dysfunction are characterized by a condition selected from the group consisting of elevated pulmonary capillary wedge pressure, diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease and congenital heart disease.

27. The method of claim 25 wherein children with pre-existing left ventricular dysfunction are characterized by systolic dysfunction and a pulmonary capillary wedge pressure of greater than or equal to 20 mg Hg.

9(A) References Deemed Most Closely Related

An Information Disclosure Statement in compliance with 37 CFR 1.98 has been filed herewith citing each of the following references deemed most closely related to the subject matter of the claims.

List of Most Closely Related References

Rosenberg, Adam A., Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution, J Pediatr 1998:133:720-2. ("Rosenberg").

Ichinose, F. et al., Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential, Circulation 2004;109;3106-3111. ("Ichinose").

Konduri GG et al., A randomized trial of early versus standard inhaled nitric oxide therapy in term and near-term newborn infants with hypoxic respiratory failure, Pediatrics 2004;113;559-564. ("Konduri").

Soto, FJ et al., Cardiopulmonary Hemodynamics in Pulmonary Hypertension: Pressure Tracings, Waveforms, and More, Advances in Pulmonary Hypertension, Winter 08-09, Vol. 7, No. 4, pp. 386-393. ("Soto").

Malloy R., Nitric Oxide Weaning, RT: For Decision Makers in Respiratory Care (December 2000). ("Malloy").

Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, UTMB Respiratory Care Services (2005). ("UTMB Procedure").

Fraisse A et al., Doppler echocardiographic predictors of outcome in newborns with persistent pulmonary hypertension, Cardiol Young 2004; 14:277-283. ("Fraisse").

9(B) Identification of Limitations Disclosed by References

Rosenberg is a review article of a selection of then-published studies concerning inhaled nitric oxide in premature infants with severe hypoxemic respiratory failure. No

new studies or data is reported. As such, Rosenberg is concerned with respiratory failure as opposed to heart failure.

Ichinose is a review article concerning inhaled nitric oxide being a selective pulmonary vasodilator. Ichinose reviews current uses and discusses the therapeutic potential of inhaled nitric oxide. No new studies or data is reported.

Konduri reports the results of a randomized trial that enrolled neonates born at ≥ 34 weeks gestation. The authors concluded that inhaled nitric oxide (iNO) improved oxygenation but does not reduce the incidence of ECMO/mortality when initiated at an oxygenation index of 15-25 compared to initiation at >25 in-term and near-term neonates with respiratory failure. (See Abstract).

Soto is a continuing medical education paper concerning cardiopulmonary hemodynamics in patients with pulmonary hypertension. Under the heading "Vasodilator challenge," Soto discusses a patient receiving iNO resulting in increased PCWP and V wave pressure upon vasodilation. (See p. 389). The findings point to LVD being the likely cause of pulmonary hypertension in the patient.

Malloy is an article pointing out that iNO is contraindicated in neonates dependent on right-to-left shunting of blood.

UTMB Procedure includes guidelines for iNO therapy. Under the heading "Indications", it discloses that iNO is indicated for use in term and near-term neonates with hypoxic respiratory failure associated with various conditions.

Fraisse discusses a study involving neonates with persistent pulmonary hypertension. The authors concluded that "an exclusively left-to-right shunt across the atrial septum increases the risk of failing to respond to nitric oxide." (P. 282 left column). Fraisse is concerned with the "predictive features of echocardiography in persistent pulmonary hypertension of the newborn." (Id. at right column).

9(C) Detailed Explanation of Patentability

Independent claim 20 involves identifying the first condition (right-to-left shunt) and the second condition (pre-existing LVD). Independent claims 21 and 25 involve informing the medical provider of the first and second risk factors (right-to-left shunt and pre-existing LVD). Claim 20 has the additional step (d) of administering iNO if the patient does not have right-to-left shunt or pre-existing LVD. Claims 21 and 25 have the additional step (a) of providing NO gas for inhalation.

None of the references disclose an increased risk of adverse events or severe adverse events associated with iNO treatment in a pediatric patient population (comprising neonates and near-term neonates) that have been diagnosed as having pre-existing left ventricular dysfunction (LVD), separate and independent from the known contraindication of iNO for neonates dependent on right-to-left shunting of blood.

Thus, claims 20-27 are patentably novel and nonobvious over the new prior art set forth herein at least because it fails to disclose or render obvious the increased risk of adverse events or serious adverse events associated with iNO treatment in a pediatric population.

9(D) Concise Statement of Utility

The instantly claimed invention is eligible subject matter under 35 USC 101 for patentable utility in that the claims are generally directed to a method of reducing the risk of adverse events and serious adverse events in patients in need of being treated with inhaled nitric oxide.

9(E) Showing of Support under 35 USC 112, First Paragraph

Support for the new claims is found in the specification of the application, as filed, including the original claims as filed and paragraphs [0007], [0011], [0014], [0020], [0023] and [0052] of the specification. In addition, with respect to the contraindication for neonates dependent on right to left shunting of blood, this language is expressly found in the prescribing information for inhaled nitric oxide, incorporated by reference in the specification at paragraph [0020], and as per the amendment to the specification above, this language is now expressly included in paragraph [0020].

9(F) Identification of References Disqualified as Prior Art under 35 USC 103(c)

None of the cited references are disqualified as prior art under 35 USC 103(c).

Respectfully Submitted,

/Christopher P. Rogers, RegNo 36,334/ Date: May 2, 2011

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UNITED STATES PATENT & TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY AMENDMENT 37 CFR 1.111(a)
ACCELERATED EXAM – TRANSMITTAL REPLY

This communication is responsive to the Final Office Action mailed November 2, 2010, setting a shortened statutory period for reply of 3 months.

Applicant respectfully requests entry of this Reply Amendment, reconsideration of the pending rejections, and allowance of the application.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims beginning on page 3 of this paper.

The **Remarks** begin on page 6 of this paper.

Amendments to the Specification

Please amend paragraph **[0020]** as follows:

[0020] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety. Section 4 of the prescribing information, Contraindications, states that INOmax® is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Amendments to the Claims

Please cancel claims 1-19. Please add new claims 20-27.

1-19. Canceled.

20. (New) A method of reducing the risk of the occurrence, in a neonate or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

(a) identifying a patient in need of inhaled nitric oxide treatment;

(b) identifying if said patient has a first condition, said first condition being where the patient is known to be dependent on right-to-left shunting of blood;

(c) further identifying if said patient has a second condition, said second condition being pre-existing left ventricular dysfunction, independent and separate from whether said patient is dependent on right-to-left shunting of blood; and

(d) administering said inhaled nitric oxide treatment to said patient if said patient does not have the first condition or the second condition.

21. (New) A method of reducing the risk of one or more adverse events or serious adverse events associated with the use of inhaled nitric oxide in term or near-term neonate patients, said method comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider;

b. informing the medical provider of a first risk factor, said first risk factor being that nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood; and,

c. informing the medical provider of a second risk factor, said second risk factor being independent and separate from said first risk factor, said second risk factor being

that in patients with elevated pulmonary capillary wedge pressure, inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema.

22. (New) The method of claim 20 wherein the patients have an elevated pulmonary capillary wedge pressure greater than or equal to 20 mg Hg.

23. (New) The method of claim 20 wherein the neonate patients are receiving inhaled nitric oxide for the treatment of hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

24. (New) The method of claim 20 wherein the source of inhaled nitric oxide is a pressurized cylinder containing nitric oxide and one or more inert gases.

25. (New) A method of reducing the risk of one or more adverse events or serious adverse events associated with the use of inhaled nitric oxide in term or near-term neonates, said method comprising:

a. providing a source of pharmaceutically acceptable nitric oxide gas for inhalation to a medical provider;

b. informing the medical provider of a first risk factor, said first risk factor being that nitric oxide is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood; and,

c. informing the medical provider of a second risk factor, said second risk factor being independent and separate from first risk factor, wherein said second risk factor being that in children with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary wedge pressure leading to pulmonary edema.

26. (New) The method of claim 25 wherein children with pre-existing left ventricular dysfunction are characterized by a condition selected from the group consisting of elevated pulmonary capillary wedge pressure, diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral

cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease and congenital heart disease.

27. (New) The method of claim 25 wherein children with pre-existing left ventricular dysfunction are characterized by systolic dysfunction and a pulmonary capillary wedge pressure of greater than or equal to 20 mg Hg.

REMARKS

In the specification, paragraph [0020] was amended to include language from the INOMAX® prescribing information, which was expressly incorporated by reference within paragraph [0020] of the original specification. The language added to paragraph [0020] is material previously incorporated by reference and the amendment to paragraph [0020] contains no new matter (see 37 CFR 1.57(f) and MPEP 608.01(p)).

Claims 1-19 have been canceled.

New claims 20 – 27 have been added. In particular, new claim 20 is analogous to claim 11, as presented in the 4th After Final Reply of March 3rd, 2011, subsequent to a discussion with Examiner Arnold on March 3, 2011. Support for the new claims is found in the specification of the application, as filed, including the original claims as filed and paragraphs [0007], [0011], [0014], [0020], [0023] and [0052] of the specification. In addition, with respect to the contraindication for neonates dependent on right to left shunting of blood, this language is expressly found in the prescribing information for inhaled nitric oxide, incorporated by reference in the specification at paragraph [0020], and as per the amendment to the specification above, this language is now expressly included in paragraph [0020].

The amendments and new claims address matters discussed during the Examiner Interview conducted on January 10, 2011, a discussion with Examiner Arnold on March 3, 2011, and Advisory Actions of February 23, 2011 and March 25, 2011.

Applicant submits that the amendments herein are in compliance with revised 37 CFR 1.121.

On March 3rd, after a telephone conference with Examiner Arnold, Applicants submitted a 4th Reply After Final seeking to amend a single claim (claim 11) that would

distinguish the present invention from the prior art. In response, on March 25, 2011 the Examiner issued an Advisory Action indicating that the March 3, 2011, amendments did not put the application in condition for allowance due to the fact that the term "patent ductus arterious" was not found in the original specification. To redress this objection, the term "patent ductus arterious" is not presented within new claims 20-27. Further, the Examiner noted that the amendments require an update to the search and examination support documents. Accordingly, with this Request for Continuation, applicants include an updated Accelerated Examination Support Document.

Applicants remain hopeful that there remains agreement with respect to the underlying fact that the INO22 study resulted in a significant medical invention not taught in the prior art and that the question presented is how appropriately to claim that invention.

Applicant sought to establish three points during the January 10, 2011, interview:

1. That the present invention is not directed to neonates reliant on right-to-left shunting of blood at the patent ductus arteriosus because it was already well known in the art at the time of the INO22 study that such patients were ineligible to receive inhaled nitric oxide treatment. This is demonstrated by the Atz et al. article cited by the Examiner and the original FDA label for inhaled nitric oxide issued by the FDA which specifically states that inhaled nitric oxide is contraindicated for this patient population. Rather, the invention claimed in the present application is directed to pediatric patients with pre-existing left ventricular dysfunction that are not reliant on such right-to-left shunting.

2. That the risk of increased adverse events and serious adverse events from administering inhaled nitric oxide to pediatric patients that are not reliant on right-to-left shunting, represented a highly surprising result to those skilled in the art, as demonstrated, e.g., by the fact that it was not recognized or considered by any of the 18

independent review boards (IRBs) at medical institutions in the United States and Europe, nor two independent National Health Authorities (the US FDA and the European Medicines Agency) as a risk to be considered in the original protocol for the INO22 study.

3. That the references cited by the Examiner are directed solely either (a) to neonates reliant on right-to-left shunting (e.g., Atz et al.); or (b) to adults suffering from an entirely different category of left ventricular dysfunction than the type that affects children. Adults with LVD suffer from diastolic dysfunction (stiff, non-compliant heart that cannot fill properly) caused by ischemic cardiomyopathy (heart failure due to coronary artery disease and resultant partial cardiac muscle death) and idiopathic dilated cardiomyopathy. By contrast, children with LVD suffer from systolic dysfunction (soft flabby heart that cannot push blood out) caused by congenital (structural) defects or cardiomyopathies (muscle diseases). For this reason, there were no existing concerns about left ventricular dysfunction in children or neonates until the INOT 22 study was analyzed and understood despite the known teachings of Loh and others with respect to adults.

It is respectfully submitted that if the above three points are agreed, the only barrier to allowance of the present application is identifying claim language that both the Examiner and Applicant agree captures the distinction between the claimed invention and the prior art. With this background, applicant respectfully submits that the new claims presented herein are believed to address the concerns raised by the Examiner in the in the Advisory Action of March 25, 2011.

As amended, claims 20-27 more clearly distinguish between the step of identifying neonates depending on right-to-left shunting of blood at the patent ductus arteriosus, and with respect to the present invention, further identifying patients with pre-existing left ventricular dysfunction, independent of whether such patients have right-to-left shunting of blood at the patent ductus arteriosus. To further clarify this

distinction, dependent claim 26 further limits the claimed definition of pre-existing left ventricular dysfunction in children to only include children characterized by a condition selected from the group consisting of elevated pulmonary capillary wedge pressure, diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease and congenital heart disease. Dependent claim 27 limits the claimed definition of pre-existing left ventricular dysfunction to children with pre-existing left ventricular dysfunction are characterized by systolic dysfunction and a pulmonary capillary wedge pressure of greater than or equal to 20 mg Hg.

Final Office Action of November 2, 2010

Rejections Under 35 USC § 102(b)

Former claim 1 was rejected as being anticipated by the NIH Clinical Center, Department Policy and Procedure Manual for the Critical Care therapy and Respiratory Care Section; Nitric Oxide Therapy, 2000 (hereinafter the "NIH Manual") and Atz, et al., Seminars in Perinatology, 1997 (hereinafter "Atz").

"Anticipation" under 35 USC102 requires that a rejection must be based on a single prior art reference. For a claim to be anticipated, each claim element must be disclosed, either expressly or inherently, in a single prior art reference, and the claimed arrangement or combination of those elements must also be disclosed, either expressly or inherently, in that same prior art reference.

In particular, the Examiner states that the NIH Manual contains a relative contraindication to the use of inhaled nitric oxide in severe left ventricular failure and that such contraindication applies to the treatment of term or near term neonates. During the interview of January 10, 2011, Applicants provided an email from Dr. Dennis

T. Brown, Section Chief, at the NIH Hospital in Bethesda, Maryland, to Jeffrey R. Smith, Esq, an attorney and expert witness at the firm representing Applicant, confirming that the NIH manual reference is limited to the use of inhaled nitric oxide therapy in adult patients being treated in the intensive care unit (a reproduction of the email is attached in Appendix A) and that the NIH Hospital does not contain a neonatal intensive care unit for the treatment of adults. Further, applicants highlight the fact that section 5.0 of the NIH Manual, Contraindications (both absolute and relative contraindications), is virtually an exact duplicate of the same Contraindications (both absolute and relative contraindications) described in B.H. Cuthbertson, P. Dellinger, O.L., Dyar, T.E. Evens, et al., *UK guidelines for the use of inhaled nitric oxide therapy in adult ICUs*. Intensive Care Med (1997) 23:1212-1218 (see page 1216, Table 1), which is cited in Section 19.0 References of the NIH Manual. Thus, the NIH Manual describes the risks associated with the use of iNO in adult patients, not patients under the age of 18 (e.g., non-adults).

Atz, page 452, states in pertinent part:

> *"Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension. In adults with ischemic cardiomyopathy, sudden pulmonary vasodilation may occasionally unload the right ventricle sufficiently to increase pulmonary blood flow and harmfully augment preload in a compromised left ventricle. The attendant increase in left atrial pressure may produce pulmonary edema. … A different, but related phenomenon may be operative in the newborn with severe left ventricular dysfunction and pulmonary hypertension. In these patients, the systemic circulation may depend in part on the ability of the right ventricle to sustain cardiac output through a right-to-left shunt across the patent ductus arteriosus. Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation. Therefore, in newborns with severe left ventricular dysfunction, predominantly left*

to right shunting at the foramen ovale and exclusively right to left shunting at the ductus arteriosus, NO should be used with extreme caution."

Thus, Atz describes two distinct phenomenon – (i) the potential effects of inhaled nitric oxide in adults, and (ii) the potential effects of inhaled nitric oxide in newborns dependent on right-to-left shunt across the patent ductus arteriosus.

A. Adults

Atz and the NIH Manual describe the potential effects of inhaled nitric oxide on a first patient population, adults with left ventricular dysfunction due primarily to ischemic or hypertensive cardiomyopathy. As explained during the interviews, adult patents are clearly distinct from children due to the fact that the etiology and pathophysiology of the left ventricular dysfunction present in non-adult patients is markedly different from adult patients (systolic vs. diastolic dysfunction). Accordingly, adults are not clinically analogous to children, particularly with respect to left ventricular dysfunction.

In particular, it should be noted that left ventricular dysfunction comes in two broad types: diastolic dysfunction (stiff, non-compliant heart that cannot fill properly) or systolic dysfunction (soft flabby heart that cannot push blood out). As detailed in the accompanying declaration of Dr. Douglas A. Greene, in children, left-sided ventricular dysfunction is generally associated with a soft, overly elastic heart that cannot push blood out, resulting in impaired emptying ("systolic dysfunction"). Conversely, in adults, left-sided ventricular dysfunction is generally ischemic or hypertensive in origin, and is associated with a stiff, non-compliant left ventricle that cannot fill properly ("diastolic dysfunction"). Because of this important clinical and etiological distinction, one would not expect an elevated risk of pulmonary edema or cardiac complications when using inhaled nitric oxide in children with impaired left ventricular dysfunction. For this reason,

there were no existing concerns about left ventricular dysfunction in children until the INOT 22 study was analyzed.

B. Neonates with Right-to-Left Shunt

In addition, Atz is further directed to the potential effects of inhaled nitric oxide in a second, distinct patient population – neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus. As discussed during the interview of January 10, 2011, pre-existing left ventricular dysfunction, as enumerated in the claims, does not include neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus. In particular, patent ductus arteriosus is a congenital disorder in the heart wherein the ductus arteriosus of a neonate (a vascular connection between the pulmonary artery and the aortic arch that allows most of the blood from the right ventricle to bypass the fetus lungs) fails to close naturally after birth (see paragraph 12 of the Declaration of Dr Greene). This condition is very specific and rather uncommon; it has essentially no clinical or physiologic overlap with any other condition discussed in this patent application. At the time of the instant invention, it was widely recognized by those of skill in the art that neonates dependent on right-to-left shunting of blood should not be treated with inhaled nitric oxide (see paragraph 14 of the Declaration of Dr Greene). In fact, this contraindication has been presented in the prescribing information (sometimes referred to as the drug "label") for INOMAX® (nitric oxide) for inhalation, since the approval of the drug by the FDA in December 1999 (see Section 4 of the INOMAX Prescribing Information – Attached hereto as Appendix B). Consequently, patients with this specific condition, were, of course, excluded from the INOT22 study that resulted in the discovery that is the subject of the presently claimed invention (see paragraph 20 of the Declaration of Dr Greene). Moreover, in 2009, based on the findings from the INOT22 study, the FDA approved the addition of the following new warnings to the INOMAX® prescribing information, independent of the existing contraindication for neonates dependent on right-to-left shunting of blood:

"*Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema"* and *"5.4 Heart Failure: Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema)."*

One would have to suppose that the FDA would not add new warnings and precautions to the label of a drug that essentially restate a known contraindication already existing on the approved drug label. Indeed, the new FDA-approved warnings for the use of nitric oxide are clinically distinct from the existing, original INOMAX contraindication disclosed by Atz, with respect to neonates with right-to-left shunt.

In contrast to Atz, the NIH Manual and other prior art references cited by the Examiner, the claimed invention relates to an important discovery in a **third patient population**--non-adult patients (i.e., children and neonates) with pre-existing left ventricular dysfunction who are eligible to receive inhaled nitric oxide treatment (i.e., those not dependent on a right-to-left shunting of blood). As discussed during the interview of January 10, 2011, adult patents are clearly distinct from children due to the fact that the etiology and pathophysiology of the left ventricular dysfunction present in non-adult patients markedly different from adult patients. Further, the pre-existing left ventricular dysfunction in non-adult patients, as claimed in the present invention, is clinically distinct from the pathophysiology within neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus.

Again, to anticipate a claim, a single prior art reference must be enabled and teach each and every element of the claimed invention. In this case, the NIH manual and Atz (with respect to the adult disclosure within Atz) fail to anticipate the claimed invention in that the prior art only discloses a risk associated with the use of inhaled

nitric oxide in adults. In contrast, the present claims are limited to neonates and children, a patient population that is clinically differentiated from adults. With respect to the disclosure in Atz regarding the use of iNO in neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus, the claimed invention pertains to a separate and distinct clinical condition, independent from neonates dependent on right-to-left shunting of blood, such clinical condition being pre-existing LVD. Dependent claims further define LVD to clinical conditions known to those skilled in the art as conditions clinically different from dependency on right-to-left shunting of blood (e.g., systolic dysfunction and elevated PCWP).

Rejection and withdrawal of the anticipation rejections in view of Atz and the NIH manual are respectfully requested.

Rejections Under 35 USC § 103(a)

The Examiner rejected claims 1-19 under 35 USC § 103(a) as being obvious over five different references. In addition to Atz and the NIH Manual, the Examiner further sites Kinsella et al. (The Lancet 1999, 354 1061-1065), Bolooki (Clinical Application of the Intra-Aortic Balloon Pump 1998, 3rd Ed. pp 252-253) and Loh et al. (Circulation 1994, 90, 2780-2785).

Section 35 USC 103 states that "a patent may not be obtained … if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.". The foundation for any determination of obviousness is dependent on the facts of each case and is subject to the factual inquiries announced by the Supreme Court in *Graham v. John Deere,* 383 U.S.1 (1966): (i) the scope and content of the prior art, (ii) differences between the claimed invention and the prior art, (iii) the level of ordinary skill in the art, and secondary indicia of nonobviousness.

As explained previously, Atz and the NIH manual describe the use and potential risks of inhaled nitric oxide therapy in adults, a patient population clinically distinct from the patients enumerated in new claims 20-27. Further, Atz describes the well known contraindication with regard to the use of inhaled nitric oxide in neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus.

Kinsella discloses a double blind study that evaluated 80 premature infants with severe hypoxic respiratory failure. The exclusion criteria was "fatal congenital anomalies or congenital heart disease (except atrial and ventricular septal defects) and the study noted the rate and severity of intracranial hemorrhage, pulmonary hemorrhage, duration of ventilation and chronic lung disease. Kinsella described the potential adverse effects of inhaled nitric oxide on platelet adhesion and the attendant risks of intracranial hemorrhage. Kinsella concluded that low dose iNO improved oxygenation and decreased the need for mechanical ventilation, as well as lowered the frequency of chronic lung disease, but did not improve survival in severely hypoxic neonates. Kinsella is silent with respect to the use of inhaled nitric oxide in non-adult patents having pre-existing left ventricular dysfunction.

Bolooki describes uses of an intra-aortic balloon pump in adult patients, as well as nitroglycerin and calcium channel blockers in the treatment of left ventricular dysfunction (pages 252-253). Bolooki is silent respect to the use of inhaled nitric oxide in non-adult patients.

Loh is a study of 19 adult patients with an average age of 52 +/- 3 years suffering from ischemic cardiomyopathy (heart failure due to coronary artery disease and resultant partial cardiac muscle death) and idiopathic dilated cardiomyopathy, which resulted in diastolic left ventricular (LV) failure. The patients also had reactive pulmonary artery hypertension (HTN) secondary to LV failure. The patients were identified as having heart failure due to LV dysfunction as classified by adult NYHA

classifications (class III and class IV). The study found that in patients with heart failure due to LV dysfunction, inhalation of nitric oxide causes a decrease in the pulmonary vascular resistance associated with an increase in LV filling pressure. Unlike the claimed invention, Loh does not disclose the use of inhaled nitric oxide in children, a patient population clinically distinct from those treated in Loh and fails to suggest or anticipated an elevated risk for the use of inhaled nitric oxide in children subject to distinct cardiac myopathies than those possessed by the adult patient in the Loh study.

As described herein, contrary to the prior art references cited by the Examiner, the claimed invention relates to an important discovery in non-adult patients with pre-existing left ventricular dysfunction who are eligible to receive inhaled nitric oxide treatment (i.e., those not dependent on a right-to-left shunting of blood). As explained during the interviews, and in the accompanying Declaration of Dr. Douglas A. Greene, those of ordinary skill in the art, prior to the instant invention, would not have found it obvious to withhold inhaled NO treatment from the claimed patient population because the etiology and pathophysiology of left ventricular dysfunction present in adult patient populations and neonates with right-to-left shunt is markedly different from the non-adult patients of the claimed invention. In fact, as described in greater detail below, the members of the INOT22 Screening Committee who designed the study and the approximately 18 Institutional Review Boards and 2 National Health Authorities who reviewed and approved the study prior to its initiation, would have been aware of the cited prior art, yet failed to predict that any untoward effects would be caused by the administration of inhaled NO within the claimed patient population.

The INOT22 Study

The INOT22 study, entitled “Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to assess the safety and effectiveness of INOMAX® as a diagnostic agent in patients undergoing

assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

Upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing left ventricular dysfunction (LVD).

The INOT22 study was an open, prospective, randomized, multi-center, controlled diagnostic trial, with an expected total enrollment of a minimum of 150 patients, in approximately 18 study sites in the US and Europe over approximately 2 years. The expected patient population for enrollment into the INOT22 trial were subjects between the ages of four (4) weeks and eighteen (18) years undergoing diagnostic right heart catheterization scheduled to include pulmonary vasodilation testing to assess pulmonary vasoreactivity. The anticipated study population were subjects with idiopathic pulmonary arterial hypertension, congenital heart disease with pulmonary hypertension and cardiomyopathies.

The INOT22 study was established and designed by the study sponsor, INO Therapeutics LLC (INOT) and a Steering Committee comprising internationally recognized experts in the field of pediatric heart and lung disease.

The original INOT22 protocol contained the following inclusion and exclusion criteria:

Inclusion Criteria

The patient must meet the following criteria:

1. Have any one of the three disease categories:

a. Idiopathic Pulmonary Arterial Hypertension

i. PAPm >25mmHg at rest, PCWP ≤ 15mmHG, and PVRI > 3 u.m^2 or diagnosed clinically with no previous catheterization

b. CHD with pulmonary hypertension repaired and unrepaired,

i. PAPm >25mmHg at rest, and PVRI > 3 u.m^2 or diagnosed clinically with no previous catheterization

c. Cardiomyopathy

i. PAPm >25mmHg at rest, and PVRI > 3 u.m^2 or diagnosed clinically with no previous catheterization

2. Schedule to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

3. Males or females, ages 4 weeks to 18 years, inclusive

4. Signed IRB/IEC approved informed consent (and assent if applicable).

Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.

2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.

3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigation medications, nitroglycerein, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.

4. Pregnant (urine HCG +).

The original INOT22 investigational plan and study protocol were further reviewed and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the participating study institutions, including review by the principal investigator within each study institution.

At no time did any member of the Steering Committee, INOT, nor any member of an IRB, IEC, or individual principal investigator, appreciate, recognize or otherwise suggest that the exclusion criteria be amended to exclude study subjects (i.e., children) with pre-existing left ventricular dysfunction, due to an anticipated or predicted risk of adverse events or serious adverse events arising from the use of iNO within these patients.

After initiation and enrollment of the first 24 subject in INOT22, there were 5 serious adverse events – a rate much higher than expected based on prior clinical experience. Each of these 5 SAEs were cardiovascular events, and included pulmonary edema, cardiac arrest and hypotension (low blood pressure).

Thereafter, in February 2005, INOT and the Steering Committee convened to review the unexpected SAEs described above, and upon review and discussion, expressed concern that the unexpected SAEs may be due to the administration of iNO in subjects having pre-existing LVD. Accordingly, based upon a review of the SAE cases, the exclusion criteria of the INOT22 protocol was amended to thereafter exclude subjects with pre-existing LVD. For the purpose of the study, the exclusion criteria was amended to exclude subjects from enrollment if the subjects demonstrated an elevated pulmonary capillary wedge pressure (PCWP), defined within the study as subjects having a PCWP greater than 20 mmHg. All study sites were notified immediately. The exclusion criteria was amended as follows:

Exclusion Criteria

The patient will be excluded from enrollment if any of the following are true:

1. Focal pulmonary infiltrates on chest radiograph.

2. Diagnosed with severe obstructive or restrictive pulmonary disease that is significantly contributing to the patient's pulmonary hypertension.

3. Received treatment with nitric oxide for inhalation within 30 days prior to study initiation, are on other investigation medications, nitroglycerein, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin.

4. Pregnant (urine HCG +).

5. Baseline PCWP > 20 mmHg.

Upon conclusion of the INOT22 study and completion of the final study report, INOT noted that subsequent to excluding patients with pre-existing LVD, the rate of serious adverse events (including serious adverse events associated with heart failure) was significantly reduced. There were 5 SAEs amongst the first 24 subjects of this type prior to the additional exclusion criteria, but only 2 SAEs amongst the last 80 subjects in the study after the additional exclusion. Furthermore, there were 2 SAEs amongst the 4 subjects with evidence of pre-existing LVD, but only 5 SAEs amongst the 120 subjects without evidence of LVD.

Therefore, based on this unexpected finding, on February 25, 2009, INO Therapeutics LLC (owner of NDA 20845) submitted a label supplement to the US Food and Drug Administration (FDA) seeking to amend the prescribing information for INOMAX® to include a warning statement for physicians such that the use of iNO in patients with pre-existing LVD could cause serious adverse events, such as pulmonary edema. On August 28, 2009, the FDA approved the INOMAX® label supplement to include the following new information:

WARNINGS AND PRECAUTIONS

Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

5 WARNINGS AND PRECAUTIONS

5.4 Heart Failure: Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

Thereafter, similar warnings were added to the INOMAX label worldwide, such as Japan, Europe, Canada and Australia.

Person of Ordinary Skill in the Art

As is well known, the determination of obviousness, while a question of law, is based on underlying factual inquiries that include the level of ordinary skill in the pertinent art. Factors that may be considered are (i) the educational level of the inventor, (ii) the type of problems encountered in the art, (iii) prior art solutions to those problems; (iv) the rapidity with which innovations are made; (v) the sophistication of the technology; and (vi) the education level of active workers in the field. Applicant notes that the members of the Steering Committee were retained because they were well recognized **experts** in the field, not because they were considered to have "ordinary skill in the art". Thus, although the Steering Committee did not predict or anticipate the risk of adverse events or serious adverse events associated with the use of iNO in study subjects with pre-existing LVD, this level of anticipation is not representative of those of ordinary skill in the art, but rather of those of presumptively **extraordinary** skill. Thus, it is all that much more surprising, and supportive of the non-obviousness of the claims, that the Steering Committee, INOT, the various Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) and the individual Principal Investigators, upon review of the original INOT22 protocol, and in view of prior art cited by the Examiner, did not predict or anticipate the risk of adverse events or serious adverse events associated with the use of iNO in non-adult patients with preexisting LVD.

Accordingly, as evidenced and supported by the findings of the INOT22 study which gave rise to the present invention, in view of the prior art, one skilled in the art at

the time of the invention would not have predicted or anticipated that pediatric patients with pre-existing LVD would be at risk of experiencing adverse events or serious adverse events arising from treatment with inhaled nitric oxide. Indeed, as described above, not only was the invention not obvious to one of ordinary skill, but even those of extraordinary skill (i.e., those directly involved in the development and analysis of the INOT22 clinical trial) failed to appreciate the unexpected clinical risks and undesirable clinical outcomes giving rise to the present invention. Importantly, based on prior clinical experience and knowledge of the prior art, these experts predicted the opposite outcome – that the use of iNO in children with pre-existing LVD would not raise an undesired safety risk. Clearly, if such a risk would have been obvious, one of the many skilled medical professionals expert in the field of pediatric cardiology that reviewed the original INOT22 protocol would have noted a predicted increased risk in the claimed patient population. Put simply, they did not. As further support of the non-obviousness of the invention, in view of the prior art, Applicants point out that the senior author of Atz, Dr. David Wessel, was a member of the Steering Committee that designed the original INOT22 protocol. As an author of the Atz reference and the disclosures therein, Dr. Wessel did not predict or anticipate that non-adult patients with pre-existing LVD would be at increased risk of experiencing adverse events or serious adverse events arising from the treatment with inhaled nitric oxide.

Therefore, the documented chain of decisions regarding the original development and subsequent amendment of the INOT22 protocol provides direct evidence of the exact perspective and clinical reasoning of a person skilled in the art (or in this instance, those of extraordinary skill) at the time of the invention. The piecing together of multiple prior art references, without support for doing so, fails to establish the obviousness of the present invention in view of the overwhelming evidence to the contrary presented herein.

In light of the above, Applicant respectfully submits that the application, as amended is in condition for allowance and respectfully requests the same. Examiner Arnold is invited to contact Chief Patent Counsel for the patent owner, Jonathan Provoost (Reg. No. 44, 292) at 908-238-6392 to discuss any of the amendments or remarks set forth above.

Please apply any additional necessary charges or credits to deposit account **12-0769**, referencing Attorney Docket No. I001-0002USC1.

Respectfully submitted,

/Jonathan N. Provoost, Reg. No. 44,292/ Dated: May 2, 2011

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APPENDIX A

From: Brown, Dennis (NIH/CC/CCMD) [E] [mailto:DBrown@cc.nih.gov]
Sent: Wednesday, December 29, 2010 11:27 AM
To: Jeffrey Smith
Cc: Allen, Sarah (NIH/CC/CCMD) [E]
Subject: RE: NIH Policy/ Procedure

Jeff,
Sorry for the delay in responding to you. We have a process in place for outside inquiries and I wanted to make sure I was in compliance. The answers to your questions are as follows:

So, just to make sure that I am not way off base in my analysis of this document, can you provide me with some direction?
Specifically:

(1) Is this document used as a policy and procedure for RT's in the MICU, giving them guidelines in the delivery of iNO to adult patients?

Yes. This is a policy/procedure in place to provide direction to respiratory therapists in the implementation of NO in the MICU to adult patients in the ICU.

(2) Does the Clinical Center (for which the attached policy pertains) have a neonatal ICU?

No. The Clinical Center at the National Institutes of Health does not have a neonatal ICU nor do we care for neonates.

Once again I apologize for the delay. Hopefully the information will provide you with the requested clarification.

Dennis T. Brown

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From: Jeffrey Smith [mailto:JeffreyS@LeeHayes.com]
Sent: Tuesday, December 21, 2010 12:49 PM
To: Brown, Dennis (NIH/CC/CCMD) [E]
Cc: Allen, Sarah (NIH/CC/CCMD) [E]
Subject: NIH Policy/ Procedure
Importance: High

Hi Dennis:

Last week I contacted Sarah Allen regarding a question about an NIH policy dealing with iNO (see my email to her below). She contacted me this morning and felt like you would be the appropriate contact regarding the request below. I have reattached the document in question.

Thanks for your help. Please let me know if you have any questions. I can be reached at my office, (509-944-4786) or via email.

Have a great day.

Jeff
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Corporate Practice Group
Life Science Practice Group
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APPENDIX B

UNITED STATES PATENT AND TRADEMARK OFFICE	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	22-JUN-2010
Title of Application	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor	JAMES S. BALDASSARRE
Assignee	IKARIA, INC.
Group Art Unit	1616
Examiner	ARNOLD, ERNST V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DOUGLAS A. GREENE, M.D.
UNDER 37 C.F.R. § 1.132

I, Douglas A. Greene, do hereby declare the following:

1. I currently hold the position of Executive Vice President and Head, Research and Development at INO Therapeutics LLC ("INO"). A copy of my *curriculum vitae* is attached as **Exhibit 1**.

2. I received an undergraduate degree in biology (*cum laude*) from Princeton University in 1966 and a doctoral degree in medicine (M.D.) from Johns Hopkins School of Medicine in 1970.

3. I spent the next thirty years of my medical career (1970-2000) practicing and teaching medicine at some of America's foremost academic medical centers, including Johns Hopkins, Penn, Pitt, and the University of Michigan. At Michigan, I was a full professor of internal medicine, director of the Michigan Diabetes Research and Training Center, and chief of the Division of Endocrinology and Metabolism.

4. In 2000, I left Michigan to join Merck as Executive Vice President in charge of clinical sciences and product development. In this role, I supervised and directly managed all clinical research at Merck Research Laboratories, among other duties.

5. In 2003, I left Merck for Sanofi-Aventis, where I became a Senior Vice President and Chief Medical Officer. My duties at Sanofi-Aventis included overseeing all aspects of pre-clinical and clinical regulatory development of the company's products and overseeing all medical aspects of the company's US business.

6. In 2010, I joined INO, where – as noted above – I am presently Executive Vice President and Head of Research and Development.

7. INO markets pharmaceutical grade nitric oxide (NO) gas under the brand name INOmax®. INOmax® is administered to patients using INO's proprietary INOvent® and INOmax® DS devices.

8. INOmax® was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999 for the treatment of term and near-term (≥ 34 weeks gestational age) neonates with hypoxic respiratory failure ("HRF") associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn ("PPHN"). From 2000 to the present, INO has been selling INOmax® throughout the United States, Canada and certain other overseas markets.

9. In addition to the approved indication, physicians employ INOmax® to treat or prevent pulmonary hypertension and improve blood oxygen levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome ("ARDS"), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, and improves pulmonary gas exchange.

10. The mechanism of action of INOmax® - the selective relaxation of pulmonary blood vessels - is particularly relevant to the transition of the newborn from the fetal to the neonatal environment. During *in utero* development, the fetal lungs are not filled with air. Accordingly, the fetus obtains oxygen from the mother across the placenta into the systemic circulation, whereas the circulation through the lungs is largely shut down because the pulmonary vessels are tightly constricted. Instead of the blood being pumped from the right side of the heart through the fetal lungs and then returning to the left side of the heart to be pumped to the rest of the body, as it is normally after birth, blood from the right side of the fetal heart bypasses the fetal lungs through a patent ductus arteriosis, a blood vessel connecting the outflow of the right heart directly to the systemic circulation.

11. In addition to the patent ductus arteriosis, the fetal heart contains a second anatomical distinction from the neonatal heart - the foramen ovale - as a means for fetal blood to circumvent the nonfunctional fetal lungs while the fetus obtains its oxygen from the placenta. The foramen ovale is a "hole" located in the wall that separates the right and left atria of the heart. The foramen ovale is usually covered by a flap of tissue known as the septum primum, which is located on the inner wall of the left atrium. The septum primum and the foramen ovale together act as a one-way valve that permits blood to be shunted from the right atrium, where blood pressure is usually high due to the high vascular resistance present in the non-functional fetal lungs, into the left atrium for distribution to the body via the left ventricle. As discussed below, nonclosure of a patent foramen ovale after birth, as well as other forms of congenital heart disease, are often associated with a large persistently patent ductus arteriosis.

12. After birth, the pressure in the pulmonary circulatory system drops, reducing the right atrial pressure below that of the left atrium. This shift in pressure causes the septum primum to close off the foramen ovale, and this flap of tissue eventually becomes incorporated into the intra-atrial wall. In certain instances, however, the foramen ovale may remain open or "patent" after birth. In one such case, elevation of pressure in the pulmonary circulatory system (i.e.: pulmonary hypertension due to various causes) can prevent the pressure shift that leads to the closure of the foramen ovale. This condition is known as patent foramen ovale, and the use

of inhaled nitric oxide to decrease pulmonary hypertension is known to be a successful treatment for right-to-left shunting through a patent foramen ovale.[1]

13. At birth, the ductus arteriosis closes and pulmonary vessels relax, thereby redirecting the outflow of the right heart to the now oxygenated lungs, with oxygenated blood then returning to the left side of the heart to be pumped to the rest of the body from the left ventricle. However, in some instances, neonates are born with severe congenital heart disease involving the left ventricle, wherein the left side of the heart lacks the ability to pump blood to the rest of the body. In these instances, a ductus arteriosis that remains open or "patent" is actually beneficial, and in fact is life-saving when combined with pulmonary hypertension, because the reverse pressure created by the pulmonary hypertension creates a right-to-left shunt through the patent ductus arteriosis, thereby permitting the right ventricle to pump oxygenated blood directly to the systemic circulation to maintain organ function; simply put, the patent ductus arteriosis permits the right ventricle to subsume the role of nonfunctional left ventricle in circulating blood to the body. In these circumstances, stealing blood circulation away from the ductus arteriosis would be potentially fatal, and significantly, pulmonary vasoconstriction is also absolutely essential for survival in order to divert sufficient blood from the right heart through the patent ductus arteriosis to the systemic circulation, thus bypassing the non-functional left side of the heart to maintain life. The terminology to describe this situation is "neonates dependent upon right-to-left shunting of blood" for survival.

14. Administration of inhaled nitric oxide (iNO) in the context of such right-to-left shunting would be catastrophic, because reducing or eliminating the pulmonary vasoconstriction would permit blood to be diverted to the lungs and away from the patent ductus arteriosis.[2] Accordingly, an absolute contraindication for the use of iNO in babies dependent upon right-to-

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1 *See* Fessler MB et al., *Right-to-left shunting through a patent foramen ovale in right ventricular infarction: improvement of hypoxemic and hemodynamics with inhaled nitric oxide*. J. Clin. Anesth. 15: 371-4, 1993, at 371.

2 *See, e.g.,* Atz AM, Wessel DL. *Inhaled nitric oxide in the neonate with cardiac disease.* Sem. Perinatol. 21:441-455, 1997, at 452.

left shunting of blood has been contained in the INOmax® prescribing information since the original approval of INOmax® by the FDA in December, 1999.[3]

15. Pulmonary engorgement also occurs in adults with serious left-sided heart disease due to coronary artery disease ("ischemic cardiomyopathy"), hypertensive heart disease ("hypertensive cardiomyopathy") or obstructive valvular disease or other conditions that similarly restrict the inflow of blood to the left side of the heart such that engorgement of the pulmonary blood vessels ensues. It is important to note that restriction of left-sided inflow is particularly prominent in the above cardiomyopathies, and is described as diastolic dysfunction.[4] Diastolic dysfunction is extremely common in adult heart disease, especially in the elderly, but is extremely rare in childhood heart disease, which is generally caused by either congenital malformations or viral infections.[5]

16. To summarize, in adults, left-sided ventricular dysfunction is generally ischemic or hypertensive in origin, and is associated with a stiff, non-compliant left ventricle that cannot

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3 *See*, Exhibit 2, section 4, Prescribing Information, INOMAX.

4 *See* "Diastolic Dysfunction" American Heart Association "Learn and Live" website visited April 13, 2011: "The heart contracts and relaxes with each heartbeat. The contraction part of this cycle is called **systole** (SIS'-to-le). The relaxation portion is called **diastole** (di-AS'-to-le). In some people with heart failure, the contraction function is normal but there's impaired relaxation of the heart. This affects the heart's lower, pumping chambers (the ventricles) specifically. If the relaxation part of the cycle is abnormal, it's called diastolic (di"as-TOL'-ik) dysfunction. Because the ventricle doesn't relax normally, the pressure in it increases and exceeds what's normal as blood for the next heartbeat. (It's harder for all of the blood to go into the ventricle.) This can cause increased pressure and fluid in the blood vessels of the lungs. (This is called pulmonary congestion.) It can also cause increased pressure and fluid in the blood vessels coming back to the heart. (This is called systemic congestion.) People with certain types of cardiomyopathy (kar"-de-o-my-OP'-ah-the) may also have diastolic dysfunction."

5 Diastolic dysfunction in children has been described in rare genetic diseases such as Marfan's syndrome [that directly affects the elasticity of connective tissue of the heart and elsewhere], Kawasaki's disease [that creates cardiac ischemia similar to that in adult ischemic cardiomyopathy] or sickle cell disease [that produces fibrotic scars in the myocardium].

fill properly ("diastolic dysfunction"). In contrast, in children, left-sided ventricular dysfunction is generally not of ischemic or hypertensive in origin and is not associated with impaired filling, but rather is associated with a soft, overly elastic heart that cannot push blood out, resulting in impaired emptying ("systolic dysfunction"). Thus, adult left ventricular diastolic dysfunction, but not childhood left ventricular systolic dysfunction, would lead to pulmonary vascular engorgement, requiring caution in the use of iNO.

17. Since the approval of iNO in December 1999, INO has from time-to-time sponsored, supported or otherwise facilitated - under its own FDA Investigational New Drug (IND) application or IND applications filed by other investigators - clinical research exploring the efficacy and safety of iNO in clinical contexts outside the approved indication for PPHN. The results of these investigations are submitted to the FDA and are often published in the medical literature. In May 2004, following detailed consultations with an expert steering committee composed of leading world authorities in pediatric heart and lung disease,[6] INO initiated a multinational randomized controlled 150-patient study entitled "Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation Plus Oxygen in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing" ("INOT22"). Prior to its initiation, the INOT22 study was reviewed and approved by the Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, and by two independent National Health Authorities (the U.S. FDA and the European Medicines Agency (EMEA)). At no time did any of the members of these boards, committees or agencies counsel against giving inhaled nitric oxide to the proposed patient population because of the risk of severe adverse events in pediatric patients (i.e., children) with left ventricular dysfunction.

18. INOT22 was designed and purposed to compare the diagnostic utility of short-term (10 minute) inhalation of iNO alone, iNO plus oxygen ("O_2") or O_2 alone to children between the ages of 4 weeks and eighteen years with either idiopathic pulmonary arterial

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6 The steering committee included Dr. David Wessel of the Department of Cardiology, Children's Hospital and the Department of Pediatrics, Harvard Medical School.

hypertension, congenital heart disease with pulmonary arterial hypertension, or childhood forms of cardiomyopathy undergoing diagnostic right heart catheterization and acute pulmonary vasodilatation testing to assess pulmonary vasoreactivity. The rationale for INOT22 were: (1) that in patients with right ventricular failure and lung disorders, the prognosis and course of treatment are determined by acute pulmonary vasodilatation testing (APVT); (2) a reduction in the mean pulmonary artery pressure and pulmonary vascular resistance with acute vasodilator treatment may be used to predict therapeutic efficacy of long-term vasodilator medication; and (3) APVT is also used to evaluate patients being considered for heart or heart/lung transplantation; elevated pulmonary artery pressures and pulmonary vascular resistance place a strain on the right ventricle leading to an increased risk of perioperative morbidity and mortality due to right heart failure post heart transplant. Accordingly, the primary objective of INOT22 was to compare the number of patients who exhibited reversible pulmonary hypertension (vasoreactivity) in response to iNO or iNO plus and oxygen as compared to 100% oxygen alone.

19. Under the direction of the expert steering committee, inclusion and exclusion criteria were established that were intended to ensure the safe use of iNO during the conduct of the study. For example, patients dependent on right-to-left shunting and thereby contraindicated for iNO treatment were not included. Patients also were excluded if they had focal pulmonary infiltrates on chest radiograph, a diagnosis of severe obstructive or restrictive pulmonary disease that significantly contributed to the patient's pulmonary hypertension, had received treatment with iNO within 30 days prior to study initiation or were on other investigational medications, nitroglycerin, sodium nitroprusside, sildenafil, other PDE-5 inhibitors, or prostacyclin, or were pregnant.

20. However, since the inclusion criteria included congenital heart disease or cardiomyopathy, many of the patients had, by design, significant childhood heart disease. This was not considered to pose a significant risk by the experts on the steering committee (1) based on the exclusion of right-to-left shunt-dependent patients, (2) based on prior extensive safe experience with iNO in pediatric patients with congenital heart disease or cardiomyopathy by the

investigators and published in the medical literature,[7] and (3) the very different nature of non-ischemic non-hypertensive childhood heart disease from the ischemic or hypertensive adult form marked by diastolic dysfunction.

21. Surprisingly and unexpectedly, severe adverse events including pulmonary edema and death were noted during the early phase of the study, and the study was stopped. Analysis of the cases revealed that the patients suffering severe adverse events had severe left ventricular dysfunction, largely due to viral cardiomyopathy, and exhibited during their right-sided cardiac catheterizations an increased pulmonary capillary wedge pressure ("PCWP") of greater than 20 mm Hg, indicative of elevated pressures in the upper chamber of the left side of the heart (the left atrium).

22. To determine if there was a correlation between the severe adverse events and the left ventricular dysfunction of the patients that had suffered them, a protocol amendment was submitted to FDA to exclude – on an ongoing basis - patients with severe left ventricular dysfunction with a PCWP greater than 20 mm Hg from further enrollment in the study. The study was then completed. On analyzing the data from the study, the inventors concluded that a correlation did, in fact, exist between the severe adverse events that had occurred during the study and the left ventricular dysfunction of the patients that had suffered them. Accordingly, INO subsequently requested that the FDA add an additional warning to the product labeling for INOmax concerning use of the drug within patients with left ventricular dysfunction. The FDA agreed and included an additional warning in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information (in the US and worldwide).[8]

23. Competent practitioners would understand that the warnings included in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information are intended as a separate warning generally applicable to all patients with left ventricular dysfunction and not limited to those patients having left ventricular dysfunction that also rely on

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[7] *See* Atz AM et al. *Combined effects of nitric oxide and oxygen during acute pulmonary vasodilator testing.* J. Amer. Coll. Cardio. 33:813-819, 1999, at 814, 818.

[8] *See* **EXHIBIT 2.**

right to left shunting of blood. This second category of patients is the subject of a separate section of the US Package Insert which expressly provides that INOmax is contraindicated for patients with this condition. The fact that administration of INOmax would be harmful to patients dependent on right to left shunting of blood has been well known for many years as demonstrated by several of the references that are of record in the present case including [e.g., Atz AM, Wessel DL. *Inhaled nitric oxide in the neonate with cardiac disease.* Sem. Perinatol. 21:441-455, 1997].

24. Furthermore, no competent practitioner would understand the separate warnings in section 5.4 and the Warnings and Precautions section of the INOmax prescribing information, or the disclosure in the present application of the potential for severe adverse events in patients with left ventricular dysfunction as referring to patients dependent on right to left shunting of blood, since it has long been known that the use of INOmax is contraindicated in such patients. Rather, the competent practitioner would understand the additional warnings added at section 5.4 and within the Warnings and Precautions section of the INOmax prescribing information, and the disclosure in the present application of the potential for severe adverse events in patients with left ventricular dysfunction, as a distinct and separate warning and disclosure that administration of INOmax to patients with left ventricular dysfunction generally (even those not dependent on right to left shunting of blood) may result in serious adverse events.

25. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the '359 patent.

26.

Dated April 29, 2011

Douglas A. Greene, M.D.

EXHIBIT 1

CURRICULUM VITAE

PERSONAL DATA

Name: Douglas Alan Greene, M.D.

EDUCATION

High School	Columbia High School, South Orange, NJ, 1962
Undergraduate	Princeton University, Princeton, NJ, BA Biology(cum laude), 1962-1966
Graduate/Professional	Johns Hopkins School of Medicine, Baltimore, MD, M.D., 1966-1970

POSTDOCTORAL TRAINING

Medical Internship:	Department of Medicine, Johns Hopkins, Baltimore, MD, 1970-1971
Medical Residency:	Department of Medicine, Johns Hopkins, Baltimore, MD, 1971-1972
Fellowship:	Medical Fellowship, Department of Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, 1970-1972
	Post-doctoral Research Fellow, Diabetes, George S. Cox Medical Research Institute; Hospital of the University of Pennsylvania, Philadelphia, PA (Dr. Albert I. Winegrad, preceptor), 1972-1975
	Medical Fellowship, Department of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, PA, 1972-1975

NON-ACADEMIC EMPLOYMENT

2000-2003 Executive Vice President, Clinical Sciences and Product Development (CSPD), Merck Research Laboratories, Rahway, New Jersey, and Corporate Officer, Merck, Inc. Supervised and directly managed all clinical research, regulatory affairs, clinical and non-clinical quality assurance and pharmaco-vigilance at Merck Research Laboratories.

2003-2006 Vice President, Head Corporate Regulatory Development, Sanofi-Aventis, Bridgewater, NJ. Overseeing all aspects of corporate regulatory development of all pre-clinical and clinical development projects/life-cycle products in Research & Development.

2006-2009 Senior Vice Preseident, Chief Medical Officer, Sanofi-Aventis, Bridgewater, NJ. Overseeing medical, regulatory, pharmocovigilance, risk management, education and medical communications for US region, Member US Executive Committee, Member Committee Operational de Development, International Clinical Development.

2009-present Senior Vice President, Senior Scientific Advisor, Sanofi-Aventis, Bridgewater, New Jersey. Member Corporate Portfolio Valuation Process and Drug Development Committees. The position at the interface between the Research and Development and Pharmaceutical Operations is responsible for providing key scientific and medical guidance for sanofi-aventis' scientific strategy within U.S. and global contexts to enhance the quality and effectiveness of the company's research and product portfolio, including assessment and guidance of internal R&D product pipeline and franchise portfolio and external commercial and academic innovation opportunities.

ACADEMIC APPOINTMENTS

1975-1980	Assistant Professor of Medicine, University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania
1980-1986	Associate Professor of Medicine, Director, General Clinical Research Center and Diabetes Research Laboratories, University of Pittsburgh, School of Medicine
1986-2000	Professor of Internal Medicine, Director, Michigan Diabetes Research and Training Center, University of Michigan School of Medicine
1991-2000	Chief, Division of Endocrinology & Metabolism, University of Michigan School of Medicine
2000-Present	Adjunct Professor, Internal Medicine, Division of Endocrinology & Metabolism, University of Michigan, School of Medicine

SELECTED SCIENTIFIC ACTIVITIES

1988-1994	Chairman, Endocrinologic and Metabolic Drug Advisory Board, Food and Drug Administration, Washington D.C (Chair, 1990-1994)
1994-2000	Chairman, Merck Scientific Board of Advisors

SELECTED SCIENTIFIC PRIZES AND AWARDS

1986	First Annual Raymond A. and Robert L. Kroc Lecturer, Eisenhower Medical Center, Palm Springs, California
1987	Moore Award, The American Association of Neuropathologists, Seattle, Washington
1987	Carol Sinicki Manuscript Award (The Diabetes Educator), American Association of Diabetes Educators, Chicago, Illinois
1988	Kellion Lecture, International Diabetes Federation, Sydney, Australia
1989	Banting and Best Lecture, Toronto General Hospital, Toronto, Canada
1994	Charles H. Best Lecturer, Toronto Diabetes Association, Toronto, Canada
1996	Invited Speaker, Seventy-fifth Anniversary Celebrating the Discovery of Insulin, Toronto, Canada
1996	First Alan Robinson Lecturer, University of Pittsburgh
1998	Outstanding Foreign Investigator Award, Japan Society of Diabetic Complications

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2. Winegrad AI, Greene DA: Diabetic polyneuropathy: The importance of insulin deficiency, hyperglycemia and alterations in myoinositol metabolism in its pathogenesis. *N. Engl. J. Med.* 295:1416-1420, 1976.

3. Greene DA, Lattimer SA: Sodium- and energy dependent uptake of myo-inositol by rabbit peripheral nerve. Competitive inhibition by glucose and lack of an insulin effect. *J. Clin. Invest.* 70:1009-1018, 1982.

4. Greene DA, Lattimer SA: Impaired rat sciatic nerve sodium-potassium ATPase in acute streptozocin diabetes and its correlation by dietary myo-inositol supplementation. *J. Clin. Invest.* 72:1058-1063, 1983.

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EXHIBIT 2

INOmax® (nitric oxide) for inhalation

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INOmax safely and effectively. See full prescribing information for INOmax.

INOmax (nitric oxide) for inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions, Heart Failure (5.4) 8/2009

INDICATIONS AND USAGE

INOmax is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (1.1).

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration (1.1).

Utilize additional therapies to maximize oxygen delivery (1.1).

DOSAGE AND ADMINISTRATION

Dosage: The recommended dose of INOmax is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).

Administration:

- INOmax must be delivered via a system which does not cause generation of excessive inhaled nitrogen dioxide (2.2).
- Do not discontinue INOmax abruptly (2.2).

DOSAGE FORMS AND STRENGTHS

INOmax (nitric oxide) is a gas available in 100 ppm and 800 ppm concentrations.

CONTRAINDICATIONS

Neonates known to be dependent on right-to-left shunting of blood (4).

WARNINGS AND PRECAUTIONS

Rebound: Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).

Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).

Elevated NO_2 Levels: NO_2 levels should be monitored (5.3).

Heart Failure: In patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

ADVERSE REACTIONS

Methemoglobinemia and elevated NO_2 levels are dose dependent adverse events. Worsening oxygenation and increasing pulmonary artery pressure occur if INOmax is discontinued abruptly. Other adverse reactions that occurred in more than 5% of patients receiving INOmax in the CINRGI study were: thrombocytopenia, hypokalemia, bilirubinemia, atelectasis, and hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and http://www.inomax.com/ or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nitric oxide donor agents: Nitric oxide donor compounds, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical formulations, may have an additive effect with INOmax on the risk of developing methemoglobinemia (7).

Revised: August 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Hypoxic Respiratory Failure

INOmax® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies *[see Clinical Studies (14)]*.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOmax administration.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but these patients did not then improve on the higher dose. As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm, doses above this level ordinarily should not be used.

2.2 Administration

The nitric oxide delivery systems used in the clinical trials provided operator-determined concentrations of nitric oxide in the breathing gas, and the concentration was constant throughout the respiratory cycle. INOmax must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. The INOvent® system and other systems meeting these criteria were used in the clinical trials. In the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms. The system should be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide, such as INOcal®. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. Oxygen levels should also be measured.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

Do not discontinue INOmax abruptly, as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax. Discontinue/wean cautiously.

3 DOSAGE FORMS AND STRENGTHS

Nitric oxide is a gas available in 100 ppm and 800 ppm concentrations.

4 CONTRAINDICATIONS

INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS

5.1 Rebound

Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

5.2 Methemoglobinemia

Methemoglobinemia increases with the dose of nitric oxide. In clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 48 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide, the methemoglobin levels returned to baseline over a period of hours.

5.3 Elevated NO_2 Levels

In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

5.4 Heart Failure

Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

6.1 Clinical Trials Experience

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax in the CINRGI study with event rates >5% and greater than placebo event rates. None of the differences in these adverse reactions were statistically significant when inhaled nitric oxide patients were compared to patients receiving placebo.

Table 1:
Adverse Reactions in the CINRGI Study

Adverse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 (10%)	13 (13%)
Withdrawal	9 (10%)	12 (12%)
Atelectasis	8 (9%)	9 (9%)
Hematuria	5 (6%)	9 (9%)
Hyperglycemia	6 (7%)	8 (8%)
Sepsis	2 (2%)	7 (7%)
Infection	3 (3%)	6 (6%)
Stridor	3 (3%)	6 (6%)
Cellulitis	0 (0%)	5 (5%)

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of INOmax. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

7 DRUG INTERACTIONS

No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

8.2 Labor and Delivery

The effect of INOmax on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

8.4 Pediatric Use

Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). No information about its effectiveness in other age populations is available.

8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

10 OVERDOSAGE

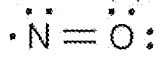
Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

11 DESCRIPTION

INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge (psig)).

The structural formula of nitric oxide (NO) is shown below:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

12.2 Pharmacodynamics

Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

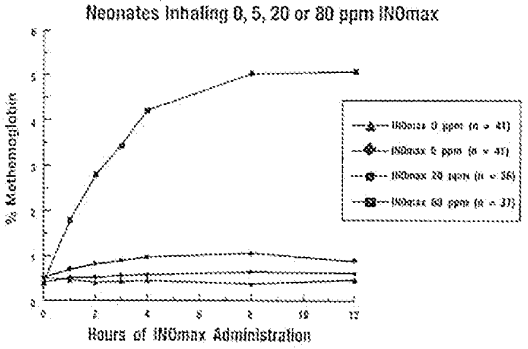
12.4 Pharmacokinetics: Uptake and Distribution

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

12.5 Pharmacokinetics: Metabolism

Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1:
Methemoglobin Concentration – Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients, but one patient did not exceed 7% until 40 hours.

12.6 Pharmacokinetics: Elimination

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 28 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

14 CLINICAL STUDIES

14.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O × fraction of inspired oxygen concentration [FIO_2]× 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 *[see Clinical Pharmacology (12.1)]*.

NINOS Study

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2:
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*,†	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups *[see Adverse Reactions (6.1)]*. Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI Study

This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 3.

Table 3:
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO*,†	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

* Extracorporeal membrane oxygenation
† ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups *[see Adverse Reactions (6.1)]*.

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

ARDS Study

In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FiO_2 <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation. Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

16 HOW SUPPLIED/STORAGE AND HANDLING

INOmax (nitric oxide) is available in the following sizes:

Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)
Size D	Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)
Size 88	Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (USPTO)	
Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1613
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Updated Pre-Examination Search Document

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Updated Pre-Examination Search Document is provided in support of the Petition for Accelerated Examination filed herewith. This Document is provided as an update of the Search Document filed on June 22, 2010.

An updated pre-examination search was conducted involving U.S. patents and patent application publications, foreign patent documents and non-patent literature as indicated below. The results of the search are provided on an Information Disclosure Statement filed concurrently herewith.

The search primarily includes the following aspects:

- The method of reducing the risk of the occurrence in neonates or near-term neonates of adverse events or serious adverse events associated with inhalation of nitric oxide (iNO) by identifying such patient in need of iNO, administering iNO to the patient unless the patient is identified as having left ventricular dysfunction (LVD) or right-to-left shunting of blood. (See new claim 20).

- The method of reducing the risk of adverse events or serious adverse events in a neonate or near-term neonate associated with iNO by providing NO gas to a medical provider, informing the provider that right-to-left shunting of blood is contraindicated, and that elevated capillary wedge pressure (PCWP) is a risk factor leading to pulmonary edema. (See new claim 21).
- Specifically, that PCWP $\geq$ 20 mm Hg is a risk factor. (See new claim 22).
- Specifically, that neonate patients are receiving iNO for treatment of respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. (See new claim 23).
- Specifically, that the iNO is sourced from a pressurized cylinder containing NO and inert gases. (See new claim 24).
- The method of reducing the risk of adverse events or serious adverse events using iNO in term or near-term neonates by providing iNO to a medical provider, and informing the provider of two risk factors being a contraindication for right-to-left shunting of blood and the risk of increasing PCWP if there is pre-existing LVD. (See new claim 25).
- Specifically, that the LVD is characterized by elevated pulmonary capillary wedge pressure, diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease or congenital heart disease. (See new claim 26).
- Specifically, that the LVD is characterized by PCWP $\geq$ 20 mm Hg. (See new claim 27).

A pre-examination search was conducted involving U.S. patents and patent application publications, foreign patent documents and non-patent literature as indicated below. The results of the search are provided on an Information Disclosure Statement filed concurrently herewith.

8 (A) Pre-examination Search

US patent classification Field of Search:

Class(es)/Subclass(es) Searched:
128/200.14, 128/200.24, 128/203.15, 128/20312, 558 /486, 600/481, 600/513

International patent classification field of Search

Section(s)/Class(es)/Subclass(es)/Main Group(s)/Sub group(s) searched
A61K 33/00, A61K 33/08, A61P 9/00, A61P 9/04, A61P 9/08, A61P 43/00, C01B 21/24

Date Conducted: April 15, 2011

Database Searches:

1) Database Service: MicroPatent, Thomson Innovation

Data Searched:
US Patent Document Databases: US-A, US-G
Foreign Patent Document Databases: EP-A, EP-B, JP, WO, GB-A, INPADOC

Search Logic:

1. (inhal*6 OR breath*3 OR gasp*3) NEAR5 (Nitrogen ADJ1 oxide OR Nitric ADJ1 oxide OR nitrogen ADJ1 monoxide OR NO OR iNO) WITH ((adverse OR undesirable OR unfavourable OR unfavorable) ADJ1 (event*1 OR consequence*1 OR indication*1 OR effect*1) OR trouble*1 OR risk* OR contraindication*1 OR danger* OR threat* OR side ADJ1 effect*1 OR toxin* OR toxic* OR safety OR caution* OR precaution OR warning*)
2. (Nitrogen ADJ1 oxide OR Nitric ADJ1 oxide OR nitrogen ADJ1 monoxide OR iNO) WITH ((adverse OR undesirable OR unfavourable OR unfavorable) ADJ1

(event*1 OR consequence*1 OR indication*1 OR effect*1) OR trouble*1 OR risk* OR contraindication*1 OR danger* OR threat* OR side ADJ1 effect*1 OR toxin* OR toxic* OR safety OR caution* OR precaution OR warning*)

3. (avoid* OR exclud*6 OR except*4 OR omit*4 OR leav*3 ADJ1 out OR tak*3 ADJ1 out) AND (infant*1 OR child*3 OR neonate*1 OR neonatal OR neo-natal OR baby OR babies OR newborn*1 OR term OR pre-term OR near-term)
4. 2 AND 3
5. (identif*8 OR select*3 OR choos*3 OR choice OR opt*4 OR pick*3 OR screen*3 OR find*3 OR segregat*4 OR separat*3 OR distinguish*3 OR detect* OR diagnos* OR test*3 OR recogni* OR spot*4 OR determin* OR assess*) NEAR5 (infant*1 OR child*3 OR neonate*1 OR neonatal OR neo-natal OR baby OR babies OR newborn*1 OR pre-term OR near-term) WITH (Nitric ADJ1 oxide OR nitrogen ADJ1 (monoxide OR oxide) OR NO OR iNO)
6. (inhal*6 OR breath*3 OR gasp*3) NEAR5 (Nitrogen ADJ1 oxide OR Nitric ADJ1 oxide OR nitrogen ADJ1 monoxide OR NO OR iNO)
7. 5 AND 6
8. 3 AND 6
9. ((RL OR R-L OR RIGHT ADJ5 LEFT OR pulmonary) ADJ5 SHUNT* OR Patent ADJ1 ductus ADJ1 arteriosus OR septal ADJ1 defect OR foramen ADJ1 ovale OR Pulmonary ADJ1 stenosis OR Overriding ADJ1 aorta OR Ventricular ADJ1 hypertrophy)
10. (left ADJ1 ventric* ADJ2 dysfunction*3 OR LVD OR left ADJ1 ventricle OR ((diastolic OR systolic) NEAR2 Dysfunction*3) OR Pulmonary ADJ1 Capillary ADJ1 wedge ADJ1 pressure OR PCWP OR Pulmonary ADJ1 edema)
11. 6 AND 9
12. (3 OR 5) AND 6 AND 9
13. 6 AND 10
14. (3 OR 5) AND 6 AND 10
15. 1 AND 9
16. 2 AND 9
17. 1 AND 10

18. 2 AND 10
19. (Treat* OR cure OR curing) NEAR5 (Hypoxic ADJ1 respiratory ADJ1 failure OR Pulmonary ADJ1 hypertension OR hypoxia OR hypoxemia)
20. 19 AND 1
21. 19 AND 6 AND 9
22. 19 AND 6 AND 10

Date Conducted: April 16, 2011

2) Database: Google, Google Scholar, The Journal of Pediatrics, American Academy of Pediatrics, MEDLINE, Journal of Medicinal Chemistry, PubMed

Search Strategy:

1. (right-to-left OR RL OR R-L) AND (shunt OR shunting OR flow OR pump) AND (Nitrogen oxide OR Nitric oxide OR nitrogen monoxide OR NO OR iNO) AND (inhalation OR inhaling OR inhale OR breath OR breathing)
2. (right-to-left OR RL OR R-L) AND (shunt OR shunting OR flow OR pump) AND (Nitrogen oxide OR Nitric oxide OR nitrogen monoxide OR NO OR iNO) AND (risk OR safety OR caution OR precaution OR warning OR contraindication OR contra-indication OR danger OR threat)
3. (right-to-left OR RL OR R-L) AND (shunt OR shunting OR flow OR pump) AND (Nitrogen oxide OR Nitric oxide OR nitrogen monoxide OR NO OR iNO) AND (side effect OR adverse OR undesirable OR unfavourable OR unfavorable)
4. (Pulmonary shunting OR Pulmonary stenosis OR Overriding aorta OR Ventricular hypertrophy OR Patent ductus arteriosus OR atrial septal defect OR Ventricular septal defect OR foramen ovale) AND (risk OR safety OR caution OR precaution OR warning OR contraindication OR contra-indication OR danger OR threat) AND (Nitrogen oxide OR Nitric oxide OR nitrogen monoxide OR NO OR iNO)
5. Inhalation AND Nitric oxide AND right-to-left shunting
6. Inhalation AND Nitric oxide AND Pulmonary shunting

7. Inhalation AND Nitric oxide AND risk AND right-to-left shunting
8. Inhalation AND Nitric oxide AND risk AND Pulmonary Capillary wedge pressure
9. Inhalation AND Nitric oxide AND risk AND left ventric dysfunction
10. Inhalation AND Nitric oxide AND risk AND left ventricular dysfunction
11. Inhalation AND Nitric oxide AND risk AND shunt

Date Conducted: April 17, 2011

8(B) Search Directed to the Invention

The pre-examination search was directed to the claimed invention, encompassing all the features of the claims and giving the claims their broadest reasonable interpretation.

8(C) Search Directed to the Disclosure

No disclosed features that are unclaimed at this time are currently seen as features that may be claimed later.

8(D) Search Report from a Foreign Patent Office

No search report from a foreign patent office is provided here as the pre-examination search.

8(E) Statement of Good Faith

All statements above in support of the petition to make special are based on a good faith belief that the search was conducted in compliance with the requirements of this rule.

Respectfully Submitted,

Lee & Hayes, PLLC
Representatives for Applicant

By: /Christopher P. Rogers, Reg No. 36334/ Dated: May 2, 2011

Christopher P. Rogers
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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(**Not for submission under 37 CFR 1.99)**

Application Number	12820866
Filing Date	2010-06-22
First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

U.S.PATENTS

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button.

U.S.PATENT APPLICATION PUBLICATIONS

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button.

FOREIGN PATENT DOCUMENTS

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	I001-0002USC1

	1	Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, Reference: UTMB RESPIRATORY CARE SERVICES Reviewed: 05/31/05	☐
	2	Ichinose, et al., Inhaled Nitric Oxide - A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential, Circulation. 2004;109:3106-3111.	☐
	3	Konduri, et al., A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure, PEDIATRICS Vol. 113 No. 3 March 2004, pp. 559-564	☐
	4	Fraisse, et al., Doppler echocardiographic predictors of outcome in newborns with persistent pulmonary hypertension, Cardiol Young. 2004 Jun;14(3):277-83.	☐
	5	Malloy, Nitric Oxide Weaning, RT: For Decision Makers in Respiratory Care, December 2000, 2 pages.	☐
	6	Rosenberg, Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution, The Journal of Pediatrics, Volume 133, Issue 6 , Pages 720-722, December 1998	☐
	7	Soto, et al., Cardiopulmonary Hemodynamics in Pulmonary Hypertension: Pressure Tracings, Waveforms, and More, Advances in Pulmonary Hypertension Winter 2008;7(4)386-393.	☐

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EXAMINER SIGNATURE

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christopher P. Rogers/	Date (YYYY-MM-DD)	2011-05-02
Name/Print	Christopher P. Rogers	Registration Number	36334

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Electronic Patent Application Fee Transmittal

Application Number:	12820866
Filing Date:	22-Jun-2010
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Lewis Carl Lee/Anna Goforth
Attorney Docket Number:	I001-0002USC1

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	555	555

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	405	405
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	10000852
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Lewis Carl Lee/Anna Goforth
Filer Authorized By:	Lewis Carl Lee
Attorney Docket Number:	I001-0002USC1
Receipt Date:	02-MAY-2011
Filing Date:	22-JUN-2010
Time Stamp:	16:42:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	3571
Deposit Account	
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		QD9029.PDF	3042148 91969dc4104c5434dbce6a595f3c24898b1fdcc0	yes	49

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Accelerated Exam - Transmittal amendment/reply	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	49

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2	Statement of preexamination search	QD9036.PDF	105452 9634a0593a04fb0f3f8c283cd884164a522fa007	no	7

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3	Request for Continued Examination (RCE)	QE1032.PDF	56653 381c14b25184d4130fb8413ff456ac58db6649f7	no	1

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4	Examination support document	QE1140.PDF	89162 4e28532ab447aa95cc5bf2664035ad9dad81f488	no	7

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5	Information Disclosure Statement (IDS) Filed (SB/08)	QD8994.PDF	35371 b48729b0e3203f20564d24f8789e05e85bd65b52	no	3

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6	NPL Documents	Q90633.PDF	226764 5440c51eb1fc032fb36dfb1e04b87d2bd700d7b2	no	4

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7	NPL Documents	Q90637.PDF	170070 6dff4dc261e8b917be34c85499d1ea96fe7e6b5b	no	7
Warnings:					
Information:					
8	NPL Documents	Q90639.PDF	184722 31f3324586eeb90818c89b67666585a99e2b0c1b	no	8
Warnings:					
Information:					
9	NPL Documents	Q90641.PDF	25419181 5c3b928db7c3e63865ecf2f3b5937e1b4135ab28	no	60
Warnings:					
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10	NPL Documents	Q90643.PDF	387048 cbbfe416f5f159e88008029bd9dd96ce306f91f3	no	4
Warnings:					
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11	NPL Documents	Q90645.PDF	87165 0842328452cc636ae2b5c7e0c553f1bc64458f0a	no	4
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12	NPL Documents	Q90647.PDF	1143774 e2c1600fa5d9258642d67c7e133d665bd8d44e86	no	8
Warnings:					
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13	Fee Worksheet (PTO-875)	fee-info.pdf	32658 b56c68f0339b6fc21949858f4184a89bb419a08a	no	2
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PTO/SB/06 (07-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/820,866	06/22/2010	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **05/02/2011**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	**0**	OR	TOTAL ADD'L FEE	

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

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/FLORENCE PATTERSON/

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Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	I001-0002USC1

U.S.PATENTS						
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	1	Ameduri, et al., Heart Failure in Children, MED-Continuing Medical Education, University of Minnesota. 2009 July 29 (cited 2010 Nov 12); available from URL: http://www.cme.umn.edu/prod/groups/med/@pub/@med/@cme/documents/content/med_content_124593.pdf	☐
	2	AU 2009202685 Office Action dated 06/17/10 (3 pages)	☐
	3	AU 2009202685 Office Action Response dated 07/29/2010, 19 pages	☐
	4	Bates, Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator,	☐
	5	Behera, et al., Nesiritide Improves Hemodynamics in Children with Dilated Cardiomyopathy: A Pilot Study, Pediatr Cardiol (2009) 30:26-34	☐
	6	Bhagavan, et al., Potential role of ubiquinone (coenzyme Q10) in pediatric cardiomyopathy, Clinical Nutrition (2005) 24, 331-338, pp. 331-338	☐
	7	Branson, Inhaled Nitric Oxide in Adults, The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts, December 7, 1997, 2 pages, retrieved at <<http://www.rcjournal.com/abstracts/1997/?id=A00000929>> on 12/22/2010	☐
	8	Braunwald, Heart Failure, chapter 233 of Harrison's Principles of Internal Medicine, 14th Edition, 1998, pp. 1287-1291 & 1360	☐
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	10	Clark, et al., Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension of the Newborn, New England Journal of Medicine, Vol 342, No 7, pp. 469-474	☐
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	12	Cox, et al., Factors Associated With Establishing a Causal Diagnosis for Chidren With Cardiology, Pediatrics, Vol 118, No 4, October 4, 2006, pp 1519-1531, published online October 2, 2006	☐
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	14	Cuthbertson et al., "UK guidelines for thee use of inhaled nitric oxide therapy in adults ICUs*", Intensive Care Med (1997), 23, Springer-Verlag, 1997, pp#1212-pp#1218	☐
	15	Dermatological Cryosurgery in Primary Care with Dimethyl Ether Propane Spray in Comparison with Liquid Nitrogen, Martinez, et al., Atnecion Primaria, Vol. 18, No. 5, (211, 216), September 30, 1996	☐
	16	Ivy, et al., "Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease", J Thorac Cardiovasc Surg 1998; 115:875-882.	☐
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	18	Early Inhaled Nitric Oxide Therapy in Term and Near Term Infants with Respiratory Failure, from ClinicalTrials.gov archive, NCT00005773, 06/23/2005	☐
	19	Ehrenkranz RA, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure", The Neonatal Inhaled Nitric Oxide Study Group, N Engl J Med, 1997, Vol. 336, No. 9, pp. 597-605.	☐
	20	Elbl, et al., Long-term serial echocardiographic examination of late anthracycline cardiotoxicity and its prevention by dexrazoxane in paediatric patients, Eur J Pediatr (2005) 164: 678-684	☐
	21	The Encarta Webster's Dictionary of the English Language (2004) is the second edition of the Encarta World Dictionary, published 1999, <<http://encarta.msn.com/encnet/features/dictionary/dictionaryhome.aspx>>; used to look up the definitions of "precaution" and "exclusion"	☐
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	23	Guideline for Industry; Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, March 1995, 17 pages	☐
	24	Harrison's Principles of Internal Medicine, Fauci, et al., p. 1287-1291 and 1360, 12th edition, McGraw Hill, 1998.	☐
	25	Headrick, Hemodynamic monitoring of the critically ill neonate, J Perinat Neonatal Nurs 1992; 5(4): 58-67	☐
	26	Huddleston, Indications for heart transplantation in children, Progress in Pediatric Cardiology 26 (2009) 3-9	☐
	27	Inhaled Nitric Oxide by Oxygen Hood in Neonates, from ClinicalTrials.gov, NCT00732537, 08/08/2008	☐
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	31	JP 2009157623 Office Action dated 02/23/2010, 3 pages	☐
	32	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	33	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐

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	34	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
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	38	Letter of Acceptance for AU 2010202422, dated 10/7/2010	☐
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	40	Lipschultz, The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia, New England Journal of Medicine 2004; 351:145-153.	☐
	41	Lipschultz, The incidence of pediatric cardiomyopathy in two regions of the United States, New England Journal of Medicine, April 24, 2003. <<http://www.nejm.org/doi/full/10.1056/NEJMoa021715>>	☐
	42	Lipshultz, et al., Cardiovascular status of infants and children of women infected with HIV-1 (P2C2 HIV): a cohort study, The Lancet, Vol 360, August 3, 2002, pp. 368-373.	☐
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	45	Lipshultz, Clinical research directions in pediatric cardiology, Current Opinion in Pediatrics 2009, 21:585-593	☐
	46	Lipshultz, Establishing norms for echocardiographic measurement of cardiovascular structures and function in children, J Appl Physiol 99: 386-388, 2005	☐
	47	Lipshultz, Frequency of clinically unsuspected myocardial injury at a children's hospital, American Heart Journal, Vol 151, No 4, pp 916-922	☐
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	49	Madriago, Heart Failure in Infants and Children, Pediatrics in Review, 2010; 31:4-12	☐
	50	http://www.medterms.com/script/main/art.asp?articlekey=17824	☐
	51	Miller, et al., Nutrition in Pediatric Cardiomyopathy, Prog Pediatr Cardiol, 2007 November; 24(1): 59-71	☐
	52	Mone, Effects of Environmental Exposures on the Cardiovascular System: Prenatal Period Through Adolescence, Pediatrics Vol 113, No 4, April 2004, pp 1058-1069	☐
	53	Murray, Angiotensin Converting Enzyme Inhibitory Peptides Derived from Food Proteins: Biochemistry, Bioactivity and Production,	☐
	54	NIH Clinical Center Services, retrieved at <http://www.cc.nih.gov/ccmd/clinical_services.html>> on 08/18/2010	☐
	55	NIH Clinical Center, Department Policy and Procedure Manual for the Critical Care Therapy and Respiratory Care Section; Nitric Oxide Therapy, 2000, sections 3.1-3.1.2 & 5.2.3	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	I001-0002USC1

	56	Notification of Reason for Rejection, mailed 7/30/2010, from Japanese Patent Application No. 2009-157623 (cites foreign references).	☐
	57	Office Action for AU 2010202422 dated 07/09/2010, 3 pages	☐
	58	Office Action from AU 2009202685 dtd 03/15/2010	☐
	59	Office Action from AU 2010206032 dated 08/16/2010 (3 pages)	☐
	60	Office Action Response for AU 2009202685 to 03/15/2010 OA, filed 06/08/2010 (16 pages)	☐
	61	Office Action Response for JP2007157623 filed on 11/12/2009 (no English translation)	☐
	62	Office Action Response to AU 2010202422 OA dated 07/09/2010, response filed 09/01/2010	☐
	63	Translated copy of the Japanese Office Action mailed February 15, 2011 for Japanese Patent Application No. 2009-157623, a counterpart foreign application for US Patent Application No. 12/494,598	☐
	64	Pazopanib Plus Lapatinib Compared to Lapatinib Alone in Subjects With Inflammatory Breast Cancer, April 22, 2010, p. 4, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/show/NCT00558103>>	☐
	65	PCT/US2010/038652 Search Report dated 07/29/2010, 16 pages	☐
	66	Ratnasamy, et al., Associations between neurohormonal and inflammatory activation and heart failure in children, American Heart Journal, March 2008, pp. 527-533	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	I001-0002USC1

	67	Response filed 08/18/2010 to EP Search Report dated 05/10/10 for EP09251949	☐
	68	NIH Clinical Center 2 Critical Care Medicine Department Sample Rotations, Updated January 2007<<http://www.cc.nih.gov/ccmd/prof_opps/rotation.html>>	☐
	69	Search Report from EP 09251949 dated 05/10/10	☐
	70	Sibutramine-metformin Combination vs. Sibutramine and Metformin Monotherapy in Obese Patients, July 15, 2009, p. 3, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/showNCT00941382>>	☐
	71	Somarriba, et al., Exercise rehabilitation in pediatric cardiomyopathy, Progress in Pediatric Cardiology 25 (2008) 91-102	☐
	72	Strauss, et al., Pediatric Cardiomyopathy - A Long Way to Go, The New England Journal of Medicine, 348; 17, April 24, 2003, pp. 1703-1705	☐
	73	Study of Comparative Effects of Oral Clonidine vs. Oral Diazepam Pre-Medication on the Extent and Duration of Sensory Blockade in Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia, Toshniwal, et al., Interenet Journal of Anesthesiology, 2009, <<http://www.britannica.com/bps/additionalcontent/18/41575551/Study-of-Comparative-Effects-Oral-Clonidine-vs-Oral-Diazepam-Pre-Medication-on-the-Extent-and-Duration-of-Sensory-Blockade-in-Patients-Undergoing-Vaginal-Hysterectomy-Under-Spinal-Anaesthesia>>	☐
	74	The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-Term Infants, from ClinicalTrials.gov archive, NCT00551642, 10/30/2007, 3 pages	☐
	75	Towbin, et al., Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children, JAMA, October 18, 2006 - Vol 296, No. 15, pp. 1867-1876	☐
	76	van Dalen, Treatment for Asymptomatic Anthracycline-Induced Cardiac Dysfunction in Childhood Cancer Survivors: The Need for Evidence, Journal of Clinical Oncology, Vol 21, No 17, (September 11) 2003, pp. 3375-3379	☐
	77	Wilkinson, et al., Epidemiological and outcomes research in children with pediatric cardiomyopathy; discussions from the international workshop on primary and idiopathic cardiomyopathies in children, Progress in Pediatric Cardiology 25 (2008) 23-25	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	I001-0002USC1

	78	http://www.cc.nih.gov/ccmd/clinical_services.html	☐
	79	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm073087.pdf>>	☐
	80	Federal Regulations 21 CFR Part 312, <<http://www.gcrc.uci.edu/rsa/aer.cfm>>	☐
	81	Yoshida, Kiyoshi, " Well-illustrated Diagnostics and Treatment of Heart Failure" Professor of Kawasaki Medical University, cardiovascular internal medicine CIRCULATION Up-to-Date Vol. 2, No. 4, 2007(343), pp. 23-28	☐

If you wish to add additional non-patent literature document citation information please click the Add button

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	12820866
	Filing Date	2010-06-22
	First Named Inventor	James S. Baldassarre
	Art Unit	1613
	Examiner Name	Ernst V. Arnold
	Attorney Docket Number	I001-0002USC1

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement.

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement.

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christopher P. Rogers, RegNo 36334/	Date (YYYY-MM-DD)	2011-05-03
Name/Print	Christopher P. Rogers	Registration Number	36,334

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
Rogers, Christopher...
LEE & HAYES, PLLC
601 West Riverside Avenue Suite 1400
Spokane WA 99201
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 29 July 2010 (29-07-2010)
Applicant's or agent's file reference I001 - 0002PCT	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US2010/038652	International filing date *(day/month/year)* 15 June 2010 (15-06-2010)
Applicant Ikaria Holdings, Inc.	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040 Fax: (+31-70) 340-3016	HODZIC, Iris Tel: +49 (0)89 2399-2084

Form PCT/ISA/220 (July 2009) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annex B).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, International Phase, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet or sheets containing a complete set of claims in replacement of all the claims previously filed must be submitted.

Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively in Arabic numerals (Section 205(a)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, National Chapters.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
I001 - 0002PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2010/038652	15/06/2010	30/06/2009
Applicant		
Ikaria Holdings, Inc.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   METHODS OF IDENTIFYING A PATIENT POPULATION ELIGIBLE FOR TREATMENT WITH NITRIC OXIDE VIA INHALATION

5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2010/038652

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The invention relates to methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/038652

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/21 A61K33/00 A61K45/06 A61P9/08 A61P9/12
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PASCAL, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LOH EVAN ET AL: "Cardiovascular Effects of Inhaled Nitric Oxide in patients With Left Ventricular Dysfunction" CIRCULATION, vol. 90, no. 6, 1994, pages 2780-2785, XP002577161 ISSN: 0009-7322 the whole document ----- -/--	1-30

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2010	29/07/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Albrecht, Silke

4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEMIGRAN MARC J ET AL: "Hemodynamic effects of inhaled nitric oxide in heart failure" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, vol. 24, no. 4, 1994, pages 982-988, XP009131903 ISSN: 0735-1097 cited in the application the whole document	1-30
X	HAYWARD C S ET AL: "Inhaled nitric oxide in cardiac failure: Vascular versus ventricular effects" JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 27, no. 1, 1996, pages 80-85, XP009131904 ISSN: 0160-2446 cited in the application the whole document	1-30
X	OVODOV ET AL: "Nitric oxide: Clinical applications" SEMINARS IN ANESTHESIA, SAUNDERS, CO, NEW YORK, NY, US LNKD- DOI:10.1053/SA.2000.6785, vol. 19, no. 2, 1 June 2000 (2000-06-01), pages 88-97, XP005426335 ISSN: 0277-0326 page 90, column 1 page 93, column 2 - page 94	1-30
X	HENRICHSEN ET AL: "Inhaled nitric oxide can cause severe systemic hypotension" JOURNAL OF PEDIATRICS, MOSBY-YEAR BOOK, ST. LOUIS, MO, US LNKD- DOI:10.1016/S0022-3476(96)70230-5, vol. 129, no. 1, 1 July 1996 (1996-07-01), page 183, XP022199226 ISSN: 0022-3476 the whole document	1-30
X	ADATIA ET AL: "Inhaled nitric oxide and hemodynamic evaluation of patients with pulmonary hypertension before transplantation" JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, ELSEVIER, NEW YORK, NY, US LNKD- DOI:10.1016/0735-1097(95)00048-9, vol. 25, no. 7, 1 June 1995 (1995-06-01), pages 1656-1664, XP005857183 ISSN: 0735-1097 page 1663, column 1	1-30

-/--

4

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CUJEC BIBIANA ET AL: "Inhaled nitric oxide reduction in systolic pulmonary artery pressure is less in patients with decreased left ventricular ejection fraction" CANADIAN JOURNAL OF CARDIOLOGY, vol. 13, no. 9, 1997, pages 816-824, XP002577162 ISSN: 0828-282X the whole document	1-30
X	FINDLAY G P: "Paradoxical haemodynamic response to inhaled nitric oxide" INTERNATIONAL JOURNAL OF INTENSIVE CARE 1998 GB, vol. 5, no. 4, 1998, pages 134-139, XP001536771 ISSN: 1350-2794 the whole document	1-30
X	BOCCHI E A ET AL: "Inhaled nitric oxide leading to pulmonary edema in stable severe heart failure" AMERICAN JOURNAL OF CARDIOLOGY, CAHNERS PUBLISHING CO., NEWTON, MA, US LNKD-DOI:10.1016/0002-9149(94)90496-0, vol. 74, no. 1, 1 July 1994 (1994-07-01), pages 70-72, XP023278686 ISSN: 0002-9149 [retrieved on 1994-07-01] cited in the application the whole document	1-30

4

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/038652	15.06.2010	30.06.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/21 A61K33/00 A61K45/06 A61P9/08 A61P9/12

Applicant
Ikaria Holdings, Inc.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Albrecht, Silke Telephone No. +49 89 2399-7864

Form PCT/ISA/237 (Cover Sheet) (July 2009)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 16-23

because:

☒ the said international application, or the said claims Nos. 16-23 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non- establishment of opinion with regard to novelty, inventive step and industrial applicability

Independent claims 16, 20 will not be examined in accordance with Rule 67.1(v) PCT, as their subject-matter is limited to mere presentations of information (i.e. informing the medical provider in accordance with feature b of claims 16, 20). Mutatis mutandis dependent claims 17-19, 21-23.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents (D1-D9) are referred to in this report; the numbering results from the order of citations found in the Search Report (SR) and will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Claims 1-15, 24-30 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Claims 1-15, 24-30 do not comply with the requirements of Article 5 PCT, the reasons being as follows:

These claims comprise i.a. the step of identifying near-term neonate, neonate or child patients eligible for/ in need of treatment with NO by inhalation. However, in the present case, the disclosure in the patent application does not give the skilled person any guidance on how to identify these patients (eg method of screening, criteria of inclusion/exclusion etc). Independent of the foregoing claims 1-15, 24-30 also lack clarity in the sense of Article 6 PCT, as the wording of feature (a) of claims 9, 24, 25 and claim 1 is vague and leaves the skilled reader in doubt about the exact scope of these claims. Mutatis mutandis dependent claims 2-8, 10-15, 26-30.

Furthermore, claims 1-15, 24-30 are also considered to be unclear in that they comprise a diagnostic step (eg feature (b) of claims 9, 24, 25), but the said diagnostic procedure is not further defined (e.g. omission of the method steps of data collection, of comparison of data with standard values, of finding of any significant deviation during the comparison). As these features are essential to the definition of the invention, but are nevertheless not mentioned in independent claims 1, 9, 24, 25,

these claims do not meet the requirement following from Article 6 PCT that any independent claim must contain all the technical features essential to the definition of the invention.

In addition, claims 28-30 as dependent claims of claims 16, 20 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The reasons are as follows:

Claims 28-30 refer to a medical treatment of a patient (i.e. reducing left ventricular afterload), whereas claims 16, 20 do not relate to any medical treatment of a patient. The method described in claims 16, 20 is merely limited to providing a medical provider with nitric oxide gas and informing him in accordance with feature b of these claims. This contradiction between the subject-matter of claims 16, 20 on one hand and claims 28-30 on the other hand produces a lack of clarity as to the scope of protection afforded by claims 28-30.

In view of the foregoing objections, novelty and inventive step cannot be discussed in detail at present. However, the following should be noted:

The core of the invention appears to reside in the discovery that patients with pre-existing LVD often experience an increased risk of (serious) adverse events when treated with NO by inhalation (cf par.5, 50, 52, 61, 68, 69 of the present application). However, this finding has already been reported in prior art. In particular, D3- D8 explicitly recommend to use inhaled NO with caution in patients with LVD. Furthermore, the authors of D1 state that inhaled NO may have adverse effects in patients with LVD and hence may not be desirable in patients with severe left ventricular failure. D2 reports on the haemodynamic effects of inhaled NO in patients with LVD and concludes that the increase in left ventricular filling pressure seen during NO administration may limit its role to that of a diagnostic agent rather than a therapeutic agent in these patients. As for the specific patient group claimed in the present claims, this cannot contribute to inventive step either, since D5 and D6 refer to neonates and children respectively.

In light of these teachings, it would be obvious for the skilled person to screen patients including neonates and children about to undergo treatment with NO by inhalation and to exclude those with LVD therefrom.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

Electronic Acknowledgement Receipt

EFS ID:	10012403
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Lewis Carl Lee/Anna Goforth
Filer Authorized By:	Lewis Carl Lee
Attorney Docket Number:	I001-0002USC1
Receipt Date:	03-MAY-2011
Filing Date:	22-JUN-2010
Time Stamp:	17:09:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	10012605
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Lewis Carl Lee/Anna Goforth
Filer Authorized By:	Lewis Carl Lee
Attorney Docket Number:	I001-0002USC1
Receipt Date:	03-MAY-2011
Filing Date:	22-JUN-2010
Time Stamp:	17:20:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:					
		Total Files Size (in bytes):	5926626		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Acknowledgement Receipt

EFS ID:	10013036
Application Number:	12820866
International Application Number:	
Confirmation Number:	2913
Title of Invention:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	49584
Filer:	Lewis Carl Lee/Anna Goforth
Filer Authorized By:	Lewis Carl Lee
Attorney Docket Number:	I001-0002USC1
Receipt Date:	03-MAY-2011
Filing Date:	22-JUN-2010
Time Stamp:	17:48:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	NPL Documents	clinical1.pdf	92093 8a83b87a169ba76fb1546d04ed5d1915c8fb2382	no	2

Warnings:	
Information:	

2	NPL Documents	clinical2.pdf	157560 83db810270c7e4447ff041e2adac6e974fca8fde	no	3
Warnings:					
Information:					
3	NPL Documents	clinical3.pdf	188994 25f8281700c23104a584e8d706e81f3049e5c835	no	4
Warnings:					
Information:					
4	NPL Documents	clinical4.pdf	234663 3eceba080e7896f877f367903bb2e62010d85e4e	no	4
Warnings:					
Information:					
5	NPL Documents	medinecinenet.pdf	223157 3246d0f55b5631620b5d8634c540ecc9f3c08fe6	no	2
Warnings:					
Information:					
6	NPL Documents	fda.pdf	122803 1a6f1ec5626919d1edf9c73e28bea38758931c9c	no	17
Warnings:					
Information:					
7	NPL Documents	StudyofComparative.pdf	318637 27dc3555afd44a241d24e2e349f5ab33548243f8	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	1337907		

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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/820,866	06/22/2010	James S. Baldassarre	I001-0002USC1	2913

49584 7590 06/08/2011

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SPOKANE, WA 99201

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	**PAPER NUMBER**
1613	

NOTIFICATION DATE	DELIVERY MODE
06/08/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

lhpto@leehayes.com

Office Action Summary for Applications Under Accelerated Examination	**Application No.** 12/820,866	**Applicant(s)** BALDASSARRE ET AL.
	Examiner ERNST ARNOLD	**Art Unit** 1613

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Since this application has been granted special status under the accelerated examination program,

NO extensions of time under 37 CFR 1.136(a) will be permitted and a SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE:

ONE MONTH OR THIRTY (30) DAYS, WHICHEVER IS LONGER,
FROM THE MAILING DATE OF THIS COMMUNICATION – if this is a non-final action or a *Quayle* action.
(Examiner: For **FINAL** actions, please use PTOL-326.)

The objective of the accelerated examination program is to complete the examination of an application within twelve months from the filing date of the application. Any reply must be filed electronically via EFS-Web so that the papers will be expeditiously processed and considered. If the reply is not filed electronically via EFS-Web, the final disposition of the application may occur later than twelve months from the filing of the application.

Status

1)☒ Responsive to communication(s) filed on *02 May 2011*.
2)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

3)☒ Claim(s) *20-27* is/are pending in the application.
3a) Of the above claim(s) _____ is/are withdrawn from consideration.
4)☐ Claim(s) _____ is/are allowed.
5)☒ Claim(s) *20-27* is/are rejected.
6)☐ Claim(s) _____ is/are objected to.
7)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

8)☒ The specification is objected to by the Examiner.
9)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
10)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

11)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

- See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/2/11; 5/3/11*.	6) ☐ Other: _____.

Search Notes	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/820,866	BALDASSARRE ET AL.	
	Examiner	Art Unit	
	ERNST ARNOLD	1613	

SEARCHED			
Class	Subclass	Date	Examiner

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
search update EAST	6/1/11	EVA
consultation Jean Vollano QAS on incorporation by reference and rejections	5/24/11	EVA
consultation Bennett Celsa QAS	3/14/11	EVA

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/2/11 has been entered.

Claims 1-19 have been cancelled and claims 20-27 are new. Claims 20-27 are pending and under examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 5/2/11 and 5/3/11 were filed after the mailing date of the Office Action on 11/02/10. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner to the extent that English language translations, abstracts or relevance has been provided for foreign references. References without a date have not been considered and a line has been drawn through the reference.

Withdrawn rejections:

Applicant's amendments and arguments filed 5/2/11 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Since Applicant has cancelled all previously rejected claims, then all previous claim rejections have been rendered moot and are withdrawn.

The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Specification

The disclosure is objected to because of the following informalities: The attempt to incorporate subject matter into the specification by reference to INOmax® is defective because the subject matter being incorporated into the claims must also be present in the specification. The same exact language is not present in the specification as used in the claims. See MPEP 608.01(p).

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation

to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 24 introduces new matter as the claim recites the limitation: "a pressurized cylinder containing nitric oxide and one or more inert gases" There is no support in the specification for this limitation. The limitation of: " a pressurized cylinder containing nitric oxide and one or more inert gases" was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses "a gaseous blend of NO and nitrogen...cylinders as a compressed gas

under high pressure" [0021] but does not describe the instantly claimed limitation. There is no guidance in the specification to select "a pressurized cylinder containing nitric oxide and one or more inert gases" which is broader in scope and represents a new concept. From MPEP 2163.06: "Applicant should therefore specifically point out the support for any amendments made to the disclosure." Applicant has not directed the Examiner to the support in the specification for the amendments. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 25 and 27 recite "children" but the method is drawn to "term or near-term neonates" which is a different patient population. While Applicant defines "children" to include those being around 4 weeks to 18 years of age [0023], the claim is internally inconsistent as a 'term or near-term neonate' does not embrace up to 18 years of age. This is especially problematic when the second risk factor is based on children, which can include 18 year olds, and not term or near-term neonates. Claim 26 is rejected as indefinite because it is based on an indefinite base claim. The claims will be examined as they read on term or near term neonates.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atz et al. (Seminars in Perinatology 1997, 21(5), pp 441-455) and Kinsella et al. (The Lancet 1999, 354, 1061-1065) and Loh et al. (Circulation 1994, 90, 2780-2785).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicants claims, for example:

> 20. (New) A method of reducing the risk of the occurrence, in a neonate or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:
>
> (a) identifying a patient in need of inhaled nitric oxide treatment;
>
> (b) identifying if said patient has a first condition, said first condition being where the patient is known to be dependent on right-to-left shunting of blood;
>
> (c) further identifying if said patient has a second condition, said second condition being pre-existing left ventricular dysfunction, independent and separate from whether said patient is dependent on right-to-left shunting of blood; and
>
> (d) administering said inhaled nitric oxide treatment to said patient if said patient does not have the first condition or the second condition.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Atz et al. teach methods using inhaled nitric oxide in the **neonate** with cardiac disease, hence an **identified patient** in need of nitric oxide treatment, (title and Abstract) which intrinsically provides pharmaceutically acceptable NO gas for inhalation to a medical provider to provide to the patient. Atz et al. warn that sudden pulmonary vasodilation may produce **pulmonary edema** (page 452, left column). Atz et al. teach that: "Caution should be exercised when administering NO to patients with severe left ventricular dysfunction and pulmonary hypertension." (page 452, left column). Since pulmonary hypetension is instantly claimed, then the subject intrinsically has hypoxic respiratory failure. Atz et al. continues with: "Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively ***right to left shunting*** at the ductus arteriosus, ***NO should be used with extreme caution, if at all***. We and others have reported ***adverse outcomes*** in this

circumstance." (page 452, left column) (Examiner added emphasis). Artz et al. thus identify conditions in the patients which is screening of the patient. Thus, Atz et al. fairly teaches excluding patients which include neonates with left ventricular dysfunction from inhaled NO treatment because the Examiner interprets "if at all" to mean no treatment and hence exclusion from treatment. The left ventricular dysfunction is intrinsically pre-existing.

To summarize, the methods disclosed by Atz et al. are interpreted to mean:

- identifying a patient eligible for NO treatment;
- diagnosing/identifying if the patient has left ventricular dysfunction;
- excluding that patient with left ventricular dysfunction from treatment with NO but treating the patient with NO for other conditions discussed by Atz et al. with inhalation of NO thereby reducing the risk of adverse events associated with the medical treatment.

Atz et al. teach neonates with pulmonary hypertension (Abstract and page 442, left column to right column) and it is irrelevant to the Examiner as to how the pulmonary hypertension was diagnosed whether by echocardiographic evidence or clinical evidence. The fact that matters is that the hypertension is diagnosed in the patient population.

Kinsella et al. teach excluding patients (premature neonates) from inhaled nitric oxide treatment if they have fatal congenital anomalies or congenital heart disease (Abstract and page 1062, Methods). Since left ventricular dysfunction is a congenital heart disease, as acknowledged by Applicant, (see specification [0028]), and it would be pre-existing, then the methods of Kinsella et al. intrinsically exclude this patient population from the method. The patients also had pulmonary hypertension which would be associated with the cardiac function (Abstract). Thus,

one or more adverse events are reduced in the neonates excluded from the method. The neonate must breathe oxygen to survive. Furthermore, if the patients are already excluded then any further limitations on the treatment are truly irrelevant. The intended patient population is intrinsically at risk of one or more adverse events. Patients are intrinsically identified for nitric oxide inhalation treatment, diagnosed for congenital heart disease which intrinsically includes left ventricular dysfunction, and if the patient meets the criteria than treatment with NO is performed thereby reducing the risk of adverse events associated with the treatment. The neonate must breathe oxygen to survive.

Loh et al. teach that inhaled nitric oxide in patients with left ventricular dysfunction may have adverse effects in patients with LV failure (Title and Abstract). Loh et al. clearly teaches that patients with pulmonary artery wedge pressure, which is synonymous with the instantly claimed pulmonary capillary wedge pressure, ***of greater than or equal to 18 mm Hg*** had a greater effect of inhaled NO due to the greater degree of reactive pulmonary hypertension present in such patients (page 2784, left column). Loh et al. state: "*Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO*." Loh et al. examined this prediction further and verified it (page 2784, left column).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Atz et al. is that Atz et al. do not expressly teach identifying patients with a second condition/risk factor and administering iNO to patients that do not have the first or second condition/risk factors of instant claims 20-27 and inform the medical provider that patients with a pulmonary capillary wedge pressure greater than 20 mm Hg that may increase pulmonary edema. This deficiency in Atz et al. is cured by the teachings of Kinsella et al. and Loh et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of Atz et al. and identify patients with a second condition/risk factor and administer iNO to patients that do not have the first or second condition/risk factors of instant claims 20-27 and inform the medical provider that patients with a pulmonary capillary wedge pressure greater than 20 mm Hg that may increase pulmonary edema, as suggested by Loh et al., and Kinsella et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because: 1) it is common sense that if the neonate is healthy then iNO therapy can be performed safely; 2) if the neonate is not healthy and has left ventricular dysfunction (LVD), then Atz et al. clearly teach using extreme caution or not using NO at all in the treatment of patients with LVD which would also render obvious all conditions/risk factors associated with LVD; and 3) the art of Kinsella et al. establishes excluding certain patients (premature neonates) from inhaled nitric oxide

treatment if they have fatal congenital anomalies or congenital heart disease. Thus it is no stretch of the imagination to exclude patients with LVD, with right to left shunting of the blood or with or without the myriad number of other conditions/risk factors independent and separate from the first risk factor, such as in instant claim 26, characterized by various medical parameters claimed by Applicant from inhaled nitric oxide therapy in order to avoid adverse outcomes as taught by Atz et al. which intrinsically include all the adverse events recited by Applicant including pulmonary edema as discussed above. The ordinary artisan would err on the side of caution for the benefit of the patient.

Furthermore, it is already known through the teachings of Loh et al. that a pulmonary capillary wedge pressure (PCWP) of greater than 18 mg Hg serves as a guidepost for alerting the artisan to adverse events from inhaled NO. Thus, it is not inventive to exclude patients with a PCWP of greater than 20 mm Hg when the art already suggests the risk of trouble of treating patients with a PCWP of 18 mm Hg because inhaled NO increases the wedge pressure as taught by Loh et al. (see entire document).

In summary, it remains the position of the Examiner, which is in alignment with the written opinion of the international search authority, that it is simply not inventive to 'inform' a medical provider that a neonate with LVD is at risk of adverse/serious adverse events from iNO therapy when the art already has established that fact and the ordinary artisan is alerted to this fact. *If the patient has LVD then they are at risk of adverse and/or serious adverse events from iNO therapy and it is not inventive to further identify other secondary conditions/risk factors associated with LVD and provide further warnings for secondary conditions/risk factors that are separate and independent from the first condition/risk factor but nevertheless associated with*

LVD to the medical provider. Screening for conditions that predispose the patient to adverse/serious adverse effects from medical treatment of iNO is obvious given the teachings above. Respectfully, the instantly claimed method steps are in the realm of common sense and not in the realm of invention because it is already known in the art that patients with pre-existing LVD are at risk of adverse effects from iNO. It is obvious to the ordinary artisan that if the neonate has LVD with or without any number of conditions/risk factors, then in order to avoid the risk of adverse or serious adverse events associated with iNO, to then exclude the neonate from iNO therapy. In other words, given the art as a whole, determination of further conditions/risk factors that would exclude the neonate from iNO therapy is obvious given the teachings in the art as discussed above which direct the artisan to screen neonates about to undergo treatment with NO by inhalation and to exclude those with LVD from such treatment.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments:

The Examiner has considered Applicants arguments as they pertain to the previous rejections of record. This is a new rejection of record and arguments directed to the previous rejections of record are now moot since those rejections have been rendered moot by the

cancellation of all previously pending claims and introduction of all new claims. As to Atz, the Examiner cannot agree with Applicant that Atz is directed to adults as Atz clearly discusses neonates as well. Furthermore, Atz clearly discusses a right to left shunting of blood which is the same limitation instantly claimed. As to Kinsella, the Examiner is not relying on Kinsella for teaching iNO in non-adult patients having pre-existing LVD as discussed above. As to Loh, the Examiner is not relying on Loh for teaching administration of iNO in children but rather the correlation between PCWP and iNO. As to the INOT22 study, the exclusion criteria was amended to exclude subjects with pre-existing LVD, subjects with a baseline PCWP>20 mm Hg (pages 19-20 of 27 in Remarks), which is in accordance with the knowledge in the art as discussed above. The expected result is a decreased rate of serious adverse events by excluding such patients which is simply common sense.

Applicant asserts that it requires extraordinary skill to recognize the risk of adverse or serious adverse events associated with the use of iNO in study subjects with pre-existing LVD. Respectfully, the Examiner cannot agree because there is clear and convincing evidence of increased risk of adverse or serious adverse events associated with the use of iNO in study subjects with pre-existing LVD as discussed in the rejection above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 20-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-28 of copending Application No. 12/820980. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more

adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach near-term neonates or neonates.

However the copending broadly teaches children patient population which would include neonates and near-term neonates as clearly neonates are children. The instant specification defines 'children' as being 4 weeks old [0023] which would include newborn and hence neonatal.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 20-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-30 of copending Application No. 12/821020. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach the intended population as having one or more conditions.

However the copending application is drawn to the same patient population which intrinsically has one or more conditions/risk factors as instantly claimed.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 20-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-29 and 37 of copending Application No. 12/821041. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant subject matter embraces or is embraced by the subject matter of the copending subject matter. Both applications are drawn to methods of reducing one or more adverse events in a patient population by excluding from treatment anyone with pre-existing left ventricular dysfunction.

The copending application does not expressly teach the intended population as having one or more conditions.

However the copending application is drawn to the same patient population which intrinsically has one or more conditions/risk factors as instantly claimed.

Therefore one of ordinary skill in the art would have recognized the obvious variation of the instant application over the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Applicant is reminded that for any amendments to the claims (including any new claim) that is not encompassed by the preexamination search and accelerated examination support documents previously filed, applicant is required to provide updated preexamination search and accelerated examination support documents that encompass the amended or new claims at the time of filing the amendment. Failure to provide such updated preexamination search and accelerated examination support documents at the time of filing the amendment will cause the amendment to be treated as not fully responsive and not to be entered. See MPEP § 708.02(a) subsection VIII.D. for more information.

If the reply is not fully responsive, the final disposition of the application may occur later than twelve months from the filing of the application.

Any reply or other papers must be filed electronically via EFS-Web so that the papers will be expeditiously processed and considered. If the papers are not filed electronically via EFS-Web, the final disposition of the application may occur later than twelve months from the filing of the application.

Any reply to this communication filed via EFS-Web must include a document that is filed using the document description of "Accelerated Exam - Transmittal amendment/reply." Applicant is reminded to use proper indexing for documents to avoid any delay in processing of follow on papers. Currently document indexing is not automated in EFS-Web and applicant must select a particular document description for each attached file. An incorrect document description for a particular file may potentially delay processing of the application. A complete

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	"20100330206".pn. and (pressure or pressurized) and inert and hypoxic	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:10
L2	0	"20100330206".pn. and cylinder and inert and hypoxic	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:10
L3	0	"20100330206".pn. and inert and hypoxic	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:11
L4	0	"20100330206".pn. and inert	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:11
L5	1	"20100330206".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:11
L6	0	"20100330206".pn. and inert	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:11
L7	1	"20100330206".pn. and nitrogen	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:11
L8	1	"20100330206".pn. and (failure or hypoxic or echocardiographic or hypertension)	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 19:39
L9	1	"20100330206".pn. and (child or childre)	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/01 20:07

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First Named Inventor	James S. Baldassarre
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

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Examiner Signature	/Ernst Arnold/	Date Considered	06/01/2011

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /E.A./

Application Serial Number	12/820,866
Confirmation Number	2913
Filing Date	June 22, 2010
Title of Application	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor	James S. Baldassarre
Assignee	Ikaria, Inc.
Group Art Unit	1616
Examiner	Arnold, Ernst V.
Attorney Docket Number	I001-0002USC1

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN REPLY TO ACTION OF JUNE 8, 2011

Please amend the above-identified application as follows:

CERTIFICATE OF MAILING BY EFS-WEB FILING

I hereby certify that this paper was filed with the Patent and Trademark Office using the EFS-WEB system on this date:

Amendments to the Specification:

Replace paragraph **[0020]** with the following amended paragraph:

[0020] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety. Section 4 of the prescribing information, Contraindications, states that INOmax® is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Amendments to the Claims

This listing of claims replaces all prior versions and listings of claims in the application.

Listing of Claims:

1-27. (Canceled)

28. (New) A method of reducing the risk of occurrence, in a term or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) identifying a term or near-term neonate patient in need of inhaled nitric oxide treatment, wherein the patient is not known to be dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has pre-existing left ventricular dysfunction; and

(c) excluding the patient from inhaled nitric oxide treatment based on the determination that the patient has pre-existing left ventricular dysfunction.

29. (New) The method of claim 28, wherein the patient has pulmonary hypertension.

30. (New) The method of claim 28, wherein the patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

31. (New) The method of claim 28, wherein the patient is a term neonate.

32. (New) A method of reducing the risk of occurrence, in a term or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) identifying a term or near-term neonate patient in need of inhaled nitric oxide treatment, wherein the patient is not known to be dependent on right-to-left shunting of blood;

(b) determining by diagnostic screening that the patient identified in (a) has pre-existing left ventricular dysfunction; and

(c) excluding the patient from treatment with inhaled nitric oxide based on the determination that the patient has pre-existing left ventricular dysfunction.

33. (New) The method of claim 32, wherein the diagnostic screening comprises echocardiography.

34. (New) The method of claim 32, wherein the patient has pulmonary hypertension.

35. (New) The method of claim 32, wherein the patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

36. (New) The method of claim 32, wherein the patient is a term neonate.

37. (New) A method of reducing the risk of occurrence, in a plurality of term or near-term neonate patients, of one or more adverse events or serious adverse events associated with medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) identifying a plurality of term or near-term neonate patients who are in need of inhaled nitric oxide treatment, wherein the patients are not known to be dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has pre-existing left ventricular dysfunction and a second patient of the plurality does not;

(c) administering the inhaled nitric oxide treatment to the second patient; and

(d) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has pre-existing left ventricular dysfunction.

38. (New) The method of claim 37, wherein the first and second patients have pulmonary hypertension.

39. (New) The method of claim 37, wherein the second patient has congenital heart disease.

40. (New) The method of claim 37, wherein the first patient has a pulmonary capillary wedge pressure that is greater than or equal to 20 mm Hg.

41. (New) The method of claim 37, wherein the first and second patients are term neonates.

42. (New) The method of claim 37, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises diagnostic screening.

REMARKS

The above amendment cancels all of the pending claims and adds new claims 28-42. The new claims are supported throughout the specification and claims as originally filed. For example, the concept of a "plurality" of patients in new claim 37 is supported by the discussion of "patients" (plural) at paragraph [0004] and "a patient population" at paragraph [0007]. Paragraph [0007] also supports the recitation in claim 37 of a first patient who is determined to have left ventricular dysfunction and so is excluded from treatment with inhaled nitric oxide. The claim 37 recitation of a second patient who is determined not to have left ventricular dysfunction and is administered inhaled nitric oxide is supported, e.g., at paragraph [0008]. (Of course, the terms "first" and "second" in claim 37 are merely standard linguistic devices useful to distinguish between two patients, and do not imply any particular temporal order.) The remaining limitations of claim 37 and of the other new claims are supported throughout the specification and original claims, e.g. at paragraphs [0004], [0007], [0008], [0012], [0018], [0020] (as amended), [0028], [0033], [0051], and [0052]. No new matter has been added.

Applicants believe that the subject matter of the present claims is encompassed by the accelerated examination support documents already on file for this application, so that an updated accelerated examination support document should not be needed.

Information Disclosure Statements

The Office action dated June 8, 2011 (the "Office action") states at page 2 that certain references cited in previously-filed information disclosure statements were not considered and their citations were lined-through on the information disclosure statement because the citations did not include dates. The enclosed new information disclosure statement includes complete citations for those references. As copies of the previously-submitted references are already of record, new copies are not being submitted. Applicants will supply new copies if requested. Consideration of the cited references is respectfully requested.

Objection to Specification

The Office action at pages 3-4 objects to the specification, alleging that the attempt to incorporate subject matter into the specification by reference is defective. In the Reply filed with an Request for Continued Examination on May 2, 2011, Applicants had requested that paragraph [0020] of the specification be amended to include certain language quoted from the FDA-approved prescribing information for INOmax®. That Applicants are entitled to do so is clear, because the specification as originally filed included the statement, **"The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety."** See paragraph [0020] in the original specification. Applicants understand the current objection to the specification to be based on the requirement under 37 CFR 1.57(f) that the amendment inserting material in the specification be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. In fact, such a statement appeared in the Reply filed May 2, 2011. See the first paragraph of the Remarks on page 6 of that Reply.

Because the amendment to paragraph [0020] in the Reply filed May 2, 2011, was apparently not entered, it is repeated in the present amendment above. The amendment adds the following language to [0020]: **"Section 4 of the prescribing information, Contraindications, states that INOmax® is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood."** The requisite Statement under 37 CFR 1.57(f) is being filed concurrently herewith, along with a copy of the US Food & Drug Administration (FDA)-approved prescribing information for INOmax® that was current as of the June 30, 2009, priority date (included in the accompanying Information Disclosure Statement and as Exhibit 1 of the Statement under 37 CFR 1.57(f). The language incorporated by reference is quoted from the second page of the prescribing information, left paragraph, Section 4. New independent claims 28, 32, and 37 include a limitation based on the material incorporated by reference: **"wherein the patient(s) is/are not known to be dependent on right-to-left shunting of blood."**

If something more is needed to effect this amendment, the Examiner is respectfully asked to clarify.

Rejection under 35 USC § 112, first paragraph

Claim 24 was rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement due to recitation of "a pressurized cylinder containing nitric oxide and one or more inert gases." Claim 24 has been canceled. As none of the currently pending claims recites that limitation, the rejection is now moot.

Rejection under 35 USC § 112, paragraph 2

Claims 25-27 were rejected under 35 USC § 112, second paragraph, as being indefinite for reciting "children." Claims 25-27 have been canceled and none of the currently pending claims recites "children," rendering the rejection moot.

Rejection under 35 USC § 103(a)

Claims 20-27 were rejected as obvious over Atz & Wessel (*Seminars in Perinatology* 1997, 21(5), 441-455), Kinsella et al. (*The Lancet* 1999, 354, 1061-1065) and Loh et al. (*Circulation* 1994, 90, 2780-2785). Claims 20-27 are canceled above for reasons unrelated to this rejection, rendering the rejection moot as to them. The new claims explicitly require a step of excluding from therapy with inhaled nitric oxide neonates with left ventricular dysfunction who are not known to be dependent on right-to-left shunting of blood. To the extent the rejection may be applied to the new claims now pending in the application, applicants emphatically traverse.

The prima facie obviousness rejection elaborated in the Office action is based on a scientifically flawed misreading of the three cited references. Furthermore, the rejection improperly fails to give due regard to the powerful objective evidence that is present in this case, where none of the many experts who reviewed and approved the initial study protocol for the

INOT22 study raised any concern about including pediatric patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood, and where the U.S. Food & Drug Administration (FDA), when informed of the present invention, required that the label for inhaled nitric oxide therapy include an additional warning about the risk for pediatric patients with left ventricular dysfunction who are not known to depend on right-to-left shunting, as first taught by the present inventors.

To further underscore the nonobviousness of the presently claimed subject matter, applicants submit herewith additional factual evidence directly contradicting the Examiner's interpretation of the references:

(a) A letter from Dr. David L. Wessel stating that neither the Atz & Wessel article, nor the medical literature, taught that a pediatric patient with left ventricular dysfunction who is not dependent on right-to-left shunting of blood would be at additional risk when treated with inhaled NO. Further, Dr. Wessel states that it is ironic that his own publication would be cited to suggest that such a risk would have been obvious to predict the unexpected adverse events within the INOT22 study when he, the senior author of the publication, failed to anticipate or predict these unexpected outcomes when assisting in the drafting of the original INOT22 protocol;

(b) Evidence that when Dr. Wessel and over 115 other medical experts individually reviewed the original INOT22 study protocol, none of them – *not a single one* - raised any concern regarding the potential for severe adverse events in pediatric patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood; and

(c) An elucidation by Douglas A. Greene, M.D., of the scientific concepts behind the passages of the cited references on which the obviousness rejection relies, thoroughly explaining why one of ordinary skill in the art would not have interpreted these passages as does the Examiner.

This evidence is discussed in detail below.

New claims 28, 32, and 37 are independent. Claim 28 reads as follows:

28. A method of reducing the risk of occurrence, in a term or near-term neonate patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) identifying a term or near-term neonate patient in need of inhaled nitric oxide treatment, wherein the patient is not known to be dependent on right-to-left shunting of blood;

(b) determining that the patient identified in (a) has pre-existing left ventricular dysfunction; and

(c) excluding the patient from inhaled nitric oxide treatment based on the determination that the patient has pre-existing left ventricular dysfunction.

Claim 32 is similar to claim 28, adding the phrase "by diagnostic screening" to step (b).

Claim 37 reads as follows:

37. (New) A method of reducing the risk of occurrence, in a plurality of term or near-term neonate patients, of one or more adverse events or serious adverse events associated with medical treatment comprising inhalation of nitric oxide gas, said method comprising:

(a) identifying a plurality of term or near-term neonate patients who are in need of inhaled nitric oxide treatment, wherein the patients are not known to be dependent on right-to-left shunting of blood;

(b) determining that a first patient of the plurality has pre-existing left ventricular dysfunction and a second patient of the plurality does not;

(c) administering the inhaled nitric oxide treatment to the second patient; and

(d) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has pre-existing left ventricular dysfunction.

With respect to the primary reference, Atz & Wessel, the Office action focuses on certain statements that appear in the section entitled "Severe Left Ventricular Dysfunction" at page 452, left column. Page 8 of the Office action provides the following summary of the Examiner's interpretation of Atz & Wessel's disclosures:

> "To summarize, the methods disclosed by Atz et al. are interpreted to mean:
> - identifying a patient eligible for NO treatment;
> - diagnosing/identifying if the patient has left ventricular dysfunction;
> - excluding that patient with left ventricular dysfunction from treatment with NO but treating the patient with NO for other conditions discussed by Atz et al. with inhalation of NO thereby reducing the risk of adverse events associated with the medical treatment."

Applicants maintain that this summary does not accurately represent what Atz & Wessel actually disclosed. Rather than teach that all patients with left ventricular dysfunction (LVD) should be excluded from treatment with inhaled nitric oxide, as implied by the Examiner's summary, Atz & Wessel at page 452 discusses two distinct subsets of LVD patients who may be harmed in different ways when their pulmonary hypertension is reduced by treatment with inhaled nitric oxide. These two subsets of LVD patients are:

> (1) adults with severe LVD combined with pulmonary hypertension and ischemic cardiomyopathy; and
>
> (2) newborns with severe LVD combined with all of the following: pulmonary hypertension, predominantly left to right shunting at the foramen ovale and exclusively right-to-left shunting at the ductus arteriosus.

Neither of these patient populations encompasses the newborns addressed in the present claims, which are specified as <u>not</u> being known to be dependent on a right-to-left shunt.

Regarding the first patient population (i.e., adults with severe LVD combined with pulmonary hypertension and ischemic cardiomyopathy), Atz & Wessel says:

> "In adults with ischemic cardiomyopathy, sudden pulmonary vasodilation may occasionally unload the right ventricle sufficiently to increase pulmonary blood flow

> and harmfully augment preload in a compromised left ventricle. The attendant increase in left atrial pressure may produce pulmonary edema."

Note that this teaching from Atz & Wessel pertains solely to adults.

Regarding the second patient population (i.e, newborns with severe LVD combined with pulmonary hypertension, predominantly left to right shunting at the foramen ovale and exclusively right-to-left shunting at the ductus arteriosus), Atz & Wessel states:

> "A different but related phenomenon may be operative in the newborn with severe left ventricular dysfunction and pulmonary hypertension. In these patients, the systemic circulation may depend in part on the ability of the right ventricle to sustain cardiac output through a right-to-left shunt across the patent ductus arteriosus. Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation. Therefore, in newborns with severe left ventricular dysfunction, predominantly left to right shunting at the foramen ovale and exclusively right-to-left shunting at the ductus arteriosus, NO should be used with extreme caution, if at all. We and others have reported adverse outcomes in this circumstance."

Thus, Atz & Wessel warns that newborns who have severe LVD and are dependent on a right-to-left shunt across the patent (i.e., open) ductus arteriosus may be harmed, rather than helped, if their pulmonary hypertension is diminished by inhaled nitric oxide treatment. As explained in paragraphs 13-14 of the Declaration of Douglas A. Greene, M.D., under 37 CFR § 1.132, submitted as Appendix B with the Reply filed May 2, 2011 (the "First Greene Declaration"), the dysfunctional left ventricle in these newborns cannot do its usual task of pumping blood into the systemic circulation. The affected infant survives without a functioning left ventricle solely because his/her ductus arteriosus remains open after birth, permitting the right ventricle to take over the function of pumping blood through the patent ductus arteriosus into the systemic circulation, bypassing the left ventricle. This is referred to as a right-to-left shunt. Without this shunt through the patent ductus arteriosus, the patient may suffer systemic circulatory collapse. Pulmonary vasoconstriction actually plays a beneficial role in such infants by helping to maintain a post-natal high blood pressure in the pulmonary artery, which in turn helps keep the ductus arteriosus open and the blood flowing through the systemic circulation. If the newborn's pulmonary hypertension is reduced by treatment with

inhaled nitric oxide, the right ventricle will pump more blood into the newly dilated pulmonary circulation and less into the systemic circulation; also, the reduced pressure in the pulmonary artery may mean the ductus arteriosus will close, cutting off the right-to-left shunt altogether. Atz & Wessel put it this way: **"Selective pulmonary vasodilation may redirect the right ventricular output to the lungs and away from the systemic circulation."**

Therefore, the warnings of Atz & Wessel about inhaled NO treatment of patients with LVD are limited to (1) adult LVD patients who have cardiomyopathy and may suffer pulmonary edema if treated with inhaled nitric oxide; and (2) newborn LVD patients who are known to be dependent on a right-to-left shunt across the patent ductus arteriosus and may suffer collapse of their systemic circulation if treated with inhaled nitric oxide. Contrary to the Office action's summary of Atz & Wessel quoted above, Atz & Wessel does not teach, not even by implication, that any and all patients diagnosed as having LVD should be excluded from treatment with inhaled NO. In fact, it is clear that the warning in Atz & Wessel regarding excluding certain newborns is based upon their dependence on right-to-left shunt in conjunction with LVD (since that warning focuses on the danger of abrogating the right-to-left shunt by redirecting blood to the lungs and away from the systemic circulation in these newborns), and not because of the LVD itself. Atz & Wessel's teachings regarding such newborns would not apply to newborns who have severe LVD but are not known to be dependent on a right-to-left shunt across the patent ductus arteriosus. That is the category of patients to which the presently claimed methods are limited. If the authors of Atz & Wessel had been aware that newborns with severe LVD who are not dependent on a right-to-left shunt also are at increased risk for adverse events when treated with inhaled nitric oxide, or even had suspected that would be the case, one would expect them to mention it in their publication. In fact, the senior author of Atz & Wessel, Dr. David L. Wessel,[1] explicitly states in the letter to Dr. Douglas A. Greene, M.D., enclosed as Exhibit 2 of the Second Declaration of Douglas A. Greene, M.D., under 37 CFR § 1.132 (attached as Appendix B, the "Second Greene Declaration"). In particular, in his letter, Dr. Wessel states that he and his co-author (Atz) **"did not disclose or predict...that neonatal patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood would be at greater risk of adverse events."** This directly contradicts the Examiner's

[1] Dr. Wessel's Curriculum Vitae is attached as Appendix A.

unduly broad interpretation of what Atz & Wessel discloses, undermining the factual basis for the entire prima facie obviousness rejection.

Furthermore, one of ordinary skill in the art would not have extrapolated from what was disclosed in Atz & Wessel about adult LVD to an expectation about what would happen if neonates with LVD were treated with inhaled nitric oxide. That person of ordinary skill in the art would have realized that Atz & Wessel's teachings about adults with LVD and ischemic cardiomyopathy are not applicable to newborns with LVD, because it is well known that LVD in a newborn is very different from LVD associated with ischemic cardiomyopathy in an adult. See, e.g., the explanation of the differences between adult and newborn LVD provided in paragraphs 15-16 of the First Greene Declaration. "LVD" is not a single condition, but rather is a generic label applied to a left ventricle that does not function properly, regardless of what causes the dysfunction (e.g., congenital malformation, viral disease, or coronary artery disease, to name a few causes) and regardless of how the dysfunction is manifested (e.g., stiffness and inability to relax (diastolic dysfunction) or "flabbiness" and inability to contract (systolic dysfunction)). Atz & Wessel's teaching that treatment of pulmonary hypertension with inhaled NO can precipitate pulmonary edema in adults with LVD associated with ischemic cardiomyopathy and diastolic dysfunction tells one of ordinary skill in the art of cardiac disease nothing useful about whether inhaled NO can be used safely in newborns with LVD typical for newborns, e.g., associated with congenital heart disease and systolic dysfunction.

This point is brought home in a very practical sense by a situation related by Dr. Wessel in his letter to Dr. Greene. Dr. Wessel was the Chair of the INOT22 Steering Committee that in 2005 designed the original protocol for the INOT22 Study, the clinical trial that ultimately led to the presently claimed invention. According to Dr. Wessel's letter,

> "At the time of the design of the INOT22 Study protocol, neither myself, the other Steering Committee members, nor the study Sponsor appreciated or anticipated that a child with left ventricular dysfunction who is not dependent on right-to-left shunting of blood would be at additional risk when treated with inhaled nitric oxide (iNO). This is the reason such children were not originally excluded from the INOT22 Study entry criteria....
>
> It is ironic that my own publication [i.e., Atz & Wessel] would be cited to suggest that it would have been obvious to predict the adverse events and outcomes of the

INOT22 Study when I, the senior author of Atz & Wessel, failed to anticipate or predict these unexpected outcomes at the time I participated in drafting the original INOT22 Study protocol. If so, I would have been acting either negligently or intentionally to harm babies, and I most certainly was not. Furthermore, to my knowledge, none of the other members of the INOT22 Steering Committee who assisted me in designing the study, nor the approximately 18 Institutional Review Boards and 2 National Health Authorities who reviewed and approved the study prior to its initiation, predicted the adverse events in children with left ventricular dysfunction who are not dependent on right-to-left shunting of blood.

In summary, although it was known that neonates whose systemic circulation was dependent on right-to-left shunt should not receive iNO, and it had been reported that adults with pre-existing left ventricular dysfunction (from coronary artery disease) may be at risk when provided iNO, it was unanticipated and surprising that children with left ventricular dysfunction who are not dependent on right-to-left shunting would be at increased risk of adverse events when administered iNO."

The evidence supplied by Dr. Wessel regarding the failure of multiple experts to predict that pediatric patients with left ventricular dysfunction who are not dependent on right-to-left shunting should be excluded from treatment with inhaled nitric oxide is fully corroborated by the Second Declaration of James S. Baldassarre, M.D., under 37 C.F.R. § 1.132 (attached as Appendix C; the "Second Baldassarre Declaration"). Dr. Baldassarre, one of the inventors of the present claims, explains in his declaration that the INOT22 study protocol was designed by the study sponsor (INO Therapeutics LLC) and a Steering Committee including internationally-recognized experts in the field of pediatric heart and lung disease. In addition, INO Therapeutics LLC regularly requested input and scientific guidance on clinical trials from its own Scientific Advisory Board. The original study protocol was reviewed by an Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) at each of the 18 participating study institutions, including review by the principal investigator within each study institution (a detailed explanation of the design, membership and responsibilities of an IRB and IEC are contained within paragraphs 9 and 10 of the Second Baldassarre Declaration). In addition, the original study protocol was reviewed by experts at FDA and each national Health Authority (European equivalent to FDA) within the four European countries participating in the INOT22 study (United Kingdom, France, Netherlands, and Spain). Neither the study sponsor, nor the experts on the Steering Committee, nor the principal investigators, nor the IRBs, nor the IECs, nor the Advisory Board members, nor the FDA experts, nor the European Health

Authority experts suggested that the exclusion criteria for the INOT22 study protocol be amended to exclude study subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt. Dr. Baldassarre estimates that the original study protocol was reviewed and approved by at least 115 experts, not one of whom raised an issue about potential risk to this population of patients. The Second Baldassarre Declaration also provides evidence that FDA, when informed of the present invention, required that the label include an additional warning, separate and distinct from the existing contraindication, that inhaled nitric oxide "should not be used in treatment of neonates known to be dependent on right-to-left shunting of blood". If the new warning had been "obvious" to those of ordinary skill all along, FDA would have required it long ago. This is further objective evidence that the presently claimed methods would not have been obvious in view of the prior art.

Applicants submit that this evidence provided by Dr. Wessel and Dr. Baldassarre conclusively establishes the nonobviousness of the presently claimed methods to those of ordinary skill. No physician who believed it "obvious" that inhaled nitric oxide treatment would be harmful to patients who have a particular condition would approve a study of inhaled nitric oxide that includes those patients. That is simply common sense. That multiple physicians who are experts in this field participated in designing, approving, and implementing the original protocol for the INOT22 Study, and none suggested excluding patients with LVD who were not dependent on right-to-left shunt, speaks volumes about the nonobviousness of the presently claimed methods. Furthermore, FDA did not require a warning regarding LVD be added to the INOmax® (nitric oxide) for inhalation prescribing information (i.e., the "label") until 2009, i.e., after the present inventors identified the problem (In contrast, the contraindication for neonates dependent on a right-to-left shunt has always appeared in the prescribing information for INOmax®). If the problem in LVD children had indeed been "obvious" to one of ordinary skill at the time Atz & Wessel was published in 1997, then FDA would have required the warning at that time, and would not have approved the INOT22 Study protocol as originally formulated.

All of this objective evidence is countered by nothing more than the Examiner's subjective interpretation of what Atz &Wessel disclosed. The Examiner is engaging in impermissible hindsight reconstruction of the prior art by deeming obvious what none of the experts in this field

was able to recognize at the time of the present invention. Given that Atz & Wessel did not disclose what the Office action claims it disclosed, the rejection fails on this ground alone.

The secondary references, Kinsella et al. and Loh et al., also do not support the rejection. The Office action at page 8 cites Kinsella et al. as teaching:

> " ... excluding patients (premature neonates) from inhaled nitric oxide treatment if they have fatal congenital anomalies or congenital heart disease....Since left ventricular dysfunction is a congenital heart disease...and it would be pre-existing, then the methods of Kinsella et al. intrinsically exclude this patient population from the method."

As explained in the Second Declaration of Douglas A. Greene, M.D, paragraph 17, the patients included in the Kinsella et al. trial are differentiated from the term and near-term neonates of the present claims by age, etiology and pathophysiology. In particular, unlike the term and near-term neonates of the present claims, the premature neonates ("preemies") of Kinsella suffer from severe respiratory failure due to immature lungs and surfactant deficiency, not pulmonary hypertension. Indeed, none of the premature neonates enrolled in Kinsella et al. suffered from pulmonary hypertension. Thus, the patients included in Kinsella et al. were clinically dissimilar from the term and near-term neonates addressed in the present claims.

Additionally, and more importantly, the exclusion of patients from a clinical study may occur for a variety of reasons other than safety concerns. While fatal congenital anomalies or congenital heart disease were indeed reported to be exclusion criteria for the Kinsella et al. study in premature infants, this does not mean the authors taught, or even hypothesized, that inhaling nitric oxide would be particularly risky for these or other patients with these congenital conditions. The exclusion criteria were most likely designed to eliminate variables (here, underlying potentially fatal conditions unrelated to the condition being studied) that would complicate interpretation of the trial results. As explained in paragraphs 18-20 of the Second Greene Declaration:

> "For example, clinical trial inclusion and exclusion criteria are often chosen to define or restrict the study population in order to maximize homogeneity, thereby minimizing the presence of potentially confounding factors. This exclusion greatly facilitates the interpretation of the study results, and increases the soundness of the conclusions reached in the study. Accordingly, patients with

> background disease sufficiently severe to overwhelm or confound an expected treatment effect are systematically identified and excluded quite independently from considerations of anticipated safety or efficacy of the test article in this particular patient group For example, patients with malignancy are often excluded from non-oncologic clinical trials, not because the test agents are unsafe, pose any specific risk in this population, or will not work, but rather because the clinical results will be confounded by the wholly unrelated effects of the underlying malignancy, thereby reducing the power of the clinical trial to answer a specific hypothesis regarding the test treatment. As a specific example, exclusion of patients with malignancy or advanced heart failure from cholesterol lowering trials does not imply that statins are unsafe or ineffective in these patients, but rather that their inclusion would confound the potential effects of statins on overall mortality or cardiovascular events. In the specific case of Kinsella et al., it is clear that one of ordinary skill in the art would understand that the patients having fatal congenital anomalities or congenital heart disease were excluded not because of a suspected safety risk of treating these patients with inhaled NO (e.g., a risk of pulmonary edema), but rather solely because the inclusion of such patients would have made it much more difficult – if not impossible - for Kinsella et al. to interpret the target outcomes of the study (i.e., would have "confounded" the results)."

That Dr. Greene's above-described view of Kinsella et al. is the view that would be shared by those of ordinary skill in the art upon reading Kinsella et al. is clear from other objective evidence. See, for example, Fraisse & Wessel, "Acute pulmonary hypertension in infants and children: cGMP-related drugs," *Pediatr Crit Care Med* 2010, Vol. 11, No. 2 (Suppl.), pages S37-S40, a copy of which is included in the accompanying Information Disclosure Statement. The abstract of this article states, **"Inhaled nitric oxide is extremely efficacious in increasing cGMP and selectively reducing mean pulmonary arterial pressure in pediatric cardiac patients. It is considered standard treatment in most centers."** See also the first full sentence in the middle column of page S37: **"Inhaled NO is extremely efficacious in selectively reducing mean pulmonary arterial pressure (PAP) in cardiac patients and is considered standard treatment in most centers."** These statements extolling the usefulness of inhaled nitric oxide in pediatric cardiac patients, most of whom have congenital heart disease, were made by the authors in 2010, *eleven years* after Kinsella et al. was published. If those of skill in the art in the years following Kinsella et al.'s publication had believed that infants with congenital heart disease in general should be excluded from treatment with

inhaled nitric oxide, this treatment would certainly not have achieved its present status of a "standard treatment" for pediatric cardiac patients. The quoted statements from Fraisse & Wessel are cogent, objective evidence that the Office action misinterpreted Kinsella et al.'s rationale for excluding congenital heart disease patients from their study and made an inaccurate assessment of how those of ordinary skill in the art would have understood Kinsella et al.'s exclusion criteria. Properly interpreted, Kinsella et al. does not support the present rejection at all.

> The Office action at page 9 cites Loh et al. as allegedly teaching:
>
> " .. that inhaled nitric oxide in patients with left ventricular dysfunction may have adverse effects in patients with LV failure...Loh et al. clearly teaches that patients with pulmonary artery wedge pressure...***of greater than or equal to 18 mm Hg*** had a greater effect of inhaled NO due to the greater degree of reactive pulmonary hypertensions present in such patients.... Loh et al. state: "*Since the degree of reactive pulmonary hypertension is generally related to the severity of hemodynamic compromise in patients with LV failure, it might be anticipated that patients with more severe heart failure will have a more marked hemodynamic response to inhaled NO.*" (Emphasis as shown in the Office action's original text.)

On page 13, the Office action responds to applicants' prior arguments regarding Loh et al. by saying "As to Loh, the Examiner is not relying on Loh for teaching administration of iNO in children but rather the correlation between PCWP and iNO."

Though the Examiner is plainly aware that Loh et al. does not teach administration of inhaled nitric oxide to children, what the Office action fails to note is that Loh et al.'s study is solely within adult patients, and thus the alleged correlation between PCWP and inhaled nitric oxide observed by Loh et al., has little if any relevance to the presently claimed methods. Loh et al.'s patients had class III or class IV (congestive) heart failure secondary to left ventricular dysfunction from ischemic cardiomyopathy or idiopathic dilated cardiomyopathy (see, page 2780, right column). As explained by Dr. Greene in the Second Greene Declaration at paragraph 22, one cannot predict from Loh et al.'s observations in adults that there would have been any risk to neonates, who typically have a very different form of LVD:

> "The underlying etiologies and hemodynamic characteristics of both the primary heart disease and the increased pulmonary vascular resistance are drastically

different from adults, as compared to non-adults, such that one cannot readily assume or anticipate clinical results within adults to translate into neonates or children. In particular, left ventricular dysfunction in neonates with congenital heart disease is primarily due to developmental structural disease of the heart, inborn errors of metabolism that impair energy generation in the heart muscle, or viral infection. Class III or class IV congestive heart failure in adults (in contrast to congenital heart disease in neonates or children) is due to ischemic or dilated cardiomyopathy, mostly secondary to coronary artery disease and/or chronic systemic hypertension. Pulmonary hypertension associated with neonatal congenital heart disease is secondary to chronic hypoxemia, developmental abnormalities of the pulmonary blood vessels and/or pulmonary vascular damage from abnormally high blood flow and/or pressure through the pulmonary vasculature, resulting in evident disease of the lung vasculature. In contrast, increased pulmonary vascular resistance in adult Class III or IV congestive heart failure is due to reactive pulmonary vasoconstriction secondary to increased sympathetic tone or circulating vasoactive molecules (Loh et al., p. 2780, left column) in otherwise structurally normal blood vessels. Therefore, the hemodynamic responses to pulmonary vasodilation by inhaled NO in children or neonates, without right-to-left shunting of blood, but with significant pulmonary hypertension and left ventricular dysfunction cannot be reasonably predicted from the hemodynamic responses to pulmonary vasodilation by inhaled NO of adults with advanced atherosclerotic congestive heart failure and reactive neuro-humoral pulmonary vascular constriction (with or without pulmonary hypertension) as described by Loh et al."

Given these marked physiological differences between Loh et al.'s adult LVD patients with congestive heart failure and the neonate LVD patients recited in the present claims, one of ordinary skill in the art would not have simply assumed, as the Examiner apparently does,[2] that results reported by Loh et al. for adults would obviously apply to neonates as well. Supporting applicants' position in this regard is the evidence offered above in the discussion of Atz & Wessel that those of ordinary (and even extraordinary) skill in the art did not consider it "obvious," even several years after Loh et al.'s 1994 publication date, that neonatal patients with LVD who are not dependent on right-to-left shunt are at increased risk for adverse events when given inhaled nitric oxide. If this

[2] See, the carryover paragraph of pages 11-12 of the Office action:

[It] is simply not inventive to "inform" a medical provider that a neonate with LVD is at risk of adverse/serious adverse events from iNO therapy when the art already has established that fact and the ordinary artisan is alerted to this fact. *If the patient has LVD then they are at risk of adverse and/or serious adverse events from iNO therapy....* (Italics in the original)

were indeed "obvious" to those of ordinary skill, the INOT22 Study protocol would have explicitly excluded these neonatal LVD patients from the start; other post-1994 clinical trials of inhaled nitric oxide in neonates would have done likewise; and FDA would have required a warning about LVD be added to the prescribing information for INOmax® (nitric oxide) for inhalation over a decade before the warning was actually added (following analysis of the INOT22 Study results).

Physicians are by nature conservative about putting their patients at risk. Any "obvious" or "predictable" risk of harm would be avoided, not ignored—to do otherwise would be tantamount to medical malpractice. If those in the art had indeed understood from the cited references (all published prior to 1999) that neonates who are not dependent on right-to-left shunt with LVD should not be treated with inhaled nitric oxide, such an understanding would of course have been explicitly memorialized in clinical trial protocols and prescribing information long before the present invention, and clearly before the INOT22 study. Since that did not occur, the logical conclusion is that practitioners did not consider such an exclusion to be medically justified.

Contrary to the assertions in the Office action about what would have been "in the realm of common sense" to predict the unexpected adverse events that occurred within the INOT22 study, it would not have been "common sense" for a physician to exclude his or her neonatal LVD patient from a potentially life-saving treatment with inhaled nitric oxide without a legitimate medical justification for doing so. The information available in the art about risk of inhaled nitric oxide in adult LVD was certainly not such a justification. Further, the Examiner's position in this regard appears to require the unjustified assumption that *none* of the individuals (at least 115) tasked with designing or reviewing and approving the original INO22 study protocol exercised "common sense", and that by failing to do so, these professionals failed to predict the unexpected serious adverse events that occurred in INOT22. This unsupported conclusion cannot stand in view of the weight of objective evidence provided prior and herein.

In view of the above arguments and cogent objective evidence of nonobviousness, applicants submit that the claims are not obvious in view of the combination of Atz & Wessel, Kinsella et al., and Loh et al.