Attorney Docket No. 26047-0003002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: James S. Baldassarre et al.	Art Unit	: 1613
Serial No.	: 12/820,866	Examiner	: Ernst V. Arnold
Filed	: June 22, 2010	Conf. No.	: 2913

Title : METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

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BRIEF ON APPEAL

This application is under Accelerated Examination.

Appellant is appealing the final rejection of claims 28-42 in the Final Office Action dated August 24, 2011. A Notice of Appeal was filed and received by the U.S. Patent and Trademark Office on September 1, 2011.

I. Real Party in Interest

The Real Party in Interest is Ikaria Holdings, Inc., the assignee of record. Affiliates of Ikaria Holdings, Inc. include Ikaria, Inc. and INO Therapeutics LLC.

II. Related Appeals and Interferences

There are no prior or pending related appeals, judicial proceedings, or interferences.

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III. Status of Claims

Claims 1-27 are canceled.

Claims 28-42 are rejected and under appeal.

IV. Status of Amendments

No amendments have been filed subsequent to the August 24, 2011, mailing date of the Final Office Action, and none are being submitted herewith.

V. Summary of Claimed Subject Matter

Independent claims 28, 32 and 37 are summarized below. Support in the specification is indicated by paragraph numbers derived from the specification as filed.

Independent claim 28 is directed to a method of reducing the risk of occurrence, in a term or near-term neonate patient (i.e., >34 weeks gestation; see the specification at paragraph [0033]), of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide gas. ("Adverse events" and "serious adverse events" are terms of art describing two related but distinct categories of events in the pharmaceutical field; see, e.g., the definitions in the specification at paragraphs [0025] and [0027].) The method includes the steps of (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. Support for claim 28 can be found, *e.g.*, at paragraphs [0004], [0007], [0008], [0020] (as amended in the Response filed July 8, 2011, to include material previously incorporated by reference), [0025], [0027], [0028], [0033], and [0051] of the specification.

Independent claim 32 is directed to 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. The method includes the steps of (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. This claim is similar to claim 28, except that step (b) of claim 32 specifies use of "diagnostic screening." See, e.g., the specification at paragraph [0028].

Support for claim 32 can be found, *e.g.*, at paragraphs [0004], [0007], [0008], [0020] (as amended in the Response filed July 8, 2011, to include material previously incorporated by reference), [0025], [0027], [0028], [0033], and [0051] of the specification.

Independent claim 37 is directed to 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. The method includes the steps of (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.

Support for claim 37 can be found, *e.g.*, at paragraphs [0004], [0007], [0008], [0020] (as amended in the Response filed July 8, 2011, to include material previously incorporated by reference), [0025], [0027], [0028], [0033], and [0051] of the specification. In particular, the concept of a "plurality" of patients is supported by the discussion of "patients" (plural) at paragraph [0004] and "a patient population" at paragraph [0007]. Paragraph [0007]

also supports the recitation of a first patient who is determined to have left ventricular dysfunction and so is excluded from treatment with inhaled nitric oxide. The recitation of a second patient who is determined not to have left ventricular dysfunction and so is administered inhaled nitric oxide is supported, e.g., at paragraph [0008]. (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.)

As required by the accelerated examination program of which this application is a part, Appellant does not separately argue the patentability of any dependent claim in this appeal brief. Appellant agrees that the dependent claims are grouped together with, and not argued separately from, the independent claim from which they depend.

VI. Ground of Rejection to be Reviewed on Appeal

The sole ground of rejection to be reviewed on appeal is whether claims 28-42 are unpatentable under 35 U.S.C. § 103(a) over a combination of four references: the 2007 drug label insert for INOmax® (nitric oxide) for inhalation ("the 2007 INOmax® insert"; included as Exhibit 1 for the Board's convenience); Atz & Wessel (*Seminars in Perinatology* 1997, 21(5), 441-455; Exhibit 2); Kinsella et al. (*The Lancet* 1999, 354, 1061-1065; Exhibit 3); and Loh et al. (*Circulation* 1994, 90, 2780-2785; Exhibit 4).[1]

Claims 28-42 are also provisionally rejected as being unpatentable for nonstatutory obviousness-type double patenting over claims 29-42 of co-pending U.S. Application No. 12/820,980; over claims 21-30 of copending Application No. 12/821,020; and over claims 21-29 and 37 of copending Application No. 12/821,041.[2] For purposes of the present appeal, Appellant does not contest these provisional rejections insofar as they are applied to the claims as currently written, and intends to file appropriate Terminal Disclaimers to moot these rejections if doing so is warranted at the time the present claims are otherwise deemed

[1] Final Office Action, August 24, 2011 (the "Final Office Action"), at 3.
[2] *Id.* at 14-17.

allowable. Accordingly, the Board of Patent Appeals and Interferences need not address the obviousness-type double patenting rejections at this time.[3]

VII. Argument

A. Summary of the Argument

The issue presented on this appeal is simple and straightforward. The claimed invention is directed to a method of reducing the risk of adverse events in neonate patients that suffer from left ventricular dysfunction (LVD) and are **not** dependent on right-to-left shunting of blood.[4] For simplicity, this set of neonates is referred to herein as the "Claimed Patient Population." The present inventors discovered that the Claimed Patient Population suffers from an elevated risk of adverse events when treated with inhaled nitric oxide.[5] The Examiner does not dispute that this discovery is novel and not anticipated by any of the cited prior art references.[6]

The prior art does teach, however, that administration of inhaled nitric oxide may result in adverse events in **two other distinct patient populations**: (i) neonate patients dependent on right-to-left shunting of blood, and (ii) adults suffering from LVD (together, the "Prior Art Patient Populations").[7] The three **very** distinct patient populations at issue are summarized in the diagram below:

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[3] *Ex Parte Moncla*, 95 U.S.P.Q.2d 1884 (B.P.A.I. June 22, 2010).
[4] *See* Declaration of Douglas A. Greene, M.D. under 37 C.F.R. § 1.132, dated April 29, 2011 ("First Greene Dec."), ¶¶ 10-14 (discussing neonate cardiology and right-to-left shunting of blood at a patent ductus arteriosus). The First Greene Dec. was originally submitted with the May 2, 2011 Reply filed by Appellant. A copy of the First Greene Dec. is enclosed in the Evidence Appendix (ix) as Exhibit 5.
[5] Declaration of David L. Wessel, M.D., under 37 CFR § 1.132 ("Wessel Dec."), ¶ 9. The Wessel Dec. was made of record on July 27, 2011, and is enclosed in the Evidence Appendix (ix) as Exhibit 6.
[6] Final Office Action at 9 ("The difference between the instant application and INOmax®, Atz et al., Loh et al., and Kinsella et al., is that INOmax®, Atz et al., Loh et al., and Kinsella et al., do not expressly teach the 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 iNO therapy comprising identifying a term or near term neonate patient in need of iNO treatment and is **not known to be dependent on right to left shunting of blood**, determining if the patient has pre-existing LVD and excluding the patient from iNO treatment if they have pre-existing LVD or administering iNO if they do not have pre-existing LVD of instant claims 28-42." (Emphasis added)).
[7] Wessel Dec. ¶ 7.

	Patient has LVD and *IS* dependent on right-to-left shunting of blood	**Patient has LVD and *IS NOT* dependent on right-to-left shunting of blood**
Adults	Not Applicable	Prior Art Patient Population
Neonates	Prior Art Patient Population	Claimed Patient Population

The Examiner contends that disclosure of an increased likelihood of adverse events in the Prior Art Patient Populations would have made it obvious to expect a similar increase in adverse events in the Claimed Patient Population.[8] The Board should reverse this rejection because: (i) it is contrary to historical fact, and (ii) the Examiner provides no analysis based upon the etiology and/or pathophysiology of the various conditions that would explain why a risk of adverse events in the Prior Art Patient Populations would lead one skilled in the art to expect an increased likelihood of adverse events in the Claimed Patient Population.[9] In fact, all of the evidence of record is to the contrary and demonstrates that the etiology and pathophysiology of these patient populations are clinically distinct and would not justify any such conclusion.[10]

The evidence of record supporting reversal of the Examiner's rejection includes the following:

1. Direct evidence that those skilled in the art were well aware for many years of the increased risk of adverse events in the Prior Art Patient Populations and nevertheless did not predict an increased risk of adverse events in the Claimed Patient Population.

a. The record includes declaration testimony (including the declaration of Dr. Wessel, senior author of the Atz & Wessel reference relied on extensively by the Examiner) that, immediately prior to Appellants' invention, three leading experts in inhaled nitric oxide

[8] Final Office Action at 9.
[9] *See generally* Final Office Action (entirely failing to address (a) Appellant's evidence of why experts in the field did not expect increased risk to the Claimed Patient Population and (b) physical attributes of the Prior Art Patient Populations that might provide a clue that the Claimed Patient Population would be adversely affected by inhaled nitric oxide).
[10] *See, e.g.*, Declaration of Douglas A. Greene, M.D. under 37 C.F.R. § 1.132, dated July 7, 2011 ("Second Greene Dec."), ¶¶ 8-9, 22, 25, 27. The Second Greene Dec. was originally submitted with the July 8, 2011 Reply. A copy of the Second Greene Dec. is enclosed in the Evidence Appendix (ix) as Exhibit 7.

therapy designed a study protocol that was reviewed and approved by 18 Institutional Review Boards and Independent Ethics Committees composed of over 100 specialists at leading medical institutions in the United States and Europe.[11] Not one of these experts or other experienced specialists predicted the increased risk of adverse events in the Claimed Patient Population that the Examiner, with 20-20 hindsight, now concludes should have been obvious to those practitioners.[12] As pointed out by Dr. Wessel in his declaration, it is ironic that his own Atz & Wessel reference is so heavily relied on by the Examiner to suggest the obviousness of an increased risk of adverse events in the Claimed Patient Population when he himself, the publication's senior author, failed to anticipate or predict this increased risk.[13] Notably, the Examiner does not dispute the historical facts described above and does not cite any evidence tending to contradict the conclusion that, in the real world prior to Appellant's invention, actual practitioners who routinely administered inhaled nitric oxide to actual neonates in need thereof did not consider the Claimed Patient Population to be at increased risk of adverse events.

b. The record includes direct evidence that, prior to Appellant's invention, experts at the U.S. Food and Drug Administration (FDA) and a number of other national Health Authorities outside the United States had multiple separate opportunities to consider the question of whether inhaled nitric oxide should be withheld from the Claimed Patient Population, and each time did not reach that conclusion.[14] Only after Appellant's invention did FDA require an amendment to the label for inhaled nitric oxide warning about the potential for increased adverse events in patients with LVD.[15] Again, the Examiner does not dispute these historical facts, and does not cite or rely on any evidence tending to contradict the conclusion that the regulatory

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[11] Wessel Dec. ¶ 8; *See also* the Declaration of James S. Baldassarre, M.D. under 37 C.F.R. § 1.132, dated July 7, 2011 ("Second Baldassarre Dec."), ¶ 11. The Second Baldassarre Dec. was originally submitted with the July 8, 2011 Reply and is enclosed in the Evidence Appendix (ix) as Exhibit 8.

[12] Second Baldassarre Dec. ¶ 8.

[13] Wessel Dec. ¶ 8.

[14] *See, e.g.*, Second Baldassarre Dec. ¶ 8-11. *See also* http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm ("Most drugs that undergo preclinical (animal) testing never even make it to human testing and review by the FDA. The drugs that do must undergo the agency's rigorous evaluation process, which scrutinizes everything about the drug--from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured.").

[15] Declaration of James S. Baldassarre, M.D. under 37 C.F.R. § 1.132, dated Sept. 29, 2010 ("First Baldassarre Dec.") ¶ 16. The First Baldassarre Dec. was originally submitted with the October 1, 2010 Reply and is included in the Evidence Appendix (ix) as Exhibit 9.

agencies actually charged with ensuring the public's safety did not consider the Claimed Patient Population to be at increased risk of adverse events before Appellant's invention.

2. Direct evidence that the etiology and pathophysiology of the Claimed Patient Population is clinically differentiated from the Prior Art Patient Populations so that it would not have been obvious to expect adverse events in the Claimed Patient Population in view of risks in the Prior Art Patient Populations.

a. The record includes declaration testimony that the physiological reason that inhaled nitric oxide is dangerous for the first Prior Art Patient Population (i.e., neonates with LVD who **are** dependent on right-to-left shunting of blood) is that these neonates have a combination of cardiac anomalies that leaves their systemic circulation utterly dependent on a right-to-left flow of blood through a patent (open) ductus arteriosus; inhaled nitric oxide, by diverting blood to the lungs at the expense of the ductus arteriosus, can precipitate collapse of the systemic circulation and death in this particular population.[16] This issue of systemic circulatory collapse is wholly inapplicable to the Claimed Patient Population since, by definition, the latter patients are **not** dependent on right-to-left shunting of blood.[17] Accordingly, the known risk of adverse events in neonates dependent on right-to-left shunting of blood through a patent ductus arteriosus would not cause one to predict similar adverse events in the Claimed Patient Population.[18] The Examiner does not address these scientific facts and does not cite or rely on any evidence tending to contradict the conclusion that adverse events from inhaled nitric oxide in neonates dependent on right-to-left shunting of blood would be considered by those skilled in the art to be irrelevant to the Claimed Patient Population.

b. The record includes declaration testimony that LVD in the second Prior Art Patient Population (i.e., adults with LVD) results primarily from **diastolic** dysfunction caused by a stiff, non-compliant heart that cannot fill properly.[19] This pathology is entirely different than that of neonates with LVD, who suffer primarily from **systolic** dysfunction resulting from a soft, flabby heart that cannot push blood out.[20] The record further includes

[16] First Greene Dec. ¶¶ 13-14.
[17] *Id.* ¶¶ 13-16.
[18] *Id.* ¶ 20.
[19] *Id.* ¶¶15-16.
[20] *Id.*

express declaration testimony that, in light of these pathological differences, "the hemodynamic responses to pulmonary vasodilation by inhaled NO in children or neonates . . . cannot be reasonably predicted from the hemodynamic responses to pulmonary vasodilation by inhaled NO of adults . . . ."[21] Again, the Examiner does not address these scientific facts and does not cite or rely on any evidence tending to contradict the conclusion that adverse events from inhaled nitric oxide in this Prior Art Patient Population would not suggest to those skilled in the art anything relevant with respect to the Claimed Patient Population.

Unlike most cases considered by this Board, the record of this case includes an overwhelming volume of highly pertinent factual evidence establishing that persons skilled in the art did not consider the claimed subject matter to be obvious at the time of Appellant's invention.[22] In fact, the factual evidence contains evidence that leading experts considered this a startling discovery.[23] Further, the record includes declaration evidence explaining in detail the etiological and pathophysiological mechanisms underlying the conditions of the Prior Art Patient Populations and why those conditions fail to suggest an increased risk of adverse events in the Claimed Patient Population.[24] In response, the Examiner cites no countervailing evidence and provides no alternative explanation that even attempts to establish any sort of etiological or pathophysiological link between the Claimed Patient Population and the Prior Art Patient Populations. It is not appropriate for the Examiner to substitute his own personal opinion without any evidence to the contrary. Accordingly, the rejection of the present claims under 35 U.S.C. § 103 for obviousness should be reversed.

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[21] Second Greene Dec. ¶ 22.
[22] *See, e.g.*, Wessel Dec. ¶ 6; First Baldassarre Dec. ¶ 11; First Greene Dec. ¶ 17.
[23] Wessel Dec. ¶ 9 ("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"); First Greene Dec. ¶ 21 ("Surprisingly and unexpectedly, severe adverse events…were noted during the early phase of the study, and the study was stopped."); Second Baldassarre Dec. ¶ 12 ("unexpected serious adverse events (including at least one death) occurred during the course of the…study" and "the study protocol was amended").
[24] Second Greene Dec. ¶ 22.

B. Background

1. *Inhaled Nitric Oxide*

Inhaled nitric oxide is a pulmonary-specific vasodilator that has been administered for more than a decade to a total of over 300,000 critically ill patients at hospitals around the world to alleviate what can be life-threatening pulmonary hypertension in neonates and other patients.[25] Nitric oxide for inhalation was approved by FDA in December 1999, and is marketed under the trademark INOmax®.[26] INOmax® is FDA-approved for term and near-term neonates (defined as >34 weeks gestation) 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 (ECMO).[27]

2. *The INOT22 Study*

Beginning in 2004, INO Therapeutics LLC ("INOT") sponsored a clinical trial formally 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"[28] and known as the INOT22 Study. The purpose of the study was to assess the safety and effectiveness of inhaled nitric oxide as a diagnostic agent in pediatric patients undergoing assessment of pulmonary hypertension (primary objective), and to confirm the hypothesis that inhaled nitric oxide is selective for the pulmonary vasculature (secondary objective).[29]

As described in the First Baldassarre Declaration, "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."[30] "The expected patient population for enrollment into the INOT22 Study were subjects between the ages of 4 weeks and 18 years with idiopathic pulmonary arterial

[25] First Greene Dec. ¶ 8; CritiCally caring about CritiCal Care, http://www.slideshare.net/changezkn/critically-caring-about-critical-care (last visited Sep. 20, 2011).
[26] INOmax, http://inomax.com/about-ikaria (last visited Sep. 20, 2011).
[27] *See* the "Indications" section at the top of page 2 of the 2007 INOmax® insert.
[28] First Baldassarre Dec. ¶ 4.
[29] First Greene Dec. ¶ 18.
[30] First Baldassarre Dec. ¶ 5.

hypertension, congenital heart disease with pulmonary hypertension and cardiomyopathies, and who were undergoing diagnostic right heart catheterization scheduled to include pulmonary vasodilation testing to assess pulmonary vasoreactivity."[31]

The INOT22 Study was designed by the study sponsor, INOT, and a Steering Committee made up of internationally recognized experts in the field of pediatric heart and lung disease.[32]

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;
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.[33]

The original exclusion criteria for the INOT22 Study did **not** exclude patients in the Claimed Patient Population (i.e., patents with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunting of blood).[34] In particular, the original INOT22 Study 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 [Congenital Heart Disease] 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*

[31] *Id.* ¶ 6.
[32] *Id.* ¶ 7.
[33] *Id.* ¶ 8.
[34] *Id.* ¶ 11.

> *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.*
>
> *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 +).*[35]

The original INOT22 investigational plan and study protocol were reviewed and approved by the 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.[36] The original study protocol was also 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.[37] In addition, INOT regularly requested input and scientific guidance on clinical trials, such as the INOT22 Study, from its own Scientific Advisory Board (SAB).[38]

At no time did the study sponsor, any of the experts on the Steering Committee, any of the principal investigators, any of the IRBs, any of the IECs, any of the SAB members,

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[35] *Id.* ¶ 9.
[36] *Id.* ¶ 10.
[37] Second Greene Dec. ¶ 26.
[38] Second Baldassarre Dec. ¶ 8.

any of the FDA experts, or any of the European Health Authority experts (altogether estimated to total at least 115 medical professionals) suggest that the exclusion criteria for the INOT22 Study protocol be amended to exclude the Claimed Patient Population.[39] **In other words, of the estimated 115+ medical professionals tasked with the duty to consider potential safety issues for INOT22 Study patients, none—*not a single one*–suggested there was a chance that inhaled nitric oxide might increase the likelihood of adverse events in the Claimed Patient Population.**[40]

Upon administration of inhaled nitric oxide to the first 24 subjects enrolled in INOT22, five serious adverse events were recorded – a rate much higher than expected based on prior clinical experience with inhaled nitric oxide. Each of these five serious adverse events (SAEs) was a cardiovascular event, such as pulmonary edema, cardiac arrest or hypotension (low blood pressure).[41]

In February 2005, INOT and the Steering Committee convened to review the unexpected SAEs described above, and upon review and discussion, submitted a protocol amendment to FDA to thereafter exclude subjects from enrollment if they demonstrated an elevated pulmonary capillary wedge pressure (PCWP), defined within the study as subjects having a PCWP greater than 20 mmHg, a symptom of LVD. All study sites were notified immediately.[42]

After conclusion of the study, analysis of the data revealed that modification of the exclusion criteria significantly reduced the rate of serious adverse events (including serious adverse events associated with heart failure). This analysis demonstrated that there were 5 SAEs among the first 24 subjects (i.e., those enrolled prior to amendment of the exclusion criteria), but only 2 SAEs among the next 80 subjects in the study (i.e., enrolled after amendment of the exclusion criteria). Further analysis of the data showed that a total of four subjects had pre-existing LVD, and of these four, 50% experienced SAEs. Of the 120 subjects not found to have

[39] *Id.*
[40] *Id.* ¶ 11.
[41] First Baldassarre Dec. ¶ 12.
[42] *Id.* ¶ 13.

evidence of LVD, only 4% experienced SAEs. This result was unexpected and came as a great surprise to those working on the study.[43]

In light of this important and unexpected result, on February 25, 2009, INOT submitted a label supplement to the FDA seeking to amend the prescribing information for INOmax® to include a new warning statement for physicians stating that use of inhaled nitric oxide in patients with LVD could cause serious adverse events, such as pulmonary edema.[44] On August 28, 2009, FDA approved an INOmax® label supplement that included the following two new warnings:

> *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).*[45]

Thereafter, similar warnings regarding this risk were added to the INOmax® label in Japan, Europe, Canada, and Australia.[46]

C. The Law of Obviousness

Obviousness is a question of law based on underlying facts.[47] The facts to be considered in determining obviousness include: (i) the scope and content of the prior art, (ii) the

[43] *Id.* ¶¶ 14-15; *See also* Wessel Dec. ¶ 9.
[44] First Baldassarre Dec. ¶ 15.
[45] See, section 5.4 on page 2 and also the Warnings and Precautions section on page 1 of the revised prescribing information for INOmax®, filed with the September 17, 2010 Reply and included in the Evidence Appendix (ix) as Exhibit 10 (the "2009 INOmax® insert").
[46] Second Greene Dec. ¶ 15.
[47] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007) (citing *Graham v. John Deere*, 383 U.S. 1, 17 (1966)).

differences between the prior art and the claims in issue, and (iii) the level of ordinary skill in the pertinent art.[48]

In making an obviousness determination, the examiner must consider the claimed invention as a whole and must view the references without using hindsight afforded by the claimed invention.[49] Any rejection of a claim for obviousness must establish that there would have been a ***reason*** that would have prompted a person of ordinary skill in the relevant field to carry out the claimed new invention.[50] As the Federal Circuit explained in *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."[51]

Objective evidence demonstrating how those of ordinary skill in the art viewed the subject matter of the invention is particularly probative on the question of obviousness.[52] As noted in *In re Kotzab*: "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references ***and the then-accepted wisdom in the field***."[53] Facts demonstrating that an invention was "contrary to the accepted wisdom [are] 'strong evidence of unobviousness.'"[54]

"Evidence traversing rejections, when timely presented, must be considered by the examiner whenever present. . . .Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements such as 'the declaration lacks technical validity' or 'the evidence is not commensurate with the scope of the claims' without an explanation supporting such findings are insufficient."[55]

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[48] *KSR*, 550 U.S. at 406; *Graham*, 383 U.S. at 17.
[49] *Graham*, 383 U.S. at 36.
[50] *KSR*, 550 U.S. at 418.
[51] 721 F.2d 1540, 1553 (Fed. Cir. 1983).
[52] *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986).
[53] 217 F.3d 1365, 1369 (Fed. Cir. 2000) (internal citations omitted; emphasis added).
[54] *Hedges*, 783 F.2d at 1041.
[55] MPEP §716.01(B).

The Examiner is not free to simply disregard facts established in submitted declarations. Rather, "[f]acts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a *prima facie* case [of obviousness] was reached . . . ."[56] Moreover, "[w]hen prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over.... An earlier decision should not [ ] be considered as set in concrete, and applicant's rebuttal evidence then be evaluated only on its knockdown ability."[57]

D. Direct and Unrebutted Evidence of Record Establishes that the Claimed Invention was Not Obvious to those Skilled in the Art.

The record includes unrebutted objective evidence demonstrating that, prior to applicants' invention, medical professionals working in the real world did not exclude the Claimed Patient Population from inhaled nitric oxide therapy.[58] As discussed below, this record evidence includes declaration testimony that, immediately prior to applicants' invention, over 100 experts worldwide and the regulatory authorities of five countries considered what patient populations to exclude from the INOT22 Study and did not exclude the Claimed Patient Population from that study.[59] **There are only two possible explanations for this fact**:

> (1) The Examiner is wrong, and it would not have been obvious to exclude the Claimed Patient Population from inhaled nitric oxide therapy at the time the INOT22 Study protocol was designed; **or**
>
> (2) All of these 115+ experts and five regulatory authorities involved in the design of the INOT22 Study protocol committed malpractice and negligently put the lives of children at risk.

It is respectfully submitted that the actions of those skilled in the art are more probative of obviousness than the alleged factual findings and inferences relied on by the Examiner in the Final Office Action. Those actions definitively demonstrate that excluding the Claimed Patient Population from inhaled nitric oxide therapy was not obvious to those skilled in the art at the time of Appellant's invention.

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[56] MPEP §716.01(d).
[57] *In re Piesecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984) (quoting *In re Rinehart*, 531 F.2d 1048, 1052 (C.C.P.A. 1976)).
[58] First Baldassarre Dec. ¶¶ 9-11.
[59] Second Baldassarre Dec. ¶ 11.

1. *Dr. David Wessel, senior author of the cited Art & Wessel reference, and over 115 other skilled persons reviewed the INOT22 Study protocol, and none of these experts predicted an increased risk of adverse events in the Claimed Patient Population*

Dr. David Wessel chaired the INOT22 Steering Committee that in 2005 designed the original protocol for the INOT22 Study.[60] This same Dr. Wessel is the senior author of Atz & Wessel, a primary reference cited by the Examiner to support his obviousness rejection.[61]

As senior author of Atz & Wessel, Dr. Wessel was obviously well aware of that reference and its teachings. It is therefore telling that Dr. Wessel did not initially exclude the Claimed Patient Population from the INOT22 Study. As Dr. Wessel explains in his declaration, he did not exclude the Claimed Patient Population from the INOT22 Study because it was unanticipated at the time the protocol was first designed that "a child with left ventricular dysfunction who is not dependent on right-to-left shunting of blood [i.e., the Claimed Patient Population] would be at additional risk when treated with inhaled nitric oxide (iNO)."[62]

Dr. Wessel was not alone in this conclusion. It was seconded by literally more than one hundred other medical professionals belonging to the IRBs and IECs at each of the 18 medical institutions in the United States and Europe that participated in the study. Each of these IRBs and IECs reviewed the original INOT22 Study protocol design prior to study initiation and enrollment. This included review by the principal investigator within each study institution.[63]

As described in the Second Baldassarre Declaration, FDA regulations require an Institutional Review Board (IRB) to comprise a group of professionals appropriately constituted and formally designated to review and monitor biomedical research involving human subjects.[64] In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role and responsibility in the protection of the rights and welfare of human research subjects and in ensuring that appropriate steps are taken to protect human subjects participating in clinical

[60] Wessel Dec. ¶ 5.
[61] *Id.* ¶ 8.
[62] *Id.* ¶ 6.
[63] Second Baldassarre Dec. ¶¶ 8-11.
[64] *Id.* ¶ 9.

research. An IRB must have at least five members, and each member must have enough expertise to make an informed decision on whether the research is ethical, the informed consent is sufficient, and the appropriate safeguards to protect patient safety have been put in place prior to starting a clinical trial.[65]

In Europe, the analog of an IRB is an Independent Ethics Committee (IEC), an independent body consisting of healthcare professionals and non-medical members whose responsibility is to protect the rights, safety, and well being of human subjects involved in a clinical trial and to provide public assurance of that protection by expressing an opinion on a proposed clinical trial protocol, the suitability of the investigators, and the adequacy of facilities involved in a trial. Like an IRB, an IEC will review a clinical trial protocol with the intent of protecting patient safety prior to clinical enrollment.[66]

In sum, IRBs and IECs are composed of qualified medical professionals tasked with reviewing all clinical trial protocols proposed at their respective institutions and empowered to make or suggest changes to a given protocol that are deemed necessary to best ensure patient safety during the clinical trial. *Naturally, any obvious safety concerns arising from a proposed clinical trial protocol will be identified by an IRB/IEC and the protocol will be amended to avoid obvious and unnecessary clinical risks.*[67] *If a given safety issue is not flagged by the reviewing IRB/IEC, it by definition is not obvious to the members of the IRB/IEC.*

In addition, the original INOT22 Study protocol was also separately reviewed by FDA and each national Health Authority within the four European countries participating in the INOT22 Study (United Kingdom, France, Netherlands and Spain) prior to study initiation and enrollment.[68] INOT also regularly requested input and scientific guidance on clinical trials from its own Scientific Advisory Board.[69] In total, at least 115 individuals experienced in, and responsible for, the review of clinical trial protocols for patient safety reviewed the original INOT22 Study protocol prior to initiating the INOT22 Study.[70] At no time did any of these 115+ members of the Steering Committee, INOT Advisory Board, IRBs, IECs, FDA or European

[65] *Id.*
[66] *Id.* ¶ 10.
[67] *Id.* ¶¶ 9-10.
[68] *Id.* ¶ 8.
[69] *Id.*
[70] *Id.* ¶ 11

Health Authorities suggest that the Claimed Patient Population should be excluded from the study.[71]

In response to this large body of direct evidence that numerous experienced medical professionals with a duty to protect the safety interests of clinical trial participants did not find it obvious to exclude the Claimed Patient Population from the INOT22 Study, the Examiner states only:

> Respectfully, none of Applicants arguments or Declarations are persuasive. The Examiner has carefully considered the Declarations of Dr. Wessel, Dr. Greene and Dr. Baldassarre as well as all remarks and arguments. However, the position of the Examiner remains immutable and the Examiner does not concede or acquiesce to any of Applicant's arguments, points or positions.[72]

This sort of general statement that none of Appellant's declarations are persuasive is insufficient as a matter of law.[73] Where, as here, Appellant has demonstrated that persons skilled in the art *and working in the real world* in fact did not consider it obvious to withhold inhaled nitric oxide therapy from the Claimed Patient Population, it is the Examiner's burden to provide some credible explanation for this fact that is consistent with his obviousness rejection.[74] In other words, the Examiner must answer the following question:

> **If, as the Examiner contends, it was obvious to withhold inhaled nitric oxide therapy from the Claimed Patent Population, why was the INOT22 Study protocol approved without excluding that population from the study?**

The Final Office Action provides no answer to this question.

2. *The claimed invention was not obvious to FDA or multiple other national Health Authorities.*

The original INOmax® drug labeling did not include a warning or exclusion for the Claimed Patient Population. Under the Food, Drug and Cosmetic Act (FDCA), FDA is

[71] *See* First Baldassarre Dec. ¶ 11; Second Baldassarre Dec. ¶ 11; Wessel Dec. ¶ 6.
[72] Final Office Action at 12.
[73] MPEP 716.01(B).
[74] *Id.*

charged with ensuring not only that drugs are safe and effective,[75] but also that their labels contain adequate directions for use, including appropriate disclosure of known safety issues.[76] A drug Sponsor, typically a pharmaceutical company, will work with FDA to design clinical trials for testing the safety and efficacy of any new, unapproved drug (typically consisting of Phase 1, 2a, 2b and 3 clinical trials). Upon completion of the clinical trial process, the Sponsor will submit a New Drug Application (NDA) to FDA to obtain marketing approval for a drug within the U.S. The NDA will contain extensive and detailed data regarding the safety and efficacy of the drug that the Sponsor obtained during its research and development. These data include the results of clinical trials, pharmacology and toxicology data, chemistry and manufacturing data, and proposed packaging and labeling information. Throughout the process, FDA and the Sponsor communicate through in-person meetings, telephone conferences, letters, e-mails, and faxes.[77]

Toward the end of the review process, FDA and the Sponsor negotiate the drug's final package label.[78] Each element of the label requires FDA approval, including the indications, dosing, directions for use, and safety information. Once all the reviews are complete, the division director and/or the office director evaluate the reviews and make FDA's decision.[79]

Inhaled nitric oxide was approved as a drug by FDA in December 1999, after extensive clinical study and FDA review.[80] Upon approval, and up to the time the present invention was made, the INOmax® label[81] contained language communicating, in pertinent part, the following general warnings and contraindication (emphasis added):

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[75] The FDA was first given responsibility for ensuring the efficacy of prescription drugs under the 1962 Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. § 301 et. seq. (1998)).
[76] See FDCA, § 502(f) (codified as amended at 21 U.S.C. § 352(f) (1998)).
[77] 21 C.F.R. § 312.
[78] 21 C.F.R. § 201.
[79] 21 C.F.R. § 314.105.
[80] 2007 INOmax® Insert (describing in detail the three major clinical studies conducted during the INOmax® approval process).
[81] *See, e.g.*, the 2007 INOmax® Insert at page 2, in the "Dosage and Administration," "Precautions" and "Contraindications" sections.

> *INOmax® should not be discontinued 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....*
>
> *Methemoglobinemia increases with the dose of nitric oxide. ... Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours....*
>
> *INOmax should be administered with monitoring for PaO_2, methemoglobin and NO_2....*
>
> ***INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.***

Thus, although the 2007 INOmax® insert (and predecessor INOmax® labels) included an express contraindication for one of the prior art patient populations cited by the Examiner (i.e., neonates dependent on right-to-left shunting of blood), it did not include any warning or precaution with respect to the Claimed Patient Population, and in fact was entirely silent about the latter.[82]

The Examiner makes no attempt to reconcile his obviousness rejection with FDA's failure to include in the original INOmax® labeling what the Examiner considers to be obvious safety information. In fact, the Final Office Action does not address this evidence at all.[83]

Neither FDA nor other National Health authorities reviewing the original protocol for the INOT22 Study suggested that the Claimed Patient Population should be excluded from this study.[84] Sponsors of clinical investigations are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data submitted to FDA.[85] Accordingly, the original INOT22 protocol was submitted to and approved by FDA prior to starting enrollment in the

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[82] *Id.* After approval by FDA, INOmax® was also approved for use in Europe, Canada, Australia, Mexico and Japan by the National Health Authorities of those countries. Like the U.S. label, the original INOmax® drug labels in those countries did not contain any warning or precaution to refrain from administrating inhaled nitric oxide to the Claimed Patient Population.

[83] *See generally* Final Office Action.

[84] Second Baldassarre Dec. ¶ 8.

[85] *See generally* Responsibilities of Sponsors and Investigators, 21 C.F.R. § 312, subpart D; *See also* Responsibilities of Sponsors, 21 C.F.R. § 812, subpart C.

study.[86] It was similarly submitted to and approved by the National Health Authorities of each country containing a clinical trial center participating in the INOT22 Study (United Kingdom, France, Netherlands and Spain).[87] Not a single individual in any of these regulatory organizations suggested that administering inhaled nitric oxide to the Claimed Patient Population might lead to an increased risk of adverse events.[88]

Again, the Examiner makes no attempt to reconcile his rejection with the actions of FDA and other National Health authorities that are entirely inconsistent with his obviousness rejection. In fact, the Final Office Action does not address this evidence at all.

The FDA and multiple other National Health authorities amended the INOmax® drug labeling as a result of Appellant's invention.[89] FDA does not take drug warnings lightly, and would not approve changes to a drug label that merely restate existing warnings.[90] As outlined above in section VII.B.2, upon conclusion of the INOT22 Study and completion of the final study report, applicants discovered that the Claimed Patient Population was at increased risk for adverse events. Because this was an important and unexpected finding, INOT submitted a label supplement to the FDA on February 25, 2009, seeking to amend the prescribing information for INOmax® to include a warning statement for physicians.[91] On August 28, 2009, 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*

[86] Second Baldassarre Dec. ¶ 8.
[87] *Id.*
[88] *Id.*
[89] First Greene Dec. ¶ 22.
[90] Second Greene Dec. ¶ 15.
[91] First Baldassarre Dec. ¶ 15.

> *for short durations, experienced serious adverse events (e.g., pulmonary edema).*[92]

Thereafter, similar warnings regarding the Claimed Patient Population were added to the INOmax® label in Japan, Europe, Canada and Australia.[93]

The Examiner makes no attempt to reconcile his obviousness rejection with this record evidence that FDA and the Health Authorities modified the INOmax® label in response to Appellant's invention. In fact, the Final Office Action does not address this evidence at all.

E. The Examiner's Rejection is Premised on Improper Fact Findings and Unwarranted Inferences Unsupported by the Prior Art

The Examiner's rejection is based on four prior art references: the 2007 INOmax® Insert, Atz & Wessel, Kinsella et al., and Loh et al.[94] From these references, the Examiner derives four alleged findings of fact. Reduced to their essence, these alleged facts are:

1. The 2007 INOmax® insert would have taught persons skilled in the art that, as a general matter, patients receiving inhaled nitric oxide are more likely to experience adverse events than those who do not.[95]

> *- As discussed in more detail in Section VII.F.1. below, this alleged fact is both irrelevant and inaccurate. In a perfect world, all neonates would be born healthy and none would require any sort of medical treatment or be subject to the adverse events that often accompany such treatment. Given that some neonates do require iNO therapy, however, the question becomes whether there exist particular patient populations at increased risk of adverse events (as compared to the general population in need of such therapy) that should be excluded from receiving the treatment. The present invention is directed to one such patient population. Moreover, contrary to the Examiner's analysis, the study results reported in the 2007 INOmax® Insert do not indicate that patients treated with inhaled*

[92] *See* 2009 INOmax® Insert; *see also* First Baldassarre Dec. ¶ 16.
[93] Second Greene Dec. ¶ 15.
[94] Final Office Action at 3.
[95] Final Office Action at 4-6.

nitric oxide fared any worse than those treated with placebo.

2. Atz & Wessel would have taught persons skilled in the art to expect adverse events from administration of INOmax® to patients with LVD.[96]

- As discussed in more detail in Section VII.F.2. below, this alleged fact is a gross overgeneralization and materially misleading. The pathologies that are associated with a dysfunctional left ventricle vary widely. Atz & Wessel mention only two of these pathologies, neither of which is applicable to patients belonging to the Claimed Patient Population.

3. Kinsella et al. would have taught persons skilled in the art that INOmax® should not be administered to patients with congenital anomalies or heart disease.[97]

- As discussed in more detail in Section VII.F.3. below, this alleged fact is simply false. Inhaled nitric oxide therapy has been routinely and successfully administered to patients with congenital heart defects since its approval in 1999 and continues to be administered to such patients today.

4. Loh et al. would have taught persons skilled in the art that INOmax® should not be administered to patients with an elevated wedge pressure of 18 mm, a symptom of LVD.[98]

- As discussed in more detail in Section VII.F.4. below, this alleged factual finding (like the Examiner's second finding) is a severe overgeneralization and materially misleading. Loh et al. deal only with one type of LVD, a type that is inapplicable to patients belonging to the Claimed Patient Population.

[96] Final Office Action at 6-7.
[97] Final Office Action at 7-8.
[98] Final Office Action at 8-9.

Starting from these overbroad and flawed findings of fact, the Examiner infers that "it is no stretch of the imagination to exclude patients, including a neonatal patient that has pre-existing left ventricular dysfunction but is not known to be dependent on right to left shunting of blood from iNO therapy to reduce the risk of occurrence of one or more adverse events . . . ."[99]

> *- Here again, the Examiner is simply wrong on the science. As discussed in more detail in Section VII.G. below, none of the prior art references relied on by the Examiner relates to the Claimed Patient Population, and those references would not teach or suggest to those skilled in the art that the Claimed Patient Population should be excluded from iNO therapy.*

F. The Examiner's Four "Findings of Fact" are Irrelevant and Inaccurate

1. *The Examiner's Finding of Fact #1 mischaracterizes the 2007 INOmax® Insert and is wholly irrelevant to the patentability of the claimed subject matter*

The Final Office Action begins at pages 4-6 by pointing to disclosure in the 2007 INOmax® Insert reporting results of early clinical trials in which inhaled nitric oxide was tested against placebo. This portion of the Final Office Action focuses on a table containing data regarding the frequency of certain adverse events observed with placebo and with inhaled nitric oxide in the so-called CINRGI clinical trial, followed by some quoted text regarding the NINOS trial.[100] Based on this, the Examiner asserts (emphasis in original):

> As can be seen in the Table, there is a higher percentage of Adverse events associated with iNO than the placebo in all categories.... This teaching fairly suggests that iNO increases the risk of adverse events over a broad variety of events above that of the placebo. Accordingly, the ordinary artisan understands that there is an increased risk of adverse events in administering iNO over that of a placebo. *In other words, the administration of iNO increases the risk of adverse events in neonates and consequently the ordinary artisan understands that by not administering iNO the risk of occurrence of adverse events is reduced as shown by the Table above.* From this piece of art, the Examiner can make the following reasonable conclusion:

[99] Final Office Action at 10.
[100] *Id.* at 5.

Finding of Fact #1: Administration of iNO is not without risk of adverse events. Inhaled NO increases the risk of adverse events in neonates and the corollary that exclusion of the patient from iNO, the placebo above, has a reduced risk of the the [sic] occurrence of adverse events from iNO.[101]

Appellant respectfully disagrees with both the above characterization of the data disclosed in the 2007 INOmax® Insert and the significance the Examiner has apparently assigned to the data. It is rather puzzling that the Examiner has chosen to lead off with a reference on the basis of its alleged disclosure that giving a placebo instead of the drug will reduce the risk of occurrence of adverse events from the drug. No drug can be said to be "without risk of adverse events." If the Examiner's point is that a disclosure such as in the table makes it obvious to refrain from treating all patients with inhaled nitric oxide in order to reduce all risk of adverse events, then no one would ever treat any patient with inhaled nitric oxide, thereby eliminating all the adverse events. (Of course, many patients would then die from lack of treatment, or would be given ECMO treatment instead[102] and would suffer the destructive adverse events routinely caused by that invasive procedure, but that aspect does not seem to have been factored into the Examiner's "finding of fact.")

If instead the Examiner is trying to make the point that the disclosure in the 2007 INOmax® Insert regarding adverse events contributes to an understanding that one should avoid giving inhaled nitric oxide to the Claimed Patient Population in particular, Appellant fails to see the connection. The cited table from the CINRGI trial and passage from the NINOS study says nothing about LVD, nor about pulmonary edema, increased wedge pressure, or any other sort of adverse event now known to be associated with administering inhaled nitric oxide to the Claimed Patient Population.[103] Nothing suggests that the patients of the CINRGI trial who suffered the various adverse events listed in the table had an underlying condition related to LVD. Thus, even if the data in the table had been accurately characterized in the Final Office Action, they would not support the obviousness rejection. It is therefore almost superfluous to point out how

[101] *Id.* at 5-6.
[102] *See* VII.B.1.
[103] Final Office Action at 5.

the data from the CINRGI table and the NINOS study have been mischaracterized and misinterpreted. Appellant will nonetheless do so, to correct the record.

First, Appellant draws the Board's attention to the actual words of the passage about the NINOS study quoted in the Final Office Action on page 5. This passage says that "**treatment groups were similar with respect to the incidence and severity**" of several types of adverse events.[104] In other words, the group treated with inhaled nitric oxide fared the same as did the group treated with placebo, with respect to those types of adverse events. Despite this passage's unambiguous characterization of the data as demonstrating that inhaled nitric oxide was as safe as placebo (i.e., the "**treatment groups were similar**"), the Examiner inexplicably interprets it as supporting the opposite conclusion, saying "**This teaching fairly suggests that iNO increases the risk of adverse events over a broad variety of events above that of the placebo.**"[105] Appellant cannot fathom how the Examiner read the passage as suggesting any such thing.

Second, the 2007 INOmax® Insert explicitly says that the table of adverse events in the CINRGI trial (i.e., the table pasted on page 5 of the Final Office Action) was limited to just those adverse events that were more common on INOmax® than on placebo.[106] There is therefore no significance to the fact emphasized in the Final Office Action that "all categories" in the table showed more adverse events with INOmax®—in fact, it is quite possible that there were several other undisclosed categories of adverse events that happened to show up in the trial as more common on placebo than on INOmax®, by random chance. The drafter of the label would have realized there was no point in presenting the latter categories on the label insert. Appellant notes that the differences between INOmax® and placebo as reported in this table are in most cases trivial, and there is no discussion of whether they are statistically or medically significant. Notably, none of the listed adverse events was considered significant enough by the drafters of the 2007 INOmax® Insert and by FDA to warrant a warning or contraindication.

Third, though the Final Office Action acknowledges on page 4 that in the NINOS trial, fewer neonates died when treated with inhaled nitric oxide than when treated with the

[104] 2007 INOmax® Insert at "Adverse Reactions" (emphasis added).
[105] Final Office Action at 5 (emphasis added).
[106] 2007 INOmax® Insert (See the sentence on page 2 of the 2007 INOmax insert immediately above the table at the bottom of the left column).

control, this fact (and the fact that neonates treated with inhaled nitric oxide were less likely than control neonates to end up having to be put on ECMO to save their lives) is simply ignored in the Final Office Action's subsequent discussion about how one of ordinary skill in the art would have considered it obvious to avoid all use of inhaled nitric oxide in all patients merely to avoid any adverse events.[107]

In sum, it is unclear why the Final Office Action has cited the 2007 INOmax® Insert at all. It would be logical to assume that any truly "obvious" risk to a defined subset of the target population of neonates would have been explicitly disclosed as a warning or contraindication on the 2007 INOmax® insert, just as the well-known risk to neonates dependent on right-to-left shunting of blood was disclosed. **Since the 2007 INOmax® insert was entirely silent about any potential risk to the Claimed Patient Population, this document actually supports Appellant's position that the claimed methods would not have been obvious to one of ordinary skill in the art at the time the invention was made.**

2. *The Examiner's Finding of Fact #2 is a Gross Overgeneralization that improperly lumps together all patients that suffer from LVD into a single patient population*

The Examiner's second fact finding is based on the Atz & Wessel reference.[108] The Final Office Action summarizes the Examiner's views with respect to this reference as follows:

> 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.
>
> * * *

[107] Final Office Action at 5-6.
[108] *Id.* at 6-7.

Finding of Fact #2: Adverse outcomes are known to occur to neonates treated with iNO that have pre-existing left ventricular dysfunction and consequently the art cautions against the use of iNO to such patients.[109]

This "finding of fact" does not accurately represent what Atz & Wessel actually disclose. Contrary to the Examiner's view, Atz & Wessel do not teach that **all** patients with left ventricular dysfunction (LVD) should be excluded from treatment with inhaled nitric oxide. Rather, as discussed below, Atz & Wessel disclose two separate and distinct patient populations that are subsets of LVD patients (neither of which overlaps with the Claimed Patient Population) who may be harmed in different ways when their pulmonary hypertension is reduced by treatment with inhaled nitric oxide.[110]

The Adult Population. The first patient population addressed by Atz & Wessel is adults suffering from LVD (the "Adult Population"). With respect to this population, Atz & Wessel state the following:

> 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.[111]

As the Board will recognize, this disclosure is explicitly limited to adult patients and does not address the potential impact of inhaled nitric oxide on neonates. Contrary to the Examiner's contention, those skilled in the art would not have extrapolated from Atz & Wessel's disclosure concerning the Adult Population to a general caution concerning all patients with all forms of LVD. Rather, as thoroughly explained in the Second Greene Declaration, persons skilled in the art would have realized that Atz & Wessel's teachings about the LVD associated with ischemic cardiomyopathy in an adult are not applicable to other forms of LVD, such as the form of LVD that occurs in newborns.[112]

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[109] *Id.* at 7.
[110] Second Greene Dec. ¶¶ 8-9.
[111] Atz & Wessel at 452.
[112] Second Greene Dec. ¶¶ 8, 27.

As Dr. Greene explains in the First Greene Declaration, the hearts of the Adult Population are clinically distinct from the hearts of the Claimed Patient Population due to the fact that the etiology and pathophysiology of the left ventricular dysfunction present in the Claimed Patient Population is markedly different from what is present in the Adult Population. Left ventricular dysfunction comes in two broad types: systolic and diastolic. As detailed in paragraphs 15-16 of the First Greene Declaration, left-sided ventricular dysfunction in the Claimed Patient Population is generally associated with a soft, overly elastic heart that cannot push blood out, resulting in impaired emptying, i.e., *systolic dysfunction*. Conversely, in the Adult Population, 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, i.e., *diastolic dysfunction*. In addition, this population is inherently different than the Claimed Patient Population in that the Adult Population does not suffer from congenital heart disease.[113] Given these dramatic anatomical differences between adult LVD and neonate LVD, those skilled in the art do not consider LVD in adults as analogous to, or predictive of risks associated with, LVD in the Claimed Patient Population.[114]

Because of this important clinical and etiological distinction, one would have had no reason to expect an elevated risk of pulmonary edema or cardiac complications (or any other adverse event) when using inhaled nitric oxide in the Claimed Patient Population. For this reason, the Examiner's inference that Atz & Wessel's disclosure concerning the Adult Population would be read as a general warning concerning all patients with LVD is simply incorrect.

The Shunt Reliant Population. The second patient population addressed by Atz & Wessel is neonates suffering from LVD that are reliant on right-to-left shunting of blood at the patent ductus arteriosus (the "Shunt Reliant Population").[115] The Shunt Reliant Population is entirely distinct from the Claimed Patient Population, and the physiological reasons why inhaled

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[113] Congenital heart disease is a problem with the heart's structure and function due to abnormal heart development before birth. "Congenital" means present at birth. National Heart Lung and Blood Institute, http://www.nhlbi.nih.gov/health/health-topics/topics/chd/.
[114] First Greene Dec. ¶¶ 15-16.
[115] Second Greene Dec. ¶ 9.

nitric oxide is not recommended for use the Shunt Reliant Population are wholly different from the physiological reasons behind the claimed invention.

With respect to the Shunt Reliant Population, Atz & Wessel disclose:

> 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.[116]

Importantly, Atz & Wessel's "caution" regarding use of inhaled nitric oxide in neonates is explicitly limited to neonates who present with a **combination of three conditions**:

> 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.[117]

As explained by Dr. Wessel and Dr. Greene in their declarations, Atz & Wessel are <u>not</u> saying that treatment with inhaled nitric oxide poses a risk for a neonate who has just one of the three conditions; in fact, inhaled nitric oxide was **routinely** used to treat pulmonary vasoconstriction in neonates presenting with left ventricular dysfunction alone OR an open foramen ovale alone OR an open ductus arteriosus alone (and continues to be used to treat the latter two groups).[118] Rather, this disclosure in Atz & Wessel is directed to one particular circumstance where inhaled nitric oxide therapy should not be used, i.e., **where the patient is dependent on right-to-left shunting.** Note that the Atz & Wessel reference includes no

[116] Atz & Wessel at 452 (emphasis added).
[117] *Id.*
[118] Wessel Dec. ¶ 6-8; First Greene Dec. ¶ 12-13.

discussion whatsoever concerning neonates with LVD who do *not* have right-to-left shunting at the ductus arteriosus, so are *not* dependent on right-to-left shunting of blood (i.e., the Claimed Patient Population).

To understand the significance of the Azt & Wessel disclosure about the Shunt Reliant Population and why it is not at all predictive of risks in the Claimed Patient Population, it is useful to review the physiology of these two distinct groups of neonates and the mechanism of inhaled nitric oxide's action in these patients.

As explained by Dr. Greene,[119] constriction of pulmonary blood vessels to minimize blood flow through the lungs is a normal and beneficial phenomenon in a fetus *in utero*. Since the fetus' blood is oxygenated by the placenta, and not by the fetal lungs, there is no need for blood to circulate through the fetal lungs prior to birth. Thus, both the right and the left sides of the fetal heart are dedicated to pumping blood through the placenta and the systemic vasculature, mostly bypassing the blood vessels of the lungs. However, once the child is born and begins breathing air, there is necessarily a dramatic shift in blood circulation. The newborn's previously-constricted pulmonary vasculature normally will dilate at birth to permit blood to flow freely through his lungs, pumped by the right side of the heart (the right atrium and right ventricle). After passing through the lungs and becoming oxygenated, the blood returns to the heart, where it enters at the left atrium and then is pumped by the left ventricle of the heart to the rest of the body.

For this shift in the circulation to take place properly after birth so that the newborn can immediately rely on his lungs for oxygenation, it is essential that the constricted blood vessels of the lungs dilate. If instead, the pre-birth pulmonary vasoconstriction persists after birth (a condition referred to as Persistent Pulmonary Hypertension of the Newborn, or PPHN), the newborn will be unable to pump blood adequately through the blood vessels of his lungs because of the abnormally high vascular resistance in the lungs. In such a PPHN patient, blood is poorly oxygenated even though the patient is breathing normally, and he appears a characteristic dusky color, i.e., a "blue baby." Treatment with inhaled nitric oxide gas (a vasodilator specific for pulmonary blood vessels) instantly relaxes the constricted pulmonary

[119] First Greene Dec. ¶¶ 8, 10-14.

blood vessels, allowing blood to flow more freely from the heart through the lungs and markedly improving the infant's overall oxygenation. The "blue baby" is transformed into a pink baby. Inhaled nitric oxide treatment has to a large extent supplanted the prior standard (and highly invasive) treatment for PPHN: extracorporeal membrane oxygenation, or "ECMO." In fact, one of the clinical trial end points described in the 2007 INOmax Insert was the reduction of initiation of ECMO in PPHN patients.[120]

Although treatment with inhaled nitric oxide has proven to be enormously beneficial to PPHN patients and other neonates with pulmonary hypertension, it was recognized early on that a particular subset of neonates with pulmonary hypertension may, because of their peculiar cardiac physiology, suffer fatal complications if they receive this therapy. This subset of neonates is identified in the 2007 INOmax Insert as those who are "dependent on right-to-left shunting of blood."[121] The First Greene Declaration explains that this condition occurs in neonates who have a particular combination of congenital conditions including, in addition to pulmonary hypertension: (a) an open (or "patent") ductus arteriosis (a passageway between the right atrium of the heart and the systemic circulation that is supposed to close at birth, when it is no longer needed); (b) a patent foramen ovale (a hole between the right and left atria that, like the ductus arteriosis, is supposed to close shortly after birth, when it is no longer needed); and (c) a dysfunctional left ventricle that is unable to handle its usual role of pumping blood through the systemic circulation. As noted by Dr. Greene, the pulmonary hypertension and resulting high vascular resistance in the lungs of these infants means that the blood pressure in the right atrium of the heart is kept abnormally high. This forces blood from the right atrium through the still-patent ductus arteriosis and directly into the systemic circulation, a situation known as "right-to-left shunting of blood." This blood entering the systemic circulation from the right atrium is partially oxygenated by virtue of oxygenated blood leaking through the patent foramen ovale from the left to the right atrium and mixing with the deoxygenated blood normally in the right atrium. Because the dysfunctional left ventricle in these patients is not able to supply the systemic circulation with blood, the patients end up relying on this abnormal right-to-left shunting of blood to keep a life-sustaining level of partially oxygenated blood flowing through

[120] 2007 INOmax Insert, page 1, right column, first paragraph.
[121] *Id.*, page 2, left column, second paragraph ("Contraindications").

their systemic circulation. *If the right-to-left shunt ceases for any reason, and there is no compensating mechanism to supply blood to the systemic circulation, the result would be catastrophic: total systemic circulatory collapse—and death.* In these infants, reducing pulmonary hypertension by treatment with inhaled nitric oxide will redirect blood flow from the right atrium into the lungs and away from the ductus arteriosus, cutting off the right-to-left shunt on which the patient desperately depends for survival. That is why this particular subset of pulmonary hypertension patients (the Shunt-Reliant Population) has long been excluded from treatment with inhaled nitric oxide. *See*, paragraphs 10-14 of the First Greene Declaration.

Thus, Atz & Wessel's teaching that the Shunt-Reliant Population should not be treated with inhaled nitric oxide reflects what was widely understood in the art years before the INOT22 Study.[122] In fact, an express contraindication for the Shunt-Reliant Population has been highlighted in the INOmax® label since the approval of the drug by FDA in December 1999,[123] and, of course, no such patients were admitted to the INOT22 Study.[124] It is absurd for the Examiner to suggest that the discovery resulting from the INOT22 Study that the Claimed Patient Population may experience an increased risk of adverse events (such as pulmonary edema) from treatment with inhaled nitric oxide therapy was somehow foreshadowed by Atz & Wessel's disclosure concerning the Shunt-Reliant Population, in whom inhalation of nitric oxide may trigger catastrophic systemic circulatory collapse due to redirection of blood away from the patent ductus arteriosus on which this group of patients relies for survival.

The differences in etiology and pathophysiology between the prior art and the claimed invention are summarized in the table below:

Adult Population	Shunt Reliant Population	Claimed Patient Population
• Congestive Heart Failure • Diastolic Dysfunction - stiff, non-compliant left ventricle	• Dependent on right-to-left shunting of blood through a patent ductus arteriosus • Heart Failure associated with Congenital Heart Disease • Systolic Dysfunction - soft, overly elastic heart	• No right-to-left shunting of blood • Heart Failure associated with Congenital Heart Disease • Systolic Dysfunction - soft, overly elastic heart

[122] First Greene Dec. ¶ 14.
[123] Second Greene Dec. ¶ 10. *See also* 2007 INOmax® Insert § 4.
[124] Second Greene Dec. ¶ 11.

As noted by the Federal Circuit: "It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art."[125] Yet the Examiner has done exactly what the Court warns is impermissible: i.e., the Examiner has "picked and chosen" only the LVD aspect of Atz & Wessel's disclosure, excluding the rest of that reference's disclosure from his summary and "Finding of Fact #2" and thereby entirely distorting what the reference says in a way that supports the rejection, but is plainly inaccurate. If, as the Examiner implies, the authors of Atz & Wessel had been aware that all patients with LVD (including neonates who are not dependent on a right-to-left shunting of blood through a patent ductus arteriosus) were at increased risk for adverse events when treated with inhaled nitric oxide, or even had suspected that would be the case, one would expect they would have mentioned it in their publication. The Examiner offers no rationale as to why Atz & Wessel failed to note this supposedly "obvious" risk to the Claimed Patient Population.

Appellant's reading of the Atz & Wessel reference is supported by Dr. Wessel's Declaration of record. In particular, 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 [i.e., the Claimed Patient Population] would be at greater risk of adverse events."[126] Dr. Wessel also declares that "it was unanticipated and surprising that children with left ventricular dysfunction who are not dependent on right-to-left shunting [i.e., the Claimed Patient Population] would be at increased risk of adverse events when administered iNO."[127]

In particular, Dr. Wessel states:

> Neither the Atz et al. article that I co-authored, nor the medical literature or medical experience of which I was aware at the time, predict this risk. Instead, Atz et al. describes two distinct, independent precautions with

[125] *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (internal citations omitted).
[126] Wessel Dec. ¶¶ 7-8 (emphasis in original).
[127] *Id.* ¶ 9.

> respect to the use of iNO. First, with respect to adults, Atz et al., stated that iNO may be more effective in newborns than in older patients, and noted that it should be used with caution in adults with ischemic cardiomyopathy in whom a risk of pulmonary edema is a consideration (see page 452, left column). Second, with respect to neonates, we stated the well-known contraindication (currently found in the INOMAX® prescribing information) that iNO should not be used in newborns dependent upon right-to-left shunting of blood across a patent ductus arteriosus to avoid circulatory collapse. What we did **not** disclose or predict was 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.
>
> It is ironic that my own publication 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 et al., 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.[128]

This evidence flatly contradicts the Examiner's unduly broad interpretation of what Atz & Wessel discloses, undermining the factual basis for the entire *prima facie* obviousness rejection. The Examiner does not explain why he does not find Dr. Wessel's evidence convincing on this point. In fact, the Final Office Action does not address the evidence at all.

Thus, contrary to the Final Office Action's summary of Atz & Wessel quoted above, and contrary to the "Finding of Fact #2," Atz & Wessel does not teach, even by implication, that any and all patients diagnosed as having LVD, nor even all neonates 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 solely upon their dependence on right-to-left shunt in conjunction with LVD (since that warning focuses on the

[128] *Id.* ¶ 7-8 (emphasis in original).

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.

3. *The Examiner's Finding of Fact # 3 is simply wrong and contrary to the INOmax® standard of care in iNO therapy*

The Final Office Action cites Kinsella et al. as allegedly teaching:

> [E]xcluding 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.[129]

From this teaching, the Examiner mistakenly derives the following finding of fact (emphasis in original):

> **Finding of Fact #3: Neonates with fatal congenital anomalies or congenital heart disease are excluded from iNO therapy but those neonates who meet the criteria for therapy are provided iNO therapy.**[130]

Once again, this fact finding significantly mischaracterizes the disclosure on which it is based. For example, the clinical trial that is the subject of Kinsella et al. did not study "neonates" in general, as implied by the Finding of Fact, but rather was limited to premature neonates – a patient population clinically distinct from the Claimed Patient Population.[131] Thus, the Examiner incorrectly implies that premature neonates ("preemies") of Kinsella et al. are the same as the Claimed Patient Population. Furthermore, Kinsella et al. studied only those premature neonates who had severe respiratory failure due to immature lungs and surfactant deficiency, rather than those suffering from pulmonary hypertension.[132] The Kinsella et al. population is therefore distinctly different in a number of important ways from the term and near-term neonates suffering from pulmonary hypertension who are the subject of the presently claimed methods.

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[129] Final Office Action at 7.
[130] *Id.* at 8.
[131] Second Greene Dec. ¶ 17.
[132] *Id.*

Finding of Fact #3 also fails to take into account the highly salient fact that Kinsella et al.'s exclusion from the trial of those preemies that have fatal congenital anomalies or congenital heart disease was due to a reason entirely unrelated to a desire to reduce the risk of treatment-related adverse events, and so irrelevant to the presently claimed methods. As explained in the Second Greene Declaration, the exclusion of patients from a clinical study may occur for a variety of reasons other than safety concerns.[133] The exclusion criteria in the Kinsella et al. study were designed to eliminate variables (here, underlying potentially fatal conditions unrelated to the condition being studied) that would complicate interpretation of the trial results. The Second Greene Declaration explains this point as follows:

> 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 anomal[]ies 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

[133] *Id.* ¶ 18-20.

> the target outcomes of the study (i.e., would have "confounded" the results).[134]

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 that reference is clear from other objective evidence already of record. See, for example, the post-filing publication Fraisse & Wessel, "Acute pulmonary hypertension in infants and children: cGMP-related drugs."[135] 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.

This view of the value of inhaled nitric oxide for treating pediatric patients with congenital heart disease is confirmed in the body of the article, where the authors again state:

> [I]nhaled NO is extremely efficacious in selectively reducing mean pulmonary arterial pressure (PAP) in cardiac patients and is considered standard treatment in most centers.[136]

These statements extolling the benefits of inhaled nitric oxide as being "extremely efficacious" and a "standard treatment" 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 had read Kinsella et al.'s exclusion criteria to mean that infants with congenital heart disease in general should be excluded from treatment with inhaled nitric oxide for safety reasons, 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 Final 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

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[134] *Id.*
[135] *Pediatric Critical Care Med.* 2010, Vol. 11, No. 2 (Suppl.), pages S37-S40; originally made of record on July 8, 2011, and now included in the Evidence Appendix (ix) as Exhibit 11.
[136] *Id.* at S37.

Kinsella et al.'s exclusion criteria. Properly interpreted, Kinsella et al. does not support the present rejection at all.

Moreover, as explained in the Second Greene Declaration, 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 preemies of Kinsella et al. 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. are totally unrelated to the term and near-term neonates addressed in the present claims. [137]

Although the above arguments and evidence regarding Kinsella et al. were presented in the July 8, 2011 Reply, the Final Office Action unfortunately does not even address them, much less offer a rebuttal. It is therefore a mystery to Appellant as to why the Examiner did not find them persuasive.

4. *The Examiner's Finding of Fact #4 (Like Finding of Fact #2) is a Gross Overgeneralization*

The Final Office Action 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 hypertension 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.*" Loh et al. examined this prediction further and verified it.
>
> From this piece of art, the Examiner can make the following reasonable conclusion:

[137] Second Greene Declaration ¶ 17.

> **Finding of Fact #4: Patients with a pulmonary capillary wedge pressure of greater than or equal to 18 mm Hg have a more marked hemodynamic response to inhaled NO which results in the finding that inhaled nitric oxide in patients with left ventricular dysfunction may have adverse effects in patients with LV failure.**[138]

Like Fact Finding #2 above, this fact finding is misleading in that it does not specify that Loh et al. was talking solely about adult patients with the adult form of LVD (i.e., diastolic dysfunction: a "stiff" left ventricle that cannot expand normally), a type of LVD that is entirely distinct from the LVD typically found in neonates (i.e., systolic dysfunction: a "flabby" left ventricle that expands readily, but is unable to contract normally). 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.[139] As explained by Dr. Greene, one cannot predict from Loh et al.'s observations in adults that there would have been any risk in the Claimed Patient Population, who typically have a very different form of LVD arising from very different causes, and also have pulmonary hypertension arising from very different causes than the pulmonary hypertension seen in adults with the type of LVD studied by Loh et al.[140]

Dr. Greene thoroughly describes the anatomic and etiologic differences between these two classes of patients, and then concludes:

> 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.[141]

Given these specific physiological traits of Loh et al.'s Adult Population with congestive heart failure, those skilled in the art would not consider Loh et al.'s teachings to

[138] *Id.* at 8, emphasis in original.
[139] Second Greene Dec. ¶ 22.
[140] *Id.*
[141] *Id.*

broadly cover all patients with LVD, and certainly would not consider those teachings to cover the Claimed Patient Population, with its entirely different pathology.

The Final Office Action does not address Appellant's evidence of record regarding these clear and important factual distinctions between the Adult Population and the Claimed Patient Population, much less explain why the Loh et al. reference continues to be cited against the claims despite Appellant's evidence of its irrelevance.

G. The Examiner's Obviousness Rejection is Based on Flawed and Legally Improper Reasoning and Should be Reversed

1. *The prima facie obviousness case is fundamentally flawed*

The Final Office Action summarizes the Examiner's view regarding obviousness as follows:

> 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 INOmax®, Atz et al., Loh et al., and Kinsella et al.**, and perform the method steps of instant claims 28-42 and produce the instant invention.[142]

Appellant does not understand this statement. The Examiner refers to "the method of INOmax®, Atz et al., Loh et al., and Kinsella et al." as though there exists one identifiable method disclosed collectively by the four cited references—which of course is not even close to the truth. Further, there is no way to imagine a single method that represents a compilation of the methods disclosed in the four references, since the references are directed to entirely different patient populations (term or near-term neonates, premature neonates, and adults) with different disease conditions characteristic of the different age groups, some of which involve pulmonary hypertension and some that do not. Accordingly, it is difficult to know what to make of the quoted statement.

[142] Final Office Action at 9 (emphasis added).

Having erroneously concluded that the four cited references disclose a single coherent method, the Examiner proceeds to explain the supposed motivation to perform that method:

> One of ordinary skill in the art would have been motivated to do this because:
>
> 1) iNO has risk of adverse events as taught by INOmax®;
>
> 2) if the neonate 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 other forms of LVD not known to be dependent on right to left shunting of blood; 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.[143]

Appellant addresses in turn each of the three points quoted above.

1) In Appellant's detailed discussion above of the 2007 INOmax® Insert, Appellant showed that this alleged conclusion is both inaccurate and irrelevant. The only adverse events that the reference clearly correlates with use of inhaled nitric oxide are in neonates dependent on right-to-left shunting of blood,[144] a subset of patients that does not overlap with the Claimed Patient Population. Moreover, if the Examiner is implying that a teaching regarding avoiding use of inhaled nitric oxide in one subset of patients makes it obvious to avoid use of inhaled nitric oxide in all patients, including those who could benefit from the treatment, Appellant believes it is sufficient to note the illogic of this position, given the acknowledged efficacy and life-saving ability of inhaled nitric oxide.

2) As apparently recognized by the Examiner, neither of the two patient populations discussed in Atz & Wessel encompasses the Claimed Patient Population, nor does Atz expressly state that one should refrain from administering inhaled nitric oxide to the Claimed Patient Population due to an increased risk of adverse events.[145] Appellant has established above that Atz & Wessel's disclosure is in fact solely directed to two set of patients: (i) the Adult

[143] Final Office Action at 9-10.
[144] 2007 INOmax® Insert.
[145] Final Office Action at 9.

Population, and (ii) the Shunt-Reliant Population (the latter characterized as having a combination of three conditions: severe left ventricular dysfunction plus predominantly left to right shunting at the foramen ovale plus exclusively right to left shunting at the ductus arteriosus).[146] The Examiner has focused on just one of those three neonatal conditions (left ventricular dysfunction) and has chosen to ignore the fact that Atz & Wessel says that it is the combination of the three, and not just one, that should trigger caution in using inhaled nitric oxide in the Shunt-Reliant population (and further that it is the right-to-left shunt that is key to the risk in this population). The Examiner persists in his position on this point despite the fact that Appellant has provided evidence explaining how those of ordinary skill in the art would have interpreted Atz & Wessel—including a declaration by Dr. Wessel himself—and objective evidence that physicians routinely used inhaled nitric oxide in LVD neonatal patients even after Atz & Wessel's publication date—clearly indicating they did not believe the danger to be "obvious."

The Examiner here makes the entirely unwarranted assertion that what Atz & Wessel say about LVD in the context of the combination of the three conditions (i.e., in the context of dependence on right-to-left shunting of blood) "would also render obvious other forms of LVD not known to be dependent on right to left shunting of blood"[147] (i.e., the Claimed Patient Population). **No justification is offered for this assertion, though it is really the crux of the obviousness rejection.** The Examiner simply deems it so. Appellant again points out that the contraindication for patients dependent on right-to-left shunting of blood is based on the danger of systemic circulatory collapse that would occur if the right-to-left shunt is bypassed, a danger that is not present in those patients who are not known to be dependent on right-to-left shunting of blood. Thus, one cannot logically extrapolate from what was taught in Atz & Wessel about neonates with the combination of three conditions that includes a right-to-left shunt, that other neonates with LVD who are not dependent on a right-to-left shunt should not get inhaled nitric oxide.

3) Appellant has explained that the group of premature neonates excluded from the Kinsella et al. study were excluded because they suffered from a confounding condition

[146] Second Greene Dec. ¶¶ 8-9.
[147] Final Office Action at 10.

unrelated to the condition Kinsella et al. sought to study. As a result, including these patients would have confounded the results of the study.[148] There is no evidence that Kinsella et al. sought to exclude these patients due to a perception that the excluded patients were at particular risk of adverse events due to inhaled nitric oxide. Appellant has submitted evidence to show that neonates with congenital heart disease in fact are routinely treated with inhaled nitric oxide to alleviate their pulmonary hypertension—in fact, this is considered a standard treatment for such patients (so long as they are not dependent on a right-to-left shunt), with no concerns expressed in the art that just because they have congenital heart disease, they are at particular risk of adverse events due to the treatment.[149] Thus, one of ordinary skill in the art would not have read Kinsella et al. as implying that patients with congenital heart disease should not be treated with inhaled nitric oxide because of a risk of adverse events. The Examiner has not explained why his reading of Kinsella et al. as being relevant to the present claims is not neutralized by the evidence supplied by Appellant. In fact, the Final Office Action does not even comment on any of the evidence supplied by Appellant, other than to dismiss it all as "not persuasive" and to opine that "Applicant has lost sight of the forest for the trees."[150] This wholesale dismissal of Appellant's evidence is improper as a matter of law.[151] It is well established that "[Objective] evidence can often serve as insurance against the insidious attraction of the siren hindsight when confronted with a difficult task of evaluating the prior art."[152] Such evidence "may be the most pertinent, probative, and revealing evidence available to aid in reaching a conclusion on the obvious/nonobvious issue."[153]

The Final Office Action continues with the following statement:

> Thus **it is simply no stretch of the imagination** to exclude patients such as term or near term neonates with LVD and not known to be dependent on right to left shunting of the blood from inhaled nitric oxide therapy in order to avoid adverse

[148] Second Greene Dec. ¶ 20.
[149] *See,* Fraisse & Wessel.
[150] Final Office Action at 13.
[151] MPEP 716.01(B) ("All entered…declarations traversing rejections [must be] acknowledged and commented upon by the examiner…[g]eneral statements such as 'the declaration lacks technical validity' or 'the evidence is not commensurate with the scope of the claims' [or 'Applicant has lost sight of the forest for the trees'] without an explanation supporting such findings are insufficient.").
[152] *W.L. Gore & Assocs., Inc. v. Garlock, Inc.,* 721 F.2d 1540, 1553 (Fed. Cir. 1983).
[153] *Id* at 1555.

> 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.[154]

First, Appellant points out that the Examiner's "**no stretch of the imagination**" test is not the proper standard to be applied in an obviousness analysis. The question is not whether it is possible for the Examiner to imagine carrying out the claimed invention, but rather whether those of ordinary skill in the art at the time the invention was made would have considered the invention to be obvious.[155] "Resolution of this issue [of obviousness] entails a difficult process of turning back the clock to a time when the invention was made and asking ***what one of ordinary skill in the art might have thought.***"[156] Appellant has provided extensive evidence explaining, in physiological terms, *why* one of ordinary skill in the art would not have expected that there was any particular risk of adverse events when giving inhaled nitric oxide treatment to the Claimed Patient Population.[157] Further, Appellant has provided extensive evidence demonstrating that, in fact, those of ordinary skill in the art—and even those considered highly expert in the art—did not hesitate to treat the Claimed Patient Population with inhaled nitric oxide.[158] This is cogent evidence that those of skill in the art did not, in fact, consider the risk to be "obvious." It is inconceivable that a physician, though recognizing as "obvious" an elevated risk in the Claimed Patient Population, would proceed to treat those patients anyway, in utter disregard of the risk.

Notably, the last sentence of the above-quoted language from the Final Office Action actually suggests that the Examiner agrees with Appellant's position on this point. If it is true that "[t]he ordinary artisan would err on the side of caution for the benefit of the patient,"[159] and if the ordinary artisan understood that the safety risk of inhaled nitric oxide treatment in the Claimed Patient Population outweighed the possible benefit of giving the treatment to those neonates, then one would expect there to be concrete evidence in the art that practitioners did

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[154] Final Office Action at 10 (emphasis added).
[155] *See, e.g.*, 35 USC § 103(a).
[156] *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1566-1567 (Fed. Cir. 1996) (emphasis added).
[157] *See, e.g.*, Second Greene Dec. ¶ 22.
[158] Wessel Dec. ¶ 8; Second Baldassarre Dec. ¶ 11.
[159] Final Office Action at 10.

"err on the side of caution," avoiding giving inhaled nitric oxide to the Claimed Patient Population. In point of fact, all of the evidence of record is to the contrary. The risk to this subset of neonates was plainly not "obvious" to anyone at the time the invention was made—if it were, it would have been widely publicized and discussed in the literature, with warnings circulated to practicing physicians.

As noted in *In re Kotzab*: "A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references ***and the then-accepted wisdom in the field***."[160] Given that the "then-accepted wisdom in the field" was that there was no particular risk to the Claimed Patient Population, and the prior art does not say otherwise, it is clear that arriving at the Examiner's determination of obviousness required the use of impermissible hindsight reconstruction of Appellant's invention,[161] despite the Examiner's protest to the contrary.[162]

Appellants submit that the *prima facie* obviousness case is so fundamentally flawed that it must be reversed.

2. *The Final Office Action fails to address Appellant's evidence and arguments of record, instead continuing to assert inappropriate interpretations of the cited references that are contrary to the evidence*

The Final Office Action states in conclusory fashion that "none of Applicants arguments or Declarations are persuasive,"[163] but provides not the slightest clue as to ***why***. The Final Office Action does inform Appellant that "the position of the Examiner remains immutable"[164] (apparently a hint that it would be a waste of time to submit further evidence or

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[160] 217 F.3d 1365, 1369 (Fed. Cir. 2000) (internal citations omitted; emphasis added).
[161] Final Office Action at 12.
[162] *KSR*, 550 U.S. at 421 ("warning against a 'temptation to read into the prior art the teachings of the invention in issue' and instructing courts to guard against slipping into use of hindsight.'" (quoting *Graham*, 383 U.S. at 36)); *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) ("To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest knowledge, is to use the invention as a template for its own reconstruction—an illogical and inappropriate process by which to determine patentability" (internal citations omitted)).
[163] Final Office Action at 12.
[164] *Id.* Given the common dictionary definition of "immutable" as "fixed; not changeable," this is a rather alarming admission by the Examiner. Appellant submits that it is the responsibility of all US Patent and Trademark Office Examiners to consider all evidence in an unbiased manner and to be open to a change of position.

arguments) and notes, "**Based on the preponderance of the evidence, the Examiner can only conclude based upon the facts and not impermissible hindsight reconstruction that the instant claims are not inventive.**"[165] Appellant's evidence puts the presently claimed methods and the prior art into the context of real world facts showing how real physicians of skill in the art truly viewed the claimed subject matter prior to the invention date. This real-world evidence should compel a conclusion of nonobviousness.[166] Despite the Federal Circuit's requirement that such evidence be given "great weight,"[167] the Examiner's above assessment of the "preponderance of the evidence"[168] is made without a single word anywhere in the Final Office Action addressing the substance of Appellant's evidence. Appellant submits that the evidence of nonobviousness in fact far outweighs the nonexistent evidence of obviousness in this case, and easily overcomes the weak *prima facie* rejection set out in the Final Office Action.

3. *The Examiner's Rejection is Contrary to Common Sense*

As part of the "Response to Arguments" section, the Final Office Action constructs an obviousness analysis suggesting that the Examiner believes obviousness is based on what can be imagined, rather than on a real-world assessment of what sensible people of ordinary skill would have actually done.[169] This line of analysis begins with the assertion, "Certainly, Applicant and the panel of experts must be aware of the adverse events associated with iNO therapy as provided by INOmax® insert. Inhaled NO is not without inherent risk of adverse events."[170] The Final Office Action then again relies on the Examiner's novel "no stretch of the imagination" standard to posit that it is obvious to refrain from administering inhaled nitric oxide therapy to **any** neonate, regardless of the neonate's condition (even "foot fungus" or "polydactyly"), because by not administering the therapy to anyone, one would necessarily reduce the risk of occurrence of all adverse events. According to the Examiner:

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[165] *Id.* (emphasis added).
[166] *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1099 (Fed. Cir. 1985) ("The human, real world story in evidence...not only reflects the inadequacy of the prior art, but compels a conclusion of nonobviousness of the claimed inventions in suit.").
[167] *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984) ("The objective evidence, again composed of real world facts, is worthy of great weight...").
[168] Final Office Action at 12.
[169] *Id.* at 12-14.
[170] *Id.* at 12.

> Consequently, the art as a whole paints a picture that patients, including neonates, are at risk of adverse events from iNO therapy even if the iNO therapy is beneficial in other aspects and it remains obvious to exclude patients, including neonates, from iNO therapy to reduce the risk of occurrence of such adverse events.[171]

That reasoning, which appears to be the fundamental basis for concluding that the present invention is obvious, is rather astonishing in that it suggests that real doctors treating real patients would consider it obvious to withhold all therapy from all patients, merely because the therapy was at some point reported to be associated with an adverse event—regardless of how beneficial the therapy is expected to be, regardless of how inconsequential the adverse event, and regardless of whether the adverse event was ever shown to be caused by the therapy or merely random chance. Since all drugs are associated with adverse events of some sort, this surprising view would effectively rule out all treatment of any patient with any drug, period. That the Examiner's purportedly "unwavering" position plainly does not reflect how real physicians behave hardly needs to be stated. One need only look to the fact that neonates in need of treatment for pulmonary hypertension were and are routinely treated with inhaled nitric oxide (despite the table reporting various adverse events with inhaled nitric oxide and with placebo in the 2007 INOmax® Insert on which the Examiner relies) to realize that physicians did not consider it "obvious" to exclude all patients from treatment with inhaled nitric oxide in order to avoid any chance that any of these adverse events might occur. A conclusion of obviousness should, at the very least, take into account the presumably rational behavior of those of ordinary skill in the art. The Examiner's "no stretch of the imagination" theory of obviousness plainly fails that test.

Appellant submits that whether or not it is "obvious" to exclude a given patient from a needed treatment depends on whether the risk of harm from an adverse event in that patient is believed to outweigh the potential benefit to the patient. One subset of neonates (the Shunt-Reliant Population) was well known in the art to be at high risk of serious adverse effects, and was explicitly identified as contraindicated in the prior art 2007 INOmax® Insert. It was certainly obvious to exclude that subset of neonates from treatment with inhaled nitric oxide, as

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[171] *Id.* at 14.

taught by the 2007 INOmax® Insert and by Atz & Wessel. The art disclosed no other subsets of neonates in whom inhaled nitric oxide treatment posed an increased risk of adverse events. Contrary to the assertions in the Final Office Action about what would have been "in the realm of common sense,"[172] it would not have been "common sense" for a physician to exclude any term or near-term neonate patient from a potentially life-saving treatment with inhaled nitric oxide without a legitimate medical justification for doing so.

Appellant was the first to discover that there is a second subset of neonates, separate and distinct from the Shunt-Reliant Population, who are also at increased risk of serious harm from inhaled nitric oxide treatment, although an entirely different type of harm than observed in the Shunt-Reliant Population. In the Shunt-Reliant Population, the potential harm is systemic circulatory collapse due to loss of the right-to-left shunt on which these patients rely to support their systemic circulation. In the Claimed Patient Population, the potential harm has nothing to do with systemic circulatory collapse, but rather stems primarily from pulmonary edema.

Until Appellant's discovery was publicized, there was no reason whatsoever to deprive the Claimed Patient Population of potentially lifesaving treatment with inhaled nitric oxide. Further, all of the evidence of record indicates that those of ordinary skill in the art did not consider it "obvious" to refrain from treating neonates of the Claimed Patient Population with inhaled nitric oxide, since if they had considered this obvious, they would have done it. As noted by the Examiner, physicians are by nature conservative about putting their patients at risk. Any "obvious" or "predictable" risk of serious harm in an identified subset of patients 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 the Claimed Patient Population 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. Appellant has provided objective evidence proving that none *–not a single one—* of the at least 115 individuals from several institutions tasked with designing or reviewing and approving the

[172] *Id.* at 11.

original INOT22 Study protocol suggested there might be a particular risk to the Claimed Patient Population. The logical conclusion is that practitioners did not consider such an exclusion to be medically justified—i.e., not an "obvious" thing to do.

VIII. Conclusion

Appellant has established that the obviousness rejection is founded on fundamental misinterpretations of each of the four cited references, on an improper legal analysis that is contrary to the statute and the case law, and on a failure to give due consideration to any of Appellant's highly pertinent objective evidence, including concrete evidence that at least 115 medical professionals of ordinary or even extraordinary skill in the art acted in a manner entirely inconsistent with what the Examiner (using his "no stretch of the imagination" standard) imagines to be "obvious." The Examiner's obviousness rejection should be reversed.

The attached Claims Appendix (viii) shows the claims under appeal.

The attached Evidence Appendix (ix) includes Exhibits 1-11.

A Related Proceedings Appendix (x) is attached as required, but is empty.

The appeal brief fee of $620 required by 37 C.F.R. § 41.20(b)(2) is being paid via the Electronic Filing System. Please apply any other necessary charges, or any credits, to Deposit Account No. 06-1050, referencing Attorney Docket No. 26047-0003002.

Respectfully submitted,

Date: October 4, 2011

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(viii) Claims Appendix

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.

(ix) Evidence Appendix

Exhibit 1: 2007 prescribing information for INOmax® ("2007 INOmax® Insert"), submitted with the September 17, 2010 Reply filed by Appellant.

Exhibit 2: Atz & Wessel, *Seminars in Perinatology* 1997, 21(5), 441-455.

Exhibit 3: Kinsella et al., *The Lancet* 1999, 354, 1061-1065.

Exhibit 4: Loh et al., *Circulation* 1994, 90, 2780-2785.

Exhibit 5: Declaration of Douglas A. Greene, M.D. under 37 C.F.R. § 1.132, dated April 29, 2011 ("First Greene Dec."), originally submitted with the May 2, 2011 Reply filed by Appellant.

Exhibit 6: Declaration of David L. Wessel, M.D. under 37 CFR § 1.132 ("Wessel Dec."), made of record on July 27, 2011.

Exhibit 7: Declaration of Douglas A. Greene, M.D. under 37 C.F.R. § 1.132, dated July 7, 2011 ("Second Greene Dec."), originally submitted with the July 8, 2011 Reply filed by Appellant.

Exhibit 8: Declaration of James S. Baldassarre, M.D. under 37 C.F.R. § 1.132, dated July 7, 2011 ("Second Baldassarre Dec."), originally submitted with the July 8, 2011 Reply filed by Appellant.

Exhibit 9: Declaration of James S. Baldassarre, M.D. under 37 C.F.R. § 1.132, dated Sept. 29, 2010 ("First Baldassarre Dec."), originally submitted with the October 1, 2010 Reply filed by Appellant.

Exhibit 10: 2009 prescribing information for INOmax® ("2009 INOmax® Insert"), submitted with the January 14, 2011 Reply filed by Appellant.

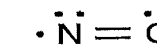
Exhibit 11: Fraisse & Wessel, *Pediatric Critical Care Medicine* 2010, Vol. 11, No. 2 (Suppl.), pages S37-S40, originally made of record on July 8, 2011.

EXHIBIT 1

INOmax® (nitric oxide) for inhalation
100 and 800 ppm (parts per million)

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:



CLINICAL PHARMACOLOGY
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 produces pulmonary vasodilation.

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.

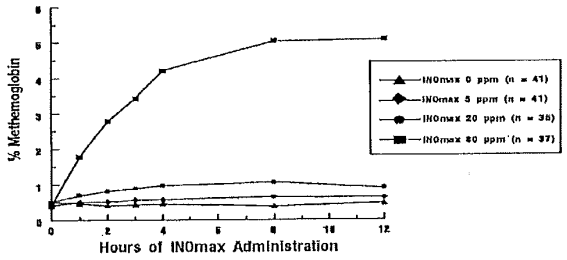
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (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).

PHARMACOKINETICS
The pharmacokinetics of nitric oxide has been studied in adults.

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.

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.

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.

CLINICAL TRIALS
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 x fraction of inspired oxygen concentration [FIO_2] x 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 (See CLINICAL PHARMACOLOGY).

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 1.

Table 1
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). 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 2.

Table 2
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).

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.

INDICATIONS
INOmax, 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.

CONTRAINDICATIONS
INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

PRECAUTIONS
Rebound
Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

Methemoglobinemia
Methemoglobinemia increases with the dose of nitric oxide. In the clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 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.

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.

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.

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.

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.

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.

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.

ADVERSE REACTIONS
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 events with an incidence of at least 5% on INOmax in the CINRGI study, and that were more common on INOmax than on placebo.

ADVERSE EVENTS IN THE CINRGI TRIAL

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%)*

OVERDOSAGE
Overdosage with INOmax will be manifest by elevations in methemoglobin and 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.

POST-MARKETING EXPERIENCE
The following adverse events have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. 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.

DOSAGE AND ADMINISTRATION
Dosage
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.

Administration
Additional therapies should be used 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 TRIALS).

INOmax should be administered with monitoring for PaO_2, methemoglobin, and NO_2.

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.

The INOmax dose should not be discontinued 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.

HOW SUPPLIED
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.

CAUTION
Federal law prohibits dispensing without a prescription.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

SPC-0303 V:3.0

EXHIBIT 2

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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0146-0005/97/2105-0008$05.00/0

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

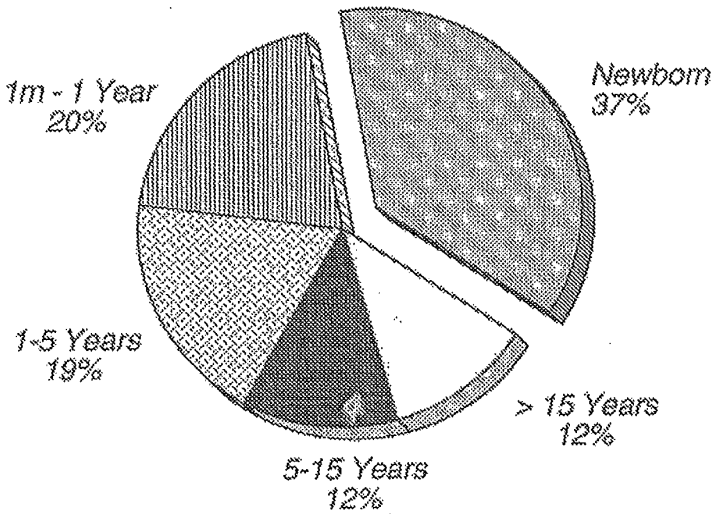

Figure 1. Age analysis of 405 consecutive patients who received inhaled NO at Children's Hospital, Boston.

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).

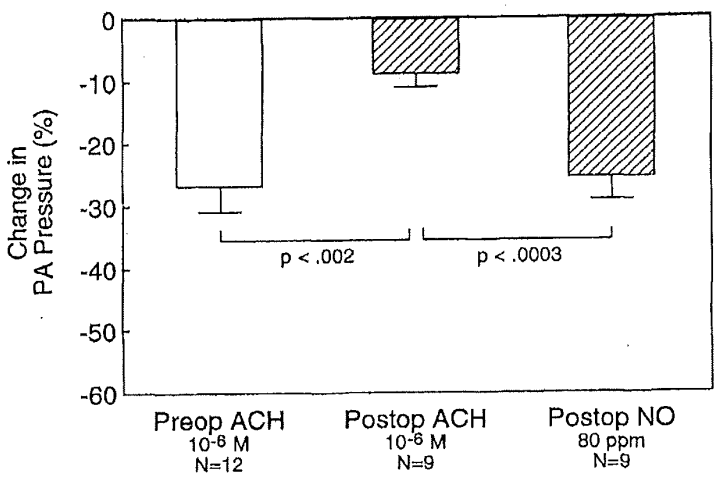

Figure 2. The percentage change in mean pulmonary artery pressure (PA) with acetylcholine (ACH) in preoperative and postoperative patients. The vasodilator response is attenuated with ACH but retained with NO in the postoperative period. (Reprinted with permission from Wessel DL, et al: Use of inhaled 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]

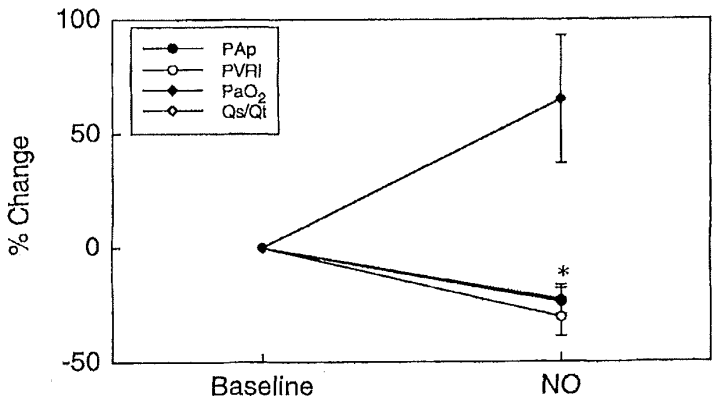

Figure 3. The effect of 80 ppm NO in six patients with transient graft dysfunction after lung transplantation. Pulmonary artery pressure (PAp), pulmonary vascular resistance (PVRI), and intrapulmonary shunt fraction (Q_S/Q_t) decreased significantly and PaO_2 increased. (Adapted and reprinted with permisssion 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

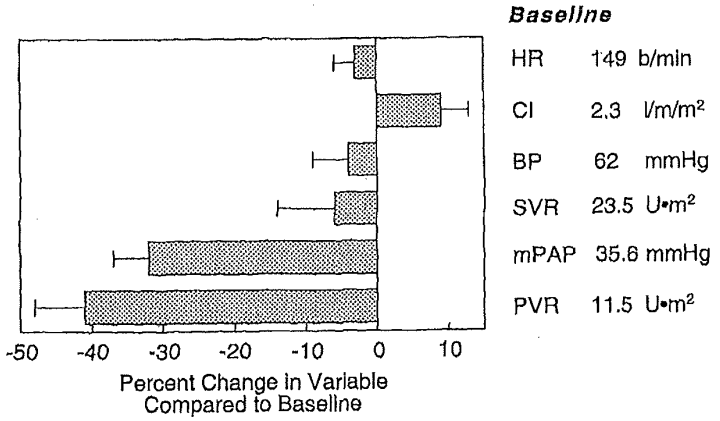

Figure 4. Percentage change in hemodynamic variables from baseline during 15 minutes of NO at 80 ppm in 9 patients with TAPVC. There is marked specificity for the pulmonary circulation.

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

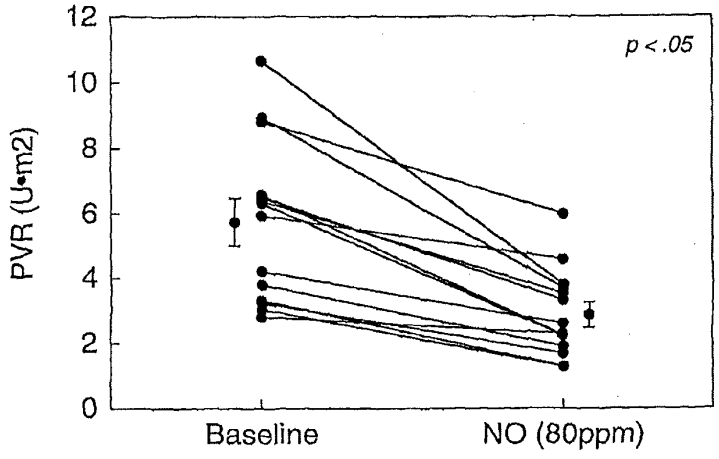

Figure 5. The effect of 80 ppm NO on pulmonary vascular resistance (PVR) in patients with congenital mitral stenosis. PVR decreased from baseline in all patients. (Reprinted with permission of the publisher from Atz AM, et al: Inhaled nitric oxide in children with pulmonary hypertension and congenital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

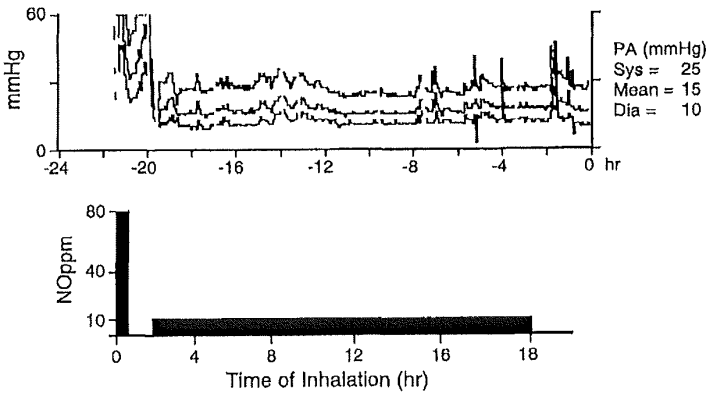

Figure 6. Bedside tracing of pulmonary artery pressure (PA) (systolic, mean, diastolic) with NO dose and duration of therapy on bottom. PA pressure decreased during 80 ppm trial. Vasodilation was sustained with 10 ppm NO for 18 hours of therapy.

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).

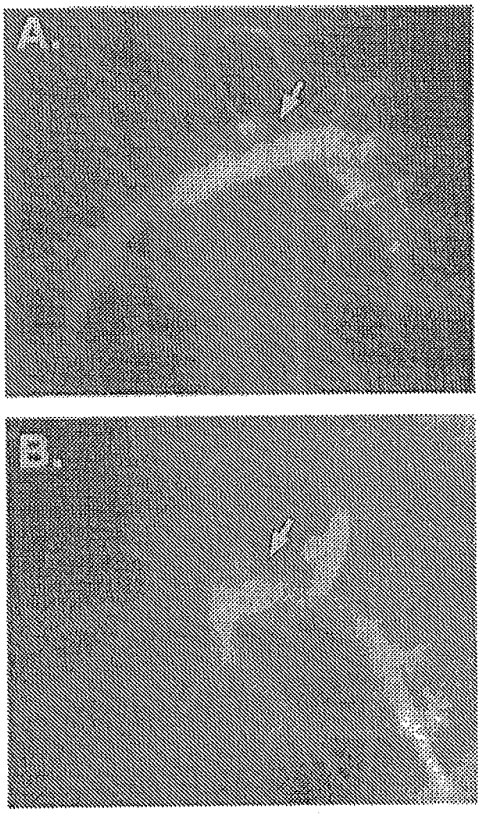

Figure 7. Anterior-posterior (A) and lateral (B) angiograms taken in a neonate with severe cyanosis and shunt-dependent pulmonary blood flow who failed to respond to inhaled NO. The arrow points to a discrete shunt narrowing that required surgical revision.

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

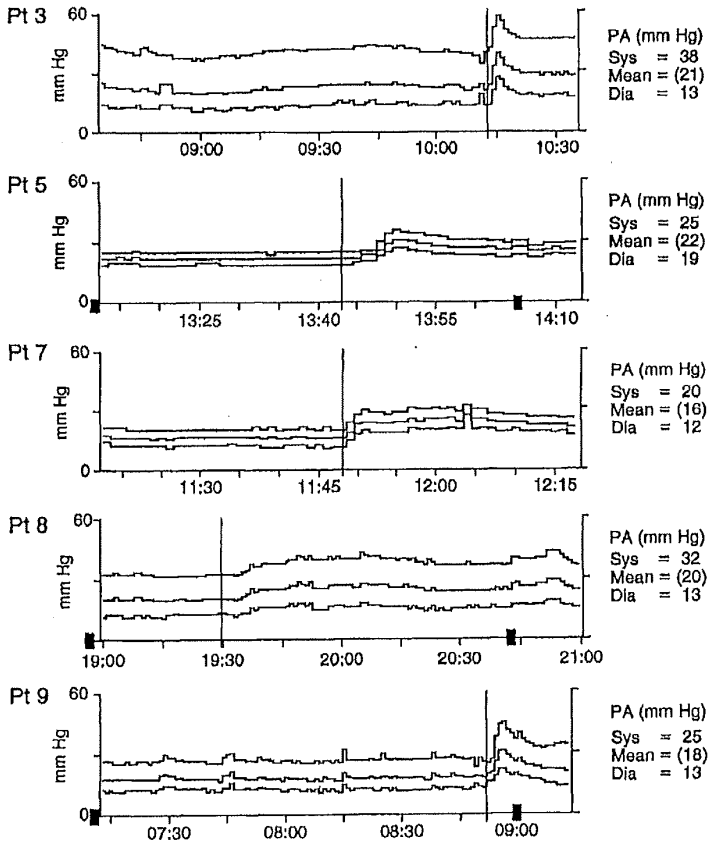

Figure 8. Bedside tracings of pulmonary artery (PA) pressure (systolic, mean, diastolic) for 5 patients (Pt) with TAPVC receiving prolonged NO plotted against time. Cursor represents time of withdrawal of NO; pulmonary artery pressures at time of withdrawal are displayed to the right of each tracing. 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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EXHIBIT 3

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.

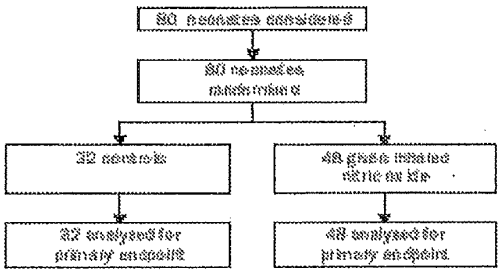

Figure 1: **Trial profile**

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 significant 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

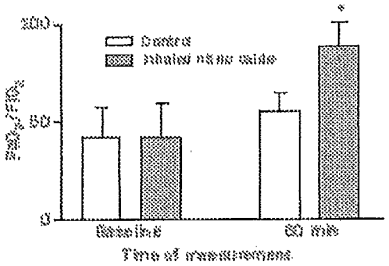

Figure 2: **PaO_2/FiO_2 results at baseline and 60 min after treatment**

*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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EXHIBIT 4

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.[16,17] 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}	226±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.[26] 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 (LVEDP), and LV +dP/dt and −dP/dt were calculated by averaging at least 50 consecutive beats under each experimental condition.

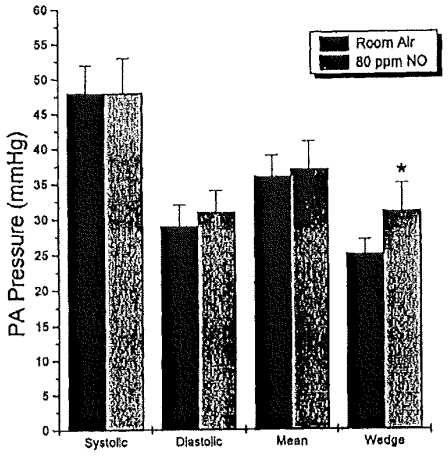

FIG 1. Bar graph showing effect of inhalation of NO gas (80 ppm, 10 minutes) on pulmonary artery (PA) pressures in 19 patients with heart failure secondary to left ventricular dysfunction. Measurements were made after the patients inhaled room air (shaded bars) or NO (solid bars) from a face mask for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

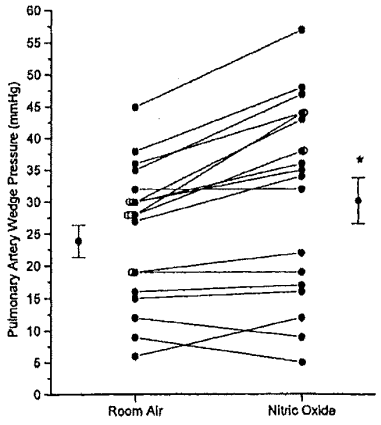

FIG 2. Graph showing pulmonary artery wedge pressure before and after a 10-minute inhalation of room air or NO. *P<.001 vs room air.

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 (FIO_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 (FIO_2, 21%; N_2, 79%) via

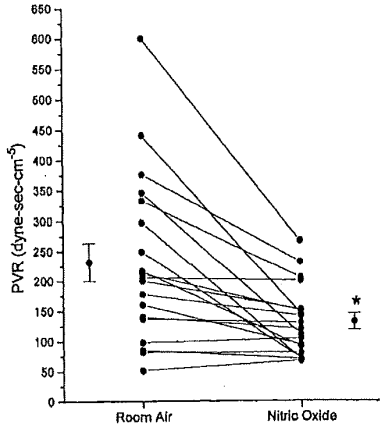

FIG 3. Graph showing effect of NO inhalation on pulmonary vascular resistance (PVR). *P<.001 vs room air.

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.

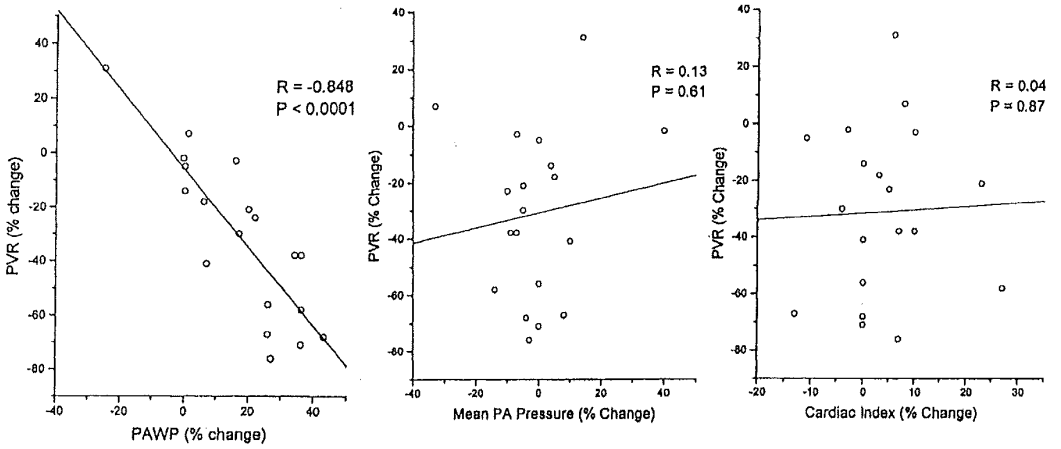

FIG 4. Scatterplots of regression analyses depicting the relation between the change in pulmonary vascular resistance (PVR) with NO (vs room air) and the change in pulmonary artery wedge pressure (PAWP) (left), mean PA pressure (middle), or cardiac index (right) in 19 patients.

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.

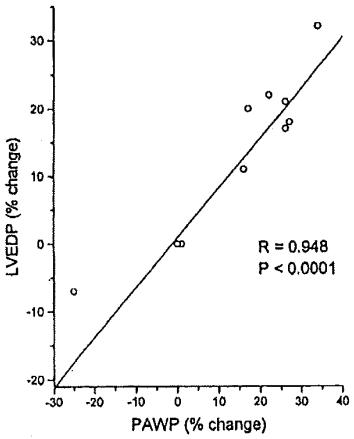

FIG 5. Scatterplot showing relation between the percent changes in pulmonary artery wedge pressure (PAWP) and left ventricular end-diastolic pressure (LVEDP) with inhaled NO in 10 patients.

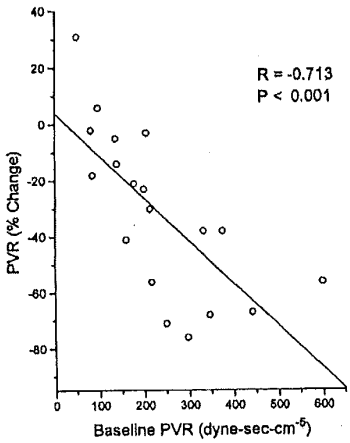

FIG 6. Scatterplot showing relation between the baseline pulmonary vascular resistance (PVR) and the percent change in PVR after inhalation of NO in 19 patients.

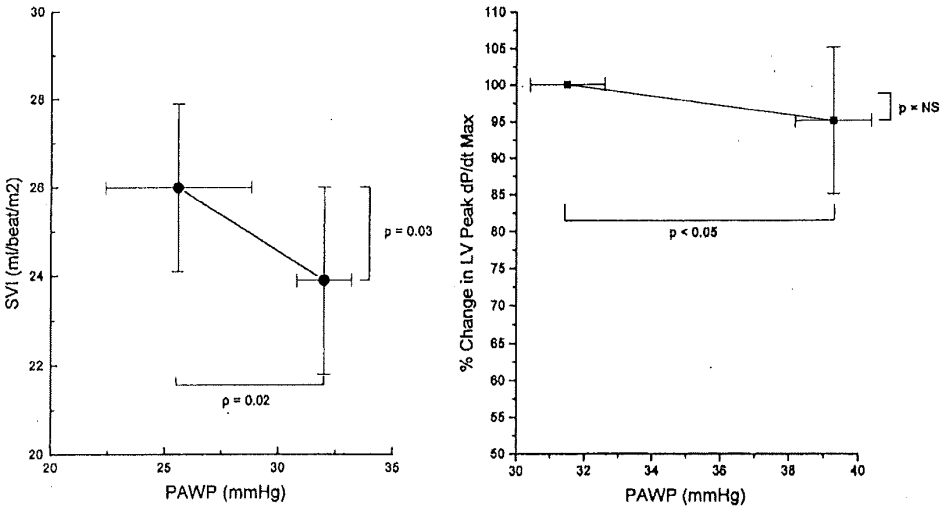

FIG 7. Graphs showing (left) effect of inhaled NO on the relation between stroke volume index (SVI) and mean pulmonary artery wedge pressure (PAWP) and (right) effect of inhaled NO on the relation between left ventricular (LV) peak +dP/dt and PAWP.

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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EXHIBIT 5

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 19, 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, hyperbilirubinemia, 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

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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%)	6 (6%)
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

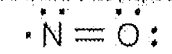
Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or 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.

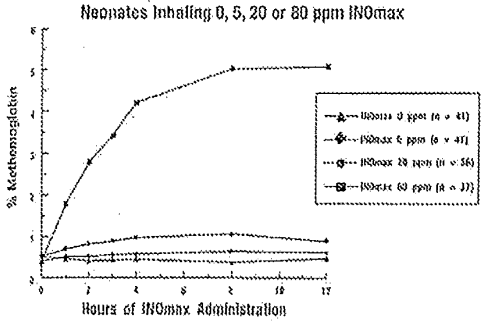
12.4 Pharmacokinetics: Uptake and Distribution

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

 SPC-0303 V:4.0

EXHIBIT 6

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 DAVID L. WESSEL, M.D.
UNDER 37 C.F.R. § 1.132

I, David L. Wessel, do hereby declare the following:

1. I currently hold the position of Senior Vice President, The Center for Hospital-based Specialties, at Children's National Medical Center in Washington, D.C., where I am also the Division Chief of Critical Care Medicine. I am also the Ikaria Distinguished Professor of Critical Care Medicine. A copy of my *curriculum vitae* is attached as **Exhibit 1.**

2. I received a bachelor's degree (B.S.) in physics from the College of William and Mary in 1972, a bachelor's degree (B.A.) in physiology from Oxford University in 1974, a doctoral degree (*cum laude*) in medicine (M.D.) from the Yale University School of Medicine in 1978, and a master's degree (M.A.) in physiology from Oxford University in 1983.

3. Following my graduation from Yale, the majority of my time as a practicing physician was spent in academic medicine, where I focused on pediatric cardiology. From 1978-1981, I performed an internship in pediatrics followed by a clinical fellowship at the Yale University School of Medicine. From 1981-1985, I was a fellow in pediatric anesthesiology at

Harvard Medical School, where I later became an instructor (1985), assistant professor (1987), associate professor (1994), and ultimately professor (2002), all in the area of pediatrics. In 2011, I will become a professor of pediatrics at the George Washington University School of Medicine and Health Sciences in Washington, DC.

4. In addition to my academic experience, I have extensive experience in the pharmaceutical industry as a member of scientific advisory boards, advisory panels or steering committees for companies such as Pfizer, Johnson & Johnson, Eli Lilly, Bristol-Myers Squibb, Sanofi-Avenits, and INO Therapeutics.[1]

5. In 2005, I chaired the Steering Committee of the Sponsor, INO Therapeutics LLC (INOT), to establish, design and oversee the INOT22 Study. In addition to being the Chair of the INOT22 Steering Committee, I also am the senior author of Atz and Wessel, *Seminars in Perinatology* 1997, 21(5), pp. 441-455 (Atz et al.).

6. At the time of the design of the INOT22 Study protocol, neither I, 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.

7. Neither the Atz et al. article that I co-authored, nor the medical literature or medical experience of which I was aware at the time, predict this risk. Instead, Atz et al. describes two distinct, independent precautions with respect to the use of iNO. First, with respect to adults, Atz et al. stated that iNO may be more effective in newborns than in older patients, and noted that it should be used with caution in adults with ischemic cardiomyopathy in whom a risk of pulmonary edema is a consideration (see page 452, left column). Second, with respect to neonates, we stated the well-known contraindication (currently found in the INOMAX®

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[1] In the interest of full disclosure, I formerly served as a consultant for INO Therapeutics LLC. I currently serve without remuneration as a member of the Ikaria Scientific Board of Advisors. In 2010, I was appointed by my institution as the Ikaria Distinguished Professor of Critical Care Medicine.

prescribing information) that iNO should not be used in newborns dependent upon right-to-left shunting of blood across a patent ductus arteriosus to avoid circulatory collapse. What we did **not** disclose or predict was 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.

8. It is ironic that my own publication 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 et al., 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.

9. In summary, although it was known that neonates dependent on right-to-left shunt should not receive iNO and it had been reported that adults with pre-existing left ventricular dysfunction 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.

10. 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.

Dated: July 15 2014

David L. Wessel, M.D.

Applicant : James S. Baldassarre et al.
Serial No. : 12/820,866
Filed : June 22, 2010

Attorney Docket No. 26047-0003002

EXHIBIT 1

CURRICULUM VITAE

1) PERSONAL DATA

Date prepared: April 2011

Name: David Lloyd Wessel

Home address: 3251 Prospect St. NW, Suite 404 Washington, D.C. 20007

Home phone: 202-342-0908

Office Address: Children's National Medical Center
111 Michigan Ave, NW Suite 3W-100 Washington, DC 20007
TEL: 202 476 5047 FAX: 202 476-5868

E-Mail Address: dwessel@childrensnational.org

Place of Birth: Newton, Iowa U.S.A.

Citizenship: United States

2) EDUCATION:

1972	B.S.	College of William and Mary (Physics), Williamsburg, VA
1974	B.A.	Oxford University (Physiology), Oxford, England
1978	M.D.	Yale University School of Medicine (Medicine), New Haven, CT
1983	M.A.	Oxford University (Physiology), Oxford, England

POSTDOCTORAL TRAINING:

Internship and Residencies:

1978-79	Intern in Pediatrics, Yale-New Haven Hospital, New Haven, CT
1979-80	Resident in Pediatrics, Yale-New Haven Hospital, New Haven, CT
1981-83	Resident in Anesthesia, Massachusetts General Hospital, Boston, MA

Fellowships:

1980-81	Fellow in Pediatric Cardiology and Intensive Care, Yale-New Haven Hospital, New Haven, CT
1983-84	Fellow in Pediatric Cardiology, Children's Hospital, Boston, MA
1984-85	Fellow in Anesthesia and Intensive Care, Children's Hospital, Boston, MA

3) EMPLOYMENT

CHILDREN'S HOSPITAL, BOSTON

1985-87	Assistant in Anesthesia
1985-88	Assistant in Cardiology
1987-00	Associate in Anesthesia
1988-89	Associate in Cardiology
1988-07	Associate in Cardiovascular Surgery
1988-02	Chief, Cardiovascular Intensive Care Unit
1989-07	Senior Associate in Cardiology
1995-02	Division Chief
2000-07	Senior Associate in Anesthesia
2002-03	Honorary Consultant, Royal Brompton Hospital, London, U.K.

CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON, DC

2007- Interim Chief, Division of Critical Care Medicine
2007-09 Executive Director, Center for Hospital Based Specialties
2009- Senior Vice President, Center for Hospital Based Specialties
2010- IKARIA Distinguished Professor of Critical Care Medicine, Children's National Medical Center, Washington, DC

ACADEMIC APPOINTMENTS:

1980-81 Fellow in Pediatrics (Cardiology), Yale School of Medicine, New Haven, CT
1981-83 Clinical Fellow in Anaesthesia, Harvard Medical School, Boston, MA
1983-84 Clinical Fellow in Pediatrics, Harvard Medical School, Boston, MA
1984-85 Clinical Fellow in Anaesthesia, Harvard Medical School, Boston, MA
1985-86 Instructor in Anaesthesia, Harvard Medical School, Boston, MA
1987-93 Assistant Professor of Anaesthesia (Pediatrics), Harvard Medical School, Boston,
1987-94 Assistant Professor of Pediatrics (Anaesthesia), Harvard Medical School, Boston, MA
1994-99 Associate Professor of Pediatrics, Harvard Medical School, Boston, MA
1999-02 Associate Professor of Pediatrics (Anaesthesia), Harvard Medical School, Boston, MA
2002-03 Visiting Professor Imperial College, University of London, London UK (4/024/03)
2002-07 Professor of Pediatrics (Anaesthesia), Harvard Medical School, Boston, MA
2011- Professor of Pediatrics, George Washington University School of Medicine and Health Sciences, Washington, DC (pending)

4) LICENSURE AND CERTIFICATION:

1979 National Board of Medical Examiners
1985-07 Massachusetts License Registration
1985 American Board of Pediatrics (Permanent)
1985 American Board of Pediatrics, Sub-board of Pediatric Cardiology (Permanent)
1986 American Board of Anesthesiology (Permanent)
1987 American Board of Pediatrics, Sub-board of Critical Care (Re-certified 1996, 2004, 2010)

5) PROFESSIONAL SOCIETIES & HONORS:

1982- American Society of Anesthesiologists
1982-2007 Massachusetts Medical Society
1986- American Academy of Pediatrics
1987- Society of Critical Care Medicine
1987- American Society of Critical Care Anesthesiologists
1987- Society of Pediatric Anesthesia
1989- American Heart Association (Fellow)
1991- Society of Cardiovascular Anesthesiologists
1995- Society of Pediatric Research
1999- Pediatric Cardiac Intensive Care Society - President 2000-2004; Vice President, Development 2010-

AWARDS, HONORS AND NAMED LECTURES:

1968 Maytag Scholar (industry sponsored competitive college scholarship)
1971 Phi Beta Kappa
1971 Omicron Delta Kappa
1971 National Physics Honor Society (President)
1972 General Honors (William and Mary)
1972 Drapers' Scholar (Oxford)
1972 Mathematics Honor Society
1974 Balliol College Prize (Oxford)
1974 First Class Honours (Oxford)
1978 Cum Laude (Yale)
1978 Alpha Omega Alpha Honor Medical Society
1978 Harry S. Greene Prize (Yale)

1994 Katkov-Lundeen Memorial Lecture, Minneapolis Children's Hospital, Minneapolis, MN
1994 Saul Usher Memorial Lecture, Montreal Children's Hospital, Montreal, Canada
1994 Farouk Idriss Memorial Lecture, Children's Memorial Hospital, Chicago, IL
1995 A. W. Conn Lecture, Hospital for Sick Children, Toronto, Canada
1995 DiCerbo Foundation Lectureship in Pediatric Critical Care, North Shore University Hospital, New York, NY
1996 Teaching Award, Pediatric Cardiology, Children's Hospital Boston
1997- Listed, *Best Doctors in America*, continuously since inception
1999 29th Annual Jennifer B. Lalin Lecture, Babies Hospital, Columbia University College of Physicians and Surgeons, New York, NY
2000 Tenth Anniversary Lecture, Taiwan Pediatric Association, Critical Care Sub Committee, Kaohsiung Veterans General Hospital, Taipei, Taiwan
2001 Recipient, Papas Gift Award for Outstanding Clinical Care ($25,000 to Children's Hospital Boston)
2002 M.A. (Honorary) Harvard University, Cambridge, MA
2004 Keynote Address, Opening Ceremony, Annual Meeting of the European Society of Pediatric and Neonatal Intensive Care, London, United Kingdom
2004 Leadership & Mentor Award: "In recognition of your contributions toward improving children's heart health," *The Fifth International Symposium on Pediatric Cardiac Intensive Care*co-sponsored by the Pediatric Cardiac Intensive Care Society and the Texas Children's Heart Center
2005 Jared Ellsworth Memorial Lecture, Rainbow Babies and Children's Hospital, Cleveland, Ohio
2006 Eddie Farrell Memorial Lecture, Massachusetts Society of Respiratory Care
2007 Robert A. Boxer, M.D. Memorial Lecture,Schneider Children's Hospital LIJ, North Shore
2010 John J. Downes, Jr.,M.D. Lecture, Cardiology 2010, Orlando, FL. Sponsored by Children's Hospital Philadelphia.
2010 Outstanding Research Award in Pediatric Cardiology (Council on Cardiovascular Disease in the Young), AHA Scientific Sessions, Chicago, IL
2010 Anthony Chang Honorary (Inaugural) Lecture. Pediatric Cardiac Intensive Care Society.

6) ADMINISTRATIVE DUTIES & UNIVERSITY ACTIVITIES

HOSPITAL AND HEALTH CARE ORGANIZATION SERVICE RESPONSIBILITIES:

CHILDREN'S HOSPITAL, BOSTON

1985-91 Attending Physician and Associate Director, Multidisciplinary Intensive Care Unit
1985-07 Attending Physician in Cardiology (Intensive Care)
1985-07 Attending Physician in Anesthesia (Cardiac)
1985-07 Associate in Cardiovascular Surgery (teaching)

CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON, DC

2007- Attending Physician in Critical Care Medicine, Cardiology, Cardiac Anesthesia
2007- Member, Children's National Heart Institute

MAJOR ADMINISTRATIVE RESPONSIBILITIES:

CHILDREN'S HOSPITAL, BOSTON

1988-02 Director, Cardiac Intensive Care Unit
1990 Associate Director, Critical Care Pediatrics Training Program
1993-02 Treasurer, Board of Directors, Boston Children's Heart Foundation including investigative and forensic accounting responsibilities surrounding departed chairman (1993-96)
1997-98 Board of Directors, Children's Hospital Physicians' Organization, Boston, MA
1998-03 Physician Leadership Council, Children's Hospital, Boston, MA
1999-02 Medical Director, Pharmacy, Children's Hospital, Boston, MA
2000-02 Clinical Sponsor, Critical Care Clinical Information System, Children's Hospital, Boston, MA
2003-04 Interdisciplinary Peer Review Assignments and Presentation of Critical Events to JCAHO
2004-05 Board of Directors, Boston Children's Heart Foundation
2004-05 Physician Leadership Council, Children's Hospital, Boston, MA

CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON DC

2007- Accountable executive for clinical Center of Excellence; $200M revenue, more than 700 full time employees. Includes divisions and departments of critical care medicine (both cardiac and pediatric ICI neonatology; hospitalist medicine (inpatient general pediatrics); emergency medicine; radiology; respira care services (respiratory therapy); infectious disease, hospital infection control and epidemiology; endocrinology and the diabetes care complex; transport medicine, fetal and transitional medicine, ECM
2007- Leadership Council
2007- Children's Hospital Foundation Board of Directors
2007- Critical Care Committee (Co-Chair)
2007- Executive Committee of the Medical Staff
2007- Executive Directors Council (Senior Vice President Council 2008-)
2007- Hospital Based Specialties (HBS) Leadership Committee (Chair)
2007- HBS Campaign Council (Chair)
2007- Strategic Planning Council
2007- Interim Chief, Division of Critical Care Medicine
2008- Healthcare Review Committee (risk management financial governance)
2009- Steering Committee Strategic Planning Council (2010-15)

MAJOR COMMITTEE ASSIGNMENTS:

HARVARD MEDICAL SCHOOL

1996-98 Futility of Care Task Force, Harvard Medical School
1999 Search Committee, Chief of Pediatric Pulmonary Medicine, Children's Hospital, Boston, MA
2005-07 Ad Hoc Evaluation Committee for Professorial Promotion

CHILDREN'S HOSPITAL, BOSTON

1988-93 Multidisciplinary Intensive Care Committee
1989-90 Chairman, Hospital Task Force on Sedation
1990-92 Hospital HMO Committee
1991-92 Medical Staff Quality Improvement Committee
1991-93 Department Quality Improvement Officer
1991 Hospital Review Committee for Department of Clinical Laboratories
1992 Chairman, Nominating Committee, Medical Staff Association
1992-99 Chairman, Special Care Units Committee
1992 Hospital Search Committee for Director of Clinical Laboratories
1992 Physician Advisory Committee on Computers
1992 Operations Improvement Committee
1993 Hospital Search Committee for MICU Director
1993-01 Cardiovascular Program, Quality Improvement Committee
1996-98 Product Standardization Council
1998-01 Planning and execution committee for ICU electronic clinical information system
1998-01 Clinical Oversight Committee for Transport
2000 Nominating Committee, Physician's Organization
2000-02 Chairman, Pharmacy and Therapeutics Committee
2000-02 Hospital Task Force on Clinical Building and New Construction
2000-06 ICU Committee
2004-05 Committee on Pension Investments, Physicians' Organization
2004-07 Quality and Outcomes Measurement, Physicians' Organization
2005-07 Program for Patient Safety and Quality Implementation Committee
2006 Hospital Search Committee for Non-invasive Cardiology Division Chief
2006-07 Hospital Peer Review Panel
2006-07 Physician Profile Task Force

DEPARTMENT OF CARDIOLOGY, CHILDREN'S HOSPITAL, BOSTON

1988-01	Fellowship Selection Committee
1998-02	Audit and Finance Committee
1998-02	Computing Committee
2004-05	Audit and Finance Committee

CHILDREN'S NATIONAL MEDICAL CENTER, WASHINGTON DC

2007-09	Facilities Leadership Committee
2007-	Growth Management/ CARE
2007-	NICU Steering Committee
2007-	Quality and Clinical Effectiveness Committee
2007-	Quality and Safety Council
2007-	Information Technology Oversight Committee
2007-09	CTI Clinical Advisory Council (electronic medical record)
2007-	Task Force on Access/Referral
2007-08	Hospital Search Committee for Cardiology Division Chief
2007-	Safety Transformation Advisory Council
2009-	Executive Oversight Committee (post graduate education)
2009-	Physicians Advisory Committee (third party payor contracts)
2011-	Physician Productivity Committee (Chair)
2011-	Internal Advisory Board, GWU / CNMC, for NIH funded CTSI Award (Chair)

NATIONAL & INTERNATIONAL

1995	Clinical Trials Review Committee (*Ad hoc* reviewer), National Institutes of Health
1995-98	Invited Speaker, Cardio-renal Advisory Panel, U.S. Food and Drug Administration
2004-06	Task Force ACC AHA AAP: Requirements for Pediatric Cardiac Critical Care Training
2005-06	Multi-Societal Committee (PCICS/EACTS/STS) Complications in Pediatric and Congenital Cardiac Surgery Project
2008-	National Institute of Allergy and Infectious Disease Transplant Data and Safety Monitoring Board (DSMB) - Member
2010	FDA Invited Speaker, Continuing Education Series
2010	International Liaison Committee on Resuscitation (ILCOR): 2010 Consensus Statement and Treatment Recommendations.
2011	Joint American Heart Association (AHA) – American Thoracic Society Expert Guidelines Statement on Pediatric Pulmonary Hypertension.

INDUSTRY

1994-97	Scientific Advisory Board on Nitric Oxide, Ohmeda Pharmaceuticals
1998-02	Curriculum Development Committee, INO Therapeutics
1999-01	Steering Committee, Prophylactic use of Primacor® in pediatric patients at high risk of developing low cardiac output syndrome following cardiac surgery. PRIMACORP study-Prophylactic intravenous use of milrinone after cardiac operation in pediatrics. Sanofi-Synthelabo Inc.
2001-06	Chairman, Advisory Panel INOTherapeutics
2001-02	Scientific Advisory Board AGA-Linde
2001-03	Protocol Planning Committee (PDE V inhibitors) Pfizer
2001-09	Scientific Advisory Board for pulmonary hypertension research development, Pfizer
2003	Steering Committee for Multicenter Trial on Diagnostic Use of Inhaled Nitric Oxide
2005-07	Steering Committee for Multicenter Trial on Use of Nesiritide in Children, SCIOS (Johnson & Johnson)
2005-07	Advisory Committee on Iloprost and Treatment of Pulmonary Hypertension in Children, Cotherix
2005-07	Advisory Board, Eli Lily Vardenafil for Pediatric Pulmonary Hypertension
2006-	Steering Committee (Chairman) for Multicenter Trial on Use of Clopidogrel in Children (CLARINET), Bristol-Myers Squibb & Sanofi-Aventis
2009	Advisory Panel, Nesiritide Use in Pediatric Cardiovascular patients, Johnson & Johnson

COMMUNITY SERVICE RELATED TO PROFESSIONAL WORK:

1994-97	Lecturer, Human Body Curriculum, Wellesley Public School System, Wellesley, MA
1996	Hospital Spokesman, Boston/Filenes' Holiday Festival
1996	Campaign for William & Mary, 25th Anniversary Committee
2000-02	Hospital Spokesman, Capital Campaign and Children's Hospital Boston Fundraising, including keynote speaker, 2000
2007-	Multiple CNMC Fundraising and Community Benefit Events presentations to Emeritus and Lady Visitor Boards, etc.
2008	Speaker, CNMC Corporate Leadership Council "What's Up, Doc?" Breakfast, World Bank, Washington D.C.

EDITORIAL BOARDS/REVIEW COMMITTEES:
Ad Hoc Reviewer:

Acta Pediatrica
American Journal of Cardiology, American Journal of Physiology
American Review of Respiratory Diseases and Critical Care
Anesthesia & Analgesia, Anesthesiology
Annals of Thoracic Surgery
Archives of Diseases of Childhood
Cardiovascular and Interventional Radiology
Chest
Circulation
Critical Care Medicine
European Heart Journal
Future Cardiology
Journal of Intensive Care Medicine
Journal of Pediatrics
Journal of Thoracic and Cardiovascular Surgery
Mayo Clinic Proceedings
Pediatrics, Pediatric Cardiology, Pediatric Critical Care Medicine, Pediatric Research
Proceedings of the National Academy of Science

Invited consultant, to review and make recommendations to institutional programs for pediatric cardiovascular care (national and international)

Asked by Children's Hospital Boston to chair ad hoc committees reviewing sentinel events, other critical incidents and report the hospital's analysis and action to the Hospital's Board of Trustees, JCAHO, etc.

7) EDUCATIONAL ACHIEVEMENTS

REPORT OF TEACHING

1. LOCAL CONTRIBUTIONS
   a) MEDICAL SCHOOL

Yale University School of Medicine, New Haven, CT

1975-76 Program leader, Cardiovascular physiology core lectures in Physician's Associate Program
Designed lecture series for new PA program; 20 hours/year

Harvard Medical School, Boston, MA

1983-98 Instructor, Cardiovascular Physiology Animal Laboratory, Harvard Medical School
Approximately 60 medical students; one day per year

1985-89 Cardiovascular Pathophysiology, Laboratory section on congenital heart disease
Approximately 30 medical students; half day per year

1985-89 PGY clerkship in Pediatrics

Lecturer in Critical Care (Multidisciplinary ICU)
2 medical students each lecture; 12 hours/year

b) GRADUATE MEDICAL EDUCATION (LOCAL)

1985-89 Didactic seminars on cardiovascular pathophysiology for pediatric critical care fellows and rotating residents
Lecture once per week, 1 hour, 6 trainees per lecture

1986-93 Developed and taught core curriculum: introduction to anesthesia and critical care for cardiologists
Lecture once per week, 1 hour, six weeks, 20 fellows and junior faculty. Preparation, 40 hours per year

1985-89 Co-developed tutorials on congenital heart disease and supervised core staff (3 tutors) for instruction of cardiology and cardiac ICU fellows during ICU rotation
Lectures three mornings per week, 1/2 hour, 3-4 fellows; preparation, 2 hours per week

1985-07 CICU attending rounds
3 pediatric residents (1985-1989), 4-8 fellows and senior surgical residents; 18 hours/week, 16-40 weeks/year (varies with year)

1990-96 Chiefs' Ward Rounds
3 medical students, 3 pediatric residents, 1 cardiology fellow; monthly 12 hous/year

1996-07 Didactic lectures to cardiology fellows teaching program
20 fellows 3 times per year

2002-03 Didactic lectures (monthly) to trainees at Royal Brompton Hospital. London

c) BOSTON INVITED TEACHING PRESENTATIONS (SELECTED)

1984 Anesthesia Grand Rounds, Children's Hospital, Boston, MA
1991 Anesthesia Grand Rounds, Children's Hospital, Boston, MA
1992 Surgical Grand Rounds, Children's Hospital, Boston, MA
1992 Medical Grand Rounds, Children's Hospital, Boston, MA
1994 Anesthesia Grand Rounds, Children's Hospital, Boston, MA
1996 Anesthesia Grand Rounds, Massachusetts General Hospital, Boston, MA
1996 PICU Teaching Sessions, Massachusetts General Hospital, Boston, MA
1997 Surgical Grand Rounds, Children's Hospital, Boston, MA
1997 Medical Grand Rounds, Children's Hospital, Boston, MA
1998 Anesthesia Grand Rounds, Children's Hospital, Boston, MA
2003 Grand Rounds and teaching rounds, Royal Brompton Hospital, London, UK
2004 Neonatology Clinical Working Group, Children's Hospital, Boston, MA
2004 Department of Respiratory Therapy Clinical Working Group, Children's Hospital, Boston, MA
2005 Department of Cardiology, Didactic Series, Children's Hospital Boston, Boston, MA

d) WASHINGTON DC AREA INVITED TEACHING PRESENTATIONS (SELECTED)

- Chief Rounds Monthly to ICU & Cardiology fellows and staff (15-20 physicians, 2hrs/month), CNMC, D(
- ICU Attending Rounds, Children's National Medical Center, DC
- Clinical Research Presentation to ICU/Cardiology Fellows 2 times per year, Children's National Medica Center, DC
- Grand Rounds, Children's National Medical Center, DC
- Grand Rounds, Mary Washington Hospital, VA
- Grand Rounds, Anne Arundel Medical Center, MD
- Teaching Rounds, Division of Critical Care Medicine, National Institutes of Health

e) CONTINUING MEDICAL EDUCATION (LOCAL)

1988 Lecturer
Harvard Medical School, Continuing Education Course in Pediatric Anesthesia
"Anesthesia for Congenital Heart Disease"

1990 Lecturer
Harvard Medical School Continuing Education Course in Pediatric Anesthesia
"Common Congenital Cardiac Lesions"

1989 Moderator
Harvard Medical School, Continuing Education Course in Pediatric Cardiovascular Disease

1993 Lecturer
Symposium on Brain Injury and Cardiac Surgery, Harvard Medical School, Boston, MA
"Choreoathetosis After Cardiopulmonary Bypass"

1996 Lecturer
Harvard Medical School Continuing Education Course in Pediatric Anesthesia
"New Vasoactive Drugs"

1998 Co-director, First Annual Course: Frontiers in the Diagnosis and Management of Congenital Heart Disease, Children's Hospital, Boston, Harvard Medical School, Boston, MA

1999 Co-director, Second Annual Course: Frontiers in the Diagnosis and Management of Congenital Heart Disease, Children's Hospital, Boston, Newport, Rhode Island

2001 Co-director, Third Annual Course: Frontiers in the Diagnosis and Management of Congenital Heart Disease, Children's Hospital, Boston, Newport, Rhode Island

f) ADVISORY AND SUPERVISORY RESPONSIBILITIES (LOCAL)

1987- Responsible for clinical supervision and educational component of critcal care for cardiology fellows in a large pediatric cardiology training program (two months each year for each of 18 fellows spread over 2-3 years of training).

1990-02 Responsible as mentor for clinical, educational and clinical research activities of2-3 senior clinical fellows each year.

1985- Shared responsibilities for cardiovascular education and clinical supervision of pediatric critical care fellows in the CICU (3-5 months per year for 5-6 fellows spread over 2-3 years of training).

1985-02 Shared responsibilities for critical care educational component of pediatric cardiovascular surgical training program (10 surgical residents each year rotating for 6 months each).

1987-02 Responsible for medical education and clinical advisory tasks for conthuing education seminars for 80 critical care nurses.

g) LEADERSHIP ROLE (LOCAL)

1998-01 Program Co-Director
Annual Course, "Frontiers in Diagnosis and Management of Congenital Heart Disease" Shared responsibility for organizing and executing post graduate course attended by 200 pediatric cardiologists cardiovascular surgeons and nurses from the US and abroad.

h) NAMES OF SELECTED TRAINEES AND/OR FORMER CICU STAFF WHO HAVE CURRENT LEADERSHIP POSITIONS

1985-88 Gil Wernovsky, MD, FACC *†§
Director of Program Development
Former Director, Cardiac Intensive Care Unit
The Children's Hospital of Philadelphia
Professor of Pediatrics
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

1988-89 Ling Chen, MD *
Director, Cardiac Intensive Care Unit
Shanghai Children's Medical Center
Shanghai, China

1989-92 Pierre C. Wong, MD *†
Cardiology Medical Director, Transplantation
Children's Hospital of Los Angeles
Los Angeles, California

1989-92 Stephen J. Roth, MD, MPH *†
Director, Cardiac Intensive Care Unit
Lucile Packard Children's Hospital
Associate Professor of Pediatrics
Stanford University School of Medicine
Palo Alto, California

1989-92 Nancy Bridges, MD
Chief, Transplantation Immunology Branch, Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Disease
Bethesda, Maryland

1990-92 Howard A. Zucker, MD, FACC*
Deputy Director of the World Health Organization
Geneva, Switzerland

1990-93 Kevin B. Churchwell, MD
Chief Executive Officer (CEO) for Nemours/Alfred I. duPont Hospital for Children
Wilmington, DE.

1990-93 Anthony C. Chang, MD *†§
Medical Director, CHOC Children's Heart Institute
Children's Hospital Orange County
Orange, California

1991-94 Ian Adatia, MB, ChB, MRCP (UK), FRCP (C) *†
Director, Pediatric Cardiac Critical and Intermediate Care Program,
Director, Pediatric Pulmonary Hypertension Clinic,
Stollery Children's Hospital,
Professor of Pediatrics
University of Alberta
Edmonton, Alberta, Canada

1992-96 Andrew M. Atz, MD *†§
Director, Pediatric Cardiac Intensive Care Unit
The Children's Heart Program
Associate Professor of Pediatrics
Medical University of South Carolina
Charleston, South Carolina

1992-96 David P. Nelson, MD, PhD *
Director, Cardiac Intensive Care
Cincinnati Children's Hospital Medical Center
Professor of Pediatrics
Cincinnati, Ohio

1992-97 Sarah Tabbutt, MD, PhD *
Director, Pediatric Cardiac Intensive Care Unit
UCSF Children's Hospital
San Francisco, California

1994-97 Ricardo A. Muñoz, MD *†§
Director, Pediatric Cardiac Intensive Care
Director, Global Business and Telemedicine
Children's Hospital Pittsburgh
Associate Professor of Pediatrics
University of Pittsburgh
Pittsburgh, Pennsylvania

1994-99 Melvin C. Almodovar, MD *†§
Medical Director, Cardiac Intensive Care Unit
Boston Children's Hospital
Assistant Professor
Harvard Medical School
Boston, Massachusetts

1995-96 Brendan O'Hare, MD *
Consultant in Anesthesia and Critical Care
Our Lady's Hospital for Sick Children
Crumlin, Dublin, Ireland

1995-96-Steven Schwartz, MD
Director of Cardiac Intensive Care
Hospital for Sick Children
Assistant Professor of Pediatrics
University of Toronto
Toronto, Ontario, Canada

1996-97 Alain Fraisse, MD *†
Chief, Clinical Pediatric Cardiology
Hopital D'Enfants de la Timone
Professer of Pediatrics
Universitaire de Marseille
Marseille, France

1997-98 Guillermo Palacio, MD
Director Pediatric Cardiac Intensive Care Unit
Fundacion Cardio Infantil
Bogota, Colombia

1997-98 Mary B. Taylor, MD *
Director, Pediatric Cardiac Critical Care
Cardiology and Critical Care
Vanderbilt Children's Hospital
Associate Professor of Pediatrics
Vanderbilt University Medical Center
Nashville, Tennessee

1997-99 Rajiv Chaturvedi, MB BChir, MRCP (UK), MD *
Pediatric Cardiology
Hospital for Sick Children
Assistant Professor
University of Toronto
Toronto, Ontario, Canada

1998-01 Ravi Thiagarajan, M.D.* † §
Director, Cardiac ECMO Program
Children's Hospital Boston
Associate Professor of Pediatrics
Harvard Medical School
Boston, Massachusetts

1998-02 Peter C. Laussen, MBBS §
Chief, Division of Cardiovascular Intensive Care
D.D. Hansen Chair in Pediatric Anesthesia
Senior Associate in Cardiology
Children's Hospital Boston
Professor of Anesthesia
Harvard Medical School
Boston, Massachusetts

1998-99 Mary P. Mullen, MD, PhD *§
Director, Pulmonary Hypertension Program
Assistant in Cardiology
Children's Hospital Boston
Assistant Professor in Pediatrics
Harvard Medical School
Boston, Massachusetts

1999 Janet M. Simsic, M.D.*
Director, Pediatric Cardiac Intensive Care Unit
Nationwide Children's Hospital
Columbus, Ohio

2000 Erica A. Kirsch, MD*
Director of Pediatric ECMO Program
Associate Professor of Pediatrics
University of Missouri-Kansas City School of Medicine
Kansas City, Missouri

2003-05 Margarita Burmester, MBBS* †
Consultant in Pediatric Intensive Care
Royal Brompton Hospital
Imperial College
London, United Kingdom

* Clinical Trainees
† Research Trainees
§ Faculty in CICU, Children's Hospital Boston during my tenure as Chief

TEACHING AND EDUCATIONAL LEADERSHIP ROLES (LOCAL AND INTERNATIONAL)

1987 Critical Care Consultant for Project Hope and the Cardiac htensive Care Unit, Xin Hua, Shanghai, China. Developed teaching program for critical care and supervised clinical training of physicians during 2-6month exchange programs.

1996- Abstract and Program Reviewer for many National and International Societies including SPR, AHA, ACC, PCICS, World Congress

2000 Invited faculty and cardiovascular program curriculum track convener
III International Congress of Pediatric Intensive Care, Montreal, Canada.

2002 Scientific Programme, Coordinator
The Third Special Topics in Paediatric Cardiac Intensive Care, The Failing Myocardium
Royal Brompton Hospital, Imperial College, London, United Kingdom

2003 Invited faculty and cardiovascular program curriculum track convener
IV International Congress of Pediatric Intensive Care, Boston, MA

2004 Discussant Leader and Co-author (after Tom Kulik) on Critical Care Training Guidelines in Cardiology (SCCM, PCICS, AHA, ACC)

2005 Scientific Program Committee Pediatric Cardiac Intensive Care Symposium 2005 (PCICS 2005), Miami, FL

2006 Planning Committee, First International Conference on Childhood Pulmonary Vascular Disease, San Francisco, CA 2007

2008 Critical Care Consultant, University of Mississippi Medical Center, Jackson, MS

TEACHING AWARD(S) RECEIVED

1996 Faculty Teaching Award, Dept. Cardiology, Children's Hospital, Harvard Medical School
2010 Top rated faculty teacher for division of critical care medicine in trainee survey

MAJOR CURRICULUM OFFERING, TEACHING CASES OR INNOVATIVE EDUCATIONAL PROGRAMS DEVELOPED

1990-02 Developed a senior clinical fellowship training program for cardiac intensive care with short term training experience available through formal training program relationships with the MICU, Children's Hospital; PICU, Massachusetts General Hospital; Neonatology, Children's Hospital; Neonatology, University of Vermont. Long term (6-36 month) training program applicants accepted (2-3 per year) from candidates in advanced levels of fellowship training from national and international programs.

1988-90 In collaboration with the Cardiovascular Nursing Director, developed, reviewed and edited algorithms for care, nursing practice and clinical practice guidelines and quality improvement manuals for the Cardiovascular Program, Children's Hospital, Bosbn.

2004 In collaboration with Pediatric Cardiac Intensive Care Society and the Training Program Directors for Pediatric Cardiology, coauthored (with T. Kulik and others) the report to the Joint Committee on Training Programs (AHA/ACC) on training requirements in critical care for pediatric cardiology trainees.

2008 As interim division chief of critical care medicine at Children's National Medical Center, I implemented and supervised a reorganization of the fellowship training program, its leadership and aspects of its curriculum

8) CONSULTANT APPOINTMENTS

VISITING PROFESSORSHIP:

1986 Visiting Professor
"Critical Care of the Child with Congenital Heart Disease"
Department of Cardiology, Children's National Medical Center, Washington, D.C.

1993 Visiting Professor,
"Perioperative Care of the Neonate with Congenital Heart Disease"
University of Southern California, Children's Hospital of Los Angeles

1993 Visiting Professor
"Nitric Oxide and ECMO Therapies for Persistent Pulmonary Hypetension of the Newborn"
Schneider Children's Hospital, Albert Einstein College of Medicine, New York, NY

1994 Visiting Professor
"Perioperative Care of the Critically Ill Neonate with Congenital Heart Disease; Perioperative Management of Low Cardiac Output"
Medical University of South Carolina, Charleston, SC

1994 Visiting Professor
"Inhaled Nitric Oxide in the Treatment of Children with Congenital Heart Disease"
Dennison Young Memorial Symposium, Montefiore Medical Center, New York, NY

1994 Visiting Professor
"Care of the Critically Ill Neonate"
Minneapolis Children's Hospital, Minneapolis, MN

1994 Visiting Professor
"Therapeutic Applications of Inhaled Nitric Oxide"
Children's Memorial Hospital, Chicago, IL

1994 Visiting Professor
Grand Rounds: "Treatment of Pulmonary Hypertension"
Montreal Children's Hospital, Montreal, Canada

1995 Visiting Professor
"Multidisciplinary Management of Complex Congenital Heart Disease"
Anesthesia and Critical Care Grand Rounds, Hospital for SickChildren
University of Toronto, Toronto, Canada

1995 Visiting Professor
"Controversy in Critical Care: New Views of Simple Gases (O_2, CO_2, H_2 and NO)"
Anesthesia Grand Rounds, Children's Hospital of Philadelphia, Philadelphia, PA

1995 Visiting Professor
"Nitric Oxide: Magic and Medicine"
Medical College of Georgia, Augusta, GA

1995 Visiting Professor
"Controversy in Critical Care: New Views of Simple Gases"
Children's Hospital of Pittsburgh, Dept of Surgery, University of Pittsburgh,Pittsburgh, PA

1995 Visiting Professor
"Perioperative Care of the Newborn with Congenital Heart Disease"
Division of Pediatric Cardiology, Yale University School of Medicine, New Haven, CT

1997 Visiting Professor
"Perioperative Care in the Child with Congenital Heart Disease"
Pediatric Grand Rounds, Vanderbilt Children's Hospital, Nashville, TN

2000 Visiting Professor
"Newborns with Heart Disease: Extending the Limits of Intervention"
Columbia-Presbyterian Medical Center, Babies Hospital, New York, NY.

2003 Visiting Professor
"Treatment of Low Cardiac Output"
Cardiovascular Rounds, Hospital for Sick Children, Great Ormand Street,
London, United Kingdom

2005 Visiting Professor
Multiple lectures. University of Pittsburgh, Department of Critical Care Medicine, University of Pittsburgh Medical
Center and the Children's Hospital of Pittsburgh

2005 Visiting Professor
" Progress and problems in the treatment of critical heart disease"
Ellsworth Memorial Lecture, Pediatric Grand Rounds, Rainbow Babies & Children's Hospital, Cleveland, OH

2006 Visiting Professor
"Navigating a career in Medicine". Health Careers Club, College of William & Mary, Williamsburg, VA

2009 Visiting Professor
"The Challenges of Postoperative Care of the Childwith CHD"
Pediatric Grand Rounds, Vanderbilt Children's Hospital, Nashville, TN

9) PRESENTATIONS

NATIONAL

1990 Seminar Moderator
"Cardiovascular Disease"
Fourth Pediatric Critical Care Colloquium, Waterville, NH

1991 Invited Lecture
"Perioperative Management of Congenital Heart Disease"
Annual Meeting, Society of Pediatric Anesthesia, San Francisco, CA

1992 Workshop Faculty
"Anesthesia for Congenital Heart Disease"
Annual Meeting of the Society of Cardiovascular Anesthesiologists, Bosbn, MA

1992 Invited Lectures
"Perioperative Management & Decision making in the Neonate with Congenital Heart Disease"
Critical Care Pediatrics Symposium, Arnold Palmer Hospital, Orlando, FL

1992 Invited Lectures
Multiple topics on Critical Care of Children with Heart Disease and
"Treatment of Pulmonary Hypertension with Inhaled Nitric Oxide"
First World Congress of Pediatric Critical Care, Baltimore, MD

1992 Anesthesia Grand Rounds
"Postoperative Care of the Child with Congenital Heart Disease"
Maine Medical Center, Portland, ME

1992 Invited Faculty
"Postoperative Management of the Open Heart Surgery Patient"
Society of Critical Care Medicine, Pediatric Critical Care Clinical Review Series,
San Antonio, TX

1993 NIH Invited Lecture
"Nitric Oxide in Congenital Heart Disease"
National Institutes of Health Workshop: The effects of Nitric Oxide on the Lung, Bethesda, MD

1993 NIH Invited Lecture
"Indications for NO in the Newborn with Heart Disease"
National Institutes of Health Workshop on Nitric Oxide and the Perinatal Period, Bethesda, MD

1993 Symposium
"Nitric Oxide Gas in the Evaluation and Management of Pulmonary Hypertension"
Annual Meeting of the American College of Cardiology, Anaheim, CA

1993 Invited Lecture
"New Strategies for Treating Pulmonary Hypertension"
Annual Meeting, American Academy of Pediatrics, Washington, DC

1993 Invited Lecture
"Use of Inhaled Nitric Oxide for the Acute Treatment of Pulmonary Hypertension in Patients with Congenital Heart Disease" Annual Meeting, American Heart Association, Atlanta, GA

1993 NIH Workshop Lecture
"Nitric Oxide in the Perinatal Period" National Institutes of Health, Bethesda, MD

1993 Invited Lecture
"Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension of the Newborn"
Fourth Annual New England ECMO Symposium, Children's Hospital, Boston, MA

1993 Symposium
"Vasodilator Therapy and Inhaled Nitric Oxide in Children" Infant Hearts and Lungs Transplantation and Alternative Strategies.
Children's Hospital of Los Angeles, Long Beach, CA

1994 Symposium
"Update on Nitric Oxide"
Annual Meeting, Society of Critical Care Medicine, Orlando, FL

1994 Symposium
"Nitric Oxide Gas in the Evaluation and Management of Pulmonary Hypertension"
Annual Meeting of the American College of Cardiology, Atlanta, GA

1994 Invited Lecture
"Nitric Oxide for Pulmonary Hypertension"
Post Graduate Course on Congenital Heart Disease
American Association of Thoracic Surgery, NewYork, NY

1994 Plenary Session
"Inhaled Nitric Oxide for the Treatment of Pulmonary Hypertension in Children"
International Conference on Biochemistry and Molecular Biology of Nitric Oxide, University of California, Los Angeles, CA

1994 Guest Faculty
"Nitric Oxide in the Treatment of Pulmonary Hypertension in Congenital Heart Disease"
Pediatric Cardiology-The Failing Heart Conference, Given Biomedical Institute, University of Colorado, Aspen, CO

1994 Invited Lecture
"Perioperative Use of Inhaled Nitric Oxide"
Annual Meeting of the American Academy of Pediatrics, Dallas, TX

1994 Invited Faculty
"Serious Heart Disease of the Neonate: Management"
American Academy of Pediatrics Neoprep Course, St. Louis, MO

1994 Invited Faculty
"Perioperative Care of the Critically Ill Child with Congenital Heart Disease"
Society of Critical Care Medicine, Pediatric Critical Care Clinical Review Series, San Francisco, CA

1995 Invited Lecture
"Pulmonary Hypertension and Nitric Oxide"
Annual Meeting, American College of Cardiology, New Orleans, LA

1995 Invited Lecture
"Current Therapeutic Applications of Inhaled Nitric Oxide"
International Business Communications, Nitric Oxide Conference, Philadelphia, PA

1995 Invited Lecture
"Choreoathetosis After Cardiopulmonary Bypass"
Annual Meeting, American Society of Extra-Corporeal Technology, Boston, MA

1995 Invited Lecture
"Nitric Oxide for Perioperative Management of Congenital Heart Disease"
Annual Meeting of the American College of Surgeons, New Orleans, LA

1995 Invited Lecture
Controversy in Critical Care: New Views of Simple Gases
DiCerbo Foundation Lectureship in Pediatric Critical Care, North Shore University Hospital, New York, NY

1995 Dinner Speaker
"Diagnostic and Therapeutic Applications of Inhaled Nitric Oxide"
Annual Dinner Meeting, New York Society of Pediatric Critical Care Medicine, New York, NY

1995 Pediatric Grand Rounds
"Controversy in Critical Care: New Views of Simple Gases"
Cornell University Medical Center, New York, NY

1995 FDA Invited Lecture
"Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension of the Newborn"
Open Meeting, Cardiovascular and Renal Drugs Advisory Committee, United States Food & Drug Administration, Bethesda, MD

1995 FDA Invited Discussant
"Use of Inhaled Nitric Oxide in Pediatrics"
Division of Cardiorenal Drug Products, U.S. Food & Drug Administration Rockville, MD

1996 Invited Lecture
"Persistent Pulmonary Hypertension and Alveolar/Capillary Dysplasia"
Pediatric Grand Rounds, Elliot Hospital, Manchester, NH

1996 Invited Lecture
"Clinical Use of Inhaled Nitric Oxide"
International Business Communications Nitric Oxide Conference, Philadelphia, PA

1996 Seminar Speaker
"Postoperative Management of Pulmonary Hypertension in Pediatric Patients with Congenital or Acquired Heart Disease" Annual Meeting, American College of Cardiology, Orlando, FL

1996 Invited Lecture
"Inhaled Nitric Oxide-Clinical Experience"
First International Meeting on Pediatric Cardiac Intensive Care, Miami, FL

1996 Invited Lecture
"Pre and Postoperative Manipulation of the Vascular Resistance"
Annual Meeting, American Heart Association, New Orleans, LA

1996 Invited Lecture
"Current Concepts in Neonatology"
Section on Perinatology, American Academy of Pediatrics and the Joint Program in Neonatology, Harvard Medical School, Boston, MA

1997 Seminar
"Medical Management of Perioperative Pulmonary Hypertension"
Annual Meeting, Society of Critical Care Medicine, San Diego, CA

1997 Invited Lecture
"Nitric Oxide and the Treatment of Postoperative Pulmonary Hypertension"
Second World Congress of Pediatric Cardiology and Cardiac Surgery, Honolulu, Hawaii

1997 Invited Lecture
"Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension of the Newborn"
Open Meeting, Division of Cardiorenal Drugs, United States Food & Drug Administration, Bethesda, MD

1997 Invited Lecture
"Perioperative Care of the Child with Congenital Heart Disease: New Treatment Strategies for Pulmonary Hypertension"
Cardiothoracic Anesthesia Meeting, Washington University, St. Louis, MO

1997 Plenary Session
"Advances and Controversies in Cardiac Management"
Tenth Annual Pediatric Critical Care Colloquium, Hot Springs, AR

1997 Invited Faculty
"Critical Care of the Child with Congenital Heart Disease" (moderator lecturer, judge)
Second International Symposium on Pediatric Cardiac Intensive Care, Palm Beach, FL

1997 Invited Speaker
"Nitric Oxide in Neonatal Care"
Topics in Neonatal and Respiratory Care, Brigham & Women's Hospital, Boston, MA

1998 Invited Lectures
"Cardiac Surgery in Neonates: Morbidity and Mortality"
Charleston Symposium on Congenital Heart Disease, Medical University of SouthCarolina, Charleston, SC

1998 Symposium
"Advances in ICU Management for Congenital Heart Disease"
Annual Meeting, American College of Cardiology, Atlanta, GA

1998 Invited Lecture
"Intensive Care After Neonatal Cardiac Surgery: State-of-the-Art"
First Annual Course on Frontiers in Diagnosis and Management of Congenital Heart Disease, Boston, MA

1999 Invited Faculty
"Myocardial Support for Low Cardiac Output"
Society of Critical Care Medicine
Current Concepts in Pediatric Critical Care Course, San Francisco, CA

1999 Invited Lecture
"Nitric Oxide and the Treatment of Pulmonary Hypertension"
Oral Presentation Moderator, Walk Rounds with the Professor
28th Scientific Symposium, Society of Critical Care Medicine, San Francisco, CA

1999 Symposium
"The Airway, Mechanical Ventilation and Cardiopulmonary Interaction"
Annual Meeting, American Heart Association, Atlanta, GA

1999 Invited Speaker
"Nitric Oxide and New Therapies"
Third International Symposium on Pediatric Cardiac Intensive Care, Miami, FL

2000 Invited Faculty
"Nitric Oxide in the Perioperative Management of CHD"
Cardiology Y2K, Annual Update on Pediatric Cardiovascular Disease, Orlando, FL

2000 Symposium
"Intensive Care Unit Management After Surgery for Single Ventricle HLHS Syndrome"
Annual Meeting, American College of Cardiology, Anaheim, CA

2000 Invited Lecture
"Perioperative Care of the Premature Newborn with Congenital Heart Disease"
Castañeda Society Meeting, Boston, MA

2000 Invited Faculty
"Perioperative Care of the Premature Newborn with Congenital Heart Disease"
Tenth Charleston Symposium on Congenital Heart Disease, Charleston, SC

2001 Invited Faculty
"Clinical Research"
The Changing Face of Pediatric Cardiology 1950-2000: A Tribute to Alexander S. Nadas, M.D.
The Cardiovascular Program at Children's Hospital, Boston, MA

2001 Invited Faculty
"Cardiopulmonary Support in the Pediatric Cardiac Intensive Care Unit"
Third Course on Frontiers in Diagnosis and Management of Congenital Heart Disease,
Newport, RI

2001 Invited Faculty
Diverse Topics
Fourth International Symposium on Pediatric Cardiac Intensive Care, Palm Beach, FL

2002 Invited Speaker
"Sildenafil for Treatment of Pulmonary Hypertension"
ECMO Meeting, Children's National Medical Center, Keystone, Colorado

2002 Invited Speaker
"Novel Pediatric Applications of Commonly Used Adult Drugs"
Back to our Future: Establishing Safety and Evidence in Pediatric Research
Duke University, FDA & Industry, Washington, DC

2002 Invited Lecturer
"The Future of Inhaled Nitric Oxide for Children with Congenital Heart Disease"
CME Course in Hematology, Northwestern University Medical School
Chicago, Illinois

2002 Invited Faculty
"Manipulating Vascular Resistance in the Newborn: Is it Feasible?"
3rd International Pediatric Cardiovascular Symposium, Atlanta, Georgia

2002 Invited Speaker
"Viagra for Pulmonary Hypertension"
Hot Topics in Neonatology, Washington, DC

2003 Plenary Speaker
"Changes in Worldwide Activity and Mortality in Cardiac Intensive Care"
Debate: "Cardiac Patients Need Their Own ICU"
Symposium Chairman: "New Strategies in Treatment of Pulmonary Hypertension"
4th World Congress of Pediatric Intensive Care, Boston, Massachusetts

2004 Invited Faculty
"Pharmacologic Management of Low Cardiac Output Syndrome After Congenital Heart Surgery" Current Concepts in Pediatric Critical Care Medicine Course
Society for Critical Care Medicine, Orlando, Florida

2004 Invited Faculty
"Structure of a Training Program in Pediatric Cardiac Intensive Care"
33rd Annual Meeting of the Society for Critical Care Medicine, Orlando, Florida

2004 Invited Faculty
"Reconciling FDA, Academic, and Industry Objectives in Pediatric ClinicalTrials"
Cardiology 2004, Orlando, Florida (Children's Hospital of Philadelphia)

2004 Invited Speaker
"Cardiac and Central Nervous System Interactions
15th Annual Pediatric Critical Care Colloquium, New York City, New York

2004 Invited Faculty
"Advances in the Management of Pulmonary Hypertension"
"Physician Perspective on Electronic Billing:
Congenital Cardiovascular Surgery Symposium, San Diego, California

2004 Invited Participant in "How To" Session
"How to Evaluate and Manage Pediatric Patients with Pulmonary Hypertension"
American Heart Association, Scientific Sessions 2004, New Orleans, LA

2004 Invited Faculty, Special Session
"Twenty Year Retrospective: The Early Years and Later"
Pediatric Cardiac Intensive Care Symposium, Miami, FL

2004 Invited Faculty
"Nitric Oxide and the Intensive Care Setting"
Pediatric Cardiac Intensive Care Symposium, Miami, FL

2004 Invited Faculty
"How to Design and Conduct Drug Trials"
Pediatric Cardiac Intensive Care Symposium, Miami, FL

2005 Invited Faculty
"Therapies to Enhance the Effect of Inhaled Nitric Oxide"
Symposium on New Directions in Nitric Oxide Therapy, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas

2005 Invited Speaker
"Pulmonary Hypertension: Approaches to Management", 21st Annual Fetus and Newborn Conference, Boston, MA

2005 Invited Moderator
"Low Birth Weight Neonates with Congenital Heart Disease", Pediatric Cardiac Intensive Care Symposium 2005 (PCICS 2005), Miami, FL

2005 Invited Faculty
Consensus Report on Treatment of Myocarditis. Pediatric Cardiac Intensive Care Symposium 2005 (PCICS 2005), Miami, FL

2006 Invited Faculty
"Challenges in Industry Sponsored Trials" and "Management of PVR in the Neonate"
Ninth Annual Update on Pediatric Cardiovascular Disease (Children's Hospital of Philadelphia), Scottsdale, AZ

2006 Invited Speaker
Eddie Farrell Memorial Lecture, Massachusetts Society of Respiratory Care, Sturbridge, MA

2006 Invited Faculty
Second International Conference on Heart Failure in Children and Young Adults Children's Hospital Orange County, Laguna Niguel, CA

2007 Invited Speaker
"Pulmonary Vascular Alterations in CHD" & "Drug Treatment for Pulmonary Hypertension".
First International Conference on Childhood Pulmonary Vascular Disease, San Francisco, CA

2008 Invited Speaker
"Cardiac Critical Care: What's New and What Matters "STS Congenital Surgical Symposium, Ft. Lauderdale, Fl.

2008 Invited Speaker
Session Chair "Anticipating the Growing ACHD Population"
Update on Pediatric Cardiovascular Disease - New and Evolving Concepts and Practices,
Speaker: "Considerations for Caring for Adult Patients in a Pediatric ICU" & "Current Status of Inpatient Therapy"
Scottsdale, AZ

2008 Invited Speaker
Forum Moderator: "Inhaled Nitric Oxide in the OR"
ASA 2008 Annual Meeting, Orlando, FL

2008 Invited Speaker
"Postoperative Management and Outcome of the Term vs. Premature Newborn with Congenital Heart Disease"
Management of Congenital Heart Disease in the Fetus & NeonateSymposium, Washington, DC

2008 Invited Speaker
"Pulmonary Hypertension"
NPCNA Annual Fall Conference, Innovation and Inquiry in Pediatric Cardiology Nursing Washington, DC

2008 Invited Speaker
"Critical Treatment Strategies for Acute Pulmonary Hypertension in Infants and Children cGMP-related Drugs »
PCICS Annual Symposium 2008, Miami, FL

2009 Invited Speaker
Session Moderator. "Cardiac Surgery"
38th Annual Critical Care Congress of the Society of Critical Care Medicine, Nashville, TN

2009 Invited Speaker
Session Moderator. "Cardiac ECMO: State-of-the-Art"
The 25th Annual CNMC Symposium: ECMO & The Advanced Therapies for Respiratory Failure
Keystone, CO

2009 Invited Speaker
Session Moderator. "Pulmonary Vascular Alterations in Congenital Heart Disease"
The 2nd International Neonatal and Childhood Pulmonary Vascular Disease Conference
San Francisco, CA

2009 Invited Speaker
"Advances in Cardiac Intensive Care"
9th Annual Cardiac Research Symposium – A.I. DuPont Hospital for Children, Nemours
Symposia, Wilmington, DE

2010 Invited Speaker
"Cardiac Intensive Care: Celebrating Successes, Meeting Challenges"
3rd Annual John J. Downes Lecture in Pediatric Anesthesia and Critical Care Medicine
Orlando, FL

2010 Invited Speaker
"A Randomized Trial of Clopidogrel to Reduce Mortality and Shunt-Related Morbidity in Infants Palliated with a Systemic to Pulmonary Artery Shunt
Outstanding Research Awards (Council on Cardiovascular Disease in the Young)
AHA Scientific Sessions, Chicago, IL

2011 Invited Speaker
"Working with the FDA & Industry in Designing Pediatric Trials"
The 27th Annual CNMC Symposium: ECMO & The Advanced Therapies for Respiratory Failure
Keystone, CO

2011 Invited Speaker
"Resuscitation of the Patient with Pulmonary Hypertension"
4th International Neonatal and Childhood Pulmonary Vascular Disease
San Francisco, CA

INTERNATIONAL

1986 Invited Lecture
"Recent Advances in the Intensive Treatment of Neonates with Congenital Heart Disease,"
A Week with the Experts, Ospedale Pediatrico Bambino Gesu, Rome, Italy

1988 Invited Lecture
"Perioperative Care of the Patient with HLHS"
European Congress on Hypoplastic Left Heart Syndrome, Ospedale Pediatrico Bambino Gesu, Rome, Italy

1990 Invited Lecture
"Perioperative Care of the Neonate with Congenital Heart Disease"
Pediatric Critical Care Conference, Hospital for Sick Children, University of Toronto, Toronto Canada

1991 Invited Lecture
"Perioperative Intensive Care of the Child with Congenital Heart Disease"
First International Pediatric Intensive Care Congress, Buenos Aires, Argentina

1993 Invited Faculty
"Regulation of the Pulmonary Circulation: Therapeutic Implications"
First European Postgraduate Course in Neonatal and Pediatric Intensive Care, Berne, Switzerland

1993 Invited Faculty
"Pulmonary Hypertension: Pathophysiologic and Therapeutic Implications in Post Surgical Patients" Third International Meeting on Pediatric Intensive Care, University of Padova, Italy

1993 Invited Lecture
"Nitric Oxide to Test Pulmonary Vascular Reactivity to Control Hypertensive Crises and as a Potential Chronic Therapy" Canadian Cardiovascular Society, Vancouver, Canada

1993 Invited Lecture
"Nitric Oxide Inhalation after Correction of Congenital Heart Defects"
International Conference on ARDS, Tutzing, Germany

1994 Plenary Presentation
"Perioperative Care of the Neonate"
Cardiac Surgery Today: State of the Art, Onassis Medical Center, Athens, Greece

1995 Invited Faculty
"Nitric Oxide in the Treatment of Congenital Heart Disease"
Annual Meeting of the Austrian Society for Lung Diseases, Gmunden, Austria

1995 Plenary Speaker
"Inhaled Nitric Oxide for Perioperative Management of Congenital Heart Disease"
The VII Brazilian Congress of Intensive Care Medicine, Recife, Brazil

1996 Invited Lecture
"Nitric Oxide in Pulmonary Hypertension after Surgery for Congenital Heart Defects"
Annual Meeting, European Society of Cardiology, Birmingham, United Kingdom

1997 Symposium
"The Failing Heart—Pediatric Aspects"
The 7th World Congress of Intensive & Critical Care Medicine, Ottawa, Canada

1997 Plenary Session
"Inhaled Nitric Oxide"
XXX Brazilian Pediatrics Congress and International Pediatric Symposium, Rio de Janeiro, Brazil

1998 Invited Faculty
Multiple lectures and workshops
Pediatric Cardiac Intensive Care at the European Heart House
European Society of Cardiology, Nice, France

1998 Invited Faculty
Lectures on Congenital Heart Disease
Argentine Congress of Cardiology, Buenos Aires, Argentina

1999 Invited Lecture
"Critical Aortic Stenosis in the Neonate"
Second Postgraduate Course on Congenital and Acquired Heart Disease, Modena, Italy

1999 Invited Lecture
"Pathophysiology and Treatment of Pulmonary Hypertension
Lund University Hospital, Lund, Sweden

1999 Invited Lecture
"Pulmonary Hypertension and Mechanical Support in Children with Heart Disease"
Lindgren Children's Hospital at the Karolinska Institute, Stockholm, Sweden

1999 Plenary Speaker
"Frontiers in Pediatric Intensive Care"
Annual Meeting, Society of Anesthesia and Critical Care, Gothenburg, Sweden

1999 Invited Faculty
"ICU Management of Two Stage Arterial switch"
"The Role of Nitric Oxide in the Cardiac Patient"
The First Hispano Latin American Course, Diagnosis and Management of Congenital Heart Disease, San Juan, Puerto Rico

1999 Invited Lecture
"Current Concepts in Post-operative Management"
"ECMO in the New Millennium"
Symposium on Pediatric Cardiology, Cordoba, Argentina

1999 Invited Speaker
"Inhaled Nitric Oxide"
"Perioperative Care of the Newborn"
The First Sino-American Symposium: New Developments in the Care of Children with Congenital Heart Disease, Shanghai Children's Medical Center, Shanghai, China

2000 Invited Faculty and Track Convener
"Issues in Perioperative Care" and multiple lectures
The Third International Symposium on Pediatric Cardiac Intensive Care, Montreal, Canada

2000 Invited Lecture
"Endothelial Cell Function During Cardiopulmonary Bypass"
5th World Congress on Trauma, Shock, Inflammation and Sepsis, Munich, Germany

2000 Invited Lecture
"Inhaled Nitric Oxide Therapy in Children after Cardiac Surgery"
American Thoracic Society, 96th International Conference, Toronto, Canada

2000 Invited Lecture
"Pulmonary Hypertension and its Impact on Hemodynamics"
Special Topics in Pediatric Cardiac Intensive Care Symposium, Royal Brompton & Harefield NHS Trust, London, United Kingdom

2000 Invited Faculty
"Critical Care and Congenital Heart Disease"- diverse topics
Pediatric FCCS Course, Taipei, Taiwan

2000 Invited Lecture
"Advances in Perioperative Care of the Child with Congenital Heart Disease"
Tenth Anniversary Lecture, Kaohsiung Veterans General Hospital, Taiwan

2000 Invited Lecture
"Postoperative Care of the Child with AV Septal Defect"
European Cardiovascular Surgery's Postgraduate Course, Frankfurt, Germany

2000 Seminar
"Postoperative Care of Patients with Hypoplastic Left Heart Syndrome"
European Association of Cardio-Thoracic Surgery, Annual Meeting, Frankfurt, Germany

2000 Plenary Lecture
"Diagnosis and Treatment of Pulmonary Hypertension"
XIX Pan American Congress of Pediatrics, Montevideo, Uruguay

2000 Invited Lecture
"Postoperative Management of the Child with D-Transposition of the Great Arteries"
"Diagnosis and Management of Pulmonary Arterial Hypertension"
I Pediatric Cardiology Symposium, Dr. Aldo Castañeda, Guatemala City, Guatemala

2001 Invited Faculty
"Pulmonary Hypertension and Nitric Oxide"
"Assessing and Managing Premature Newborns for Surgical and Catheter Intervention"
Harvard Winter Course in Congenital Heart Management, Dubai, United Arab Emirates

2001 Invited Lecture
"Brain Protection During CPB"
V European Postgraduate Course in Neonatal and Pediatric Intensive Care, Bern, Switzerland

2001 Invited Lecture
"Strategic Management of the Patient after Surgery"
Third World Congress of Pediatric Cardiology and Cardiac Surgery, Toronto, Canada

2001 Invited Faculty
Special Topics in Paediatric Cardiac Intensive Care– 2001, The Challenging Neonate,
The Royal Brompton Hospital & The National Heart & Lung Institute, London, England

2002 Moderator
European Consensus Meeting on Inhaled Nitric Oxide
European Society of Pediatric and Neonatal Intensive Care, Rome, Italy

2002 Invited Faculty
"Assessment of Myocardial Function in the ICU"
"Postoperative Management After Staged Repair of HLHS"
"ECMO Management of the Single Ventricle Circulation"
New Era in Congenital Heart Management
Universidad Complutense Madrid and Real Colegio Complutense en Harvard, The Heart Institute Hospital, Universitario "12 de Octubre", Madrid, Spain

2002 Guest Lecturer
"Failing Hearts: The Paediatric Problem and Current Treatments"
"Inhaled Nitric Oxide and Pulmonary Vasodilators for the Failing Right Heart"
"Routine ECMO for Resuscitation"
The Third Special Topics in Paediatric Cardiac Intensive Care, The Failing Myocardium
Royal Brompton Hospital, Imperial College, London, United Kingdom

2003 Invited Faculty
"Support for the Failing Ventricle"
"Management of Pulmonary Hypertension: From the OR to the Home"
Debate: "Early Extubation is the Best Defense Against Postoperative Complications"
First Asia Pacific Symposium on Pediatric Cardiac Intensive Care, Phuket, Thailand

2003 Guest Lecturer
"Pharmacologic Management of Pulmonary Hypertension" and Other Topics
IX Curso de Actualización en Cardiología Pediátrica, Madrid, Spain

2003 Guest Lecturer
"Recent Advances in the Use of Inhaled Nitric Oxide in Patients with Congenital Heart Disease". Inhaled Nitric Oxygen Symposium for Neonatologists. Madrid, Spain

2003 Invited Participant
Third World Symposium on Pulmonary Arterial Hypetension (WHO). Venice, Italy

2003 Special Guest Lecturer
"Indications for Inhaled Nitric Oxide in the Neonatal and Postoperative Care of Critically Ill Children"
Annual Meeting of the German Society of Pediatric Cardiology. Weimar, Germany

2003 Invited Speaker
"Predicting and Treating Low Cardiac Output in the Postoperative Patient"
Annual Meeting of the European Association of Cardiothoracic Surgeons. Vienna, Austria

2003 Invited Faculty
"The Paperless ICU"
"Pulmonary and Systemic Vasodilators"
"Genetic Basis for Heterotaxy"
Harvard Medical International, Children's Hospital Boston Course in Congenital Heart Disease
Abu Dhabi, United Arab Emirates

2003 Invited Speaker
"Extracorporeal Membrane Oxygenation for Cardiopulmonary Resuscitation in Children"
Hammersmith Hospital Workshop on Perfusion. London, United Kingdom

2004 Keynote Speaker
"Pulmonary Hypertension Therapy—Now and in the Future"
Pulmonary Hypertension in Early Life, St. Guys and St. Thomas' Hospital
London, United Kingdom

2004 Keynote Address
"Pulmonary Hypertension: State of the Art"
Opening Ceremony, Annual Meeting of the European Society of Pediatric and Neonatal Intensive Care, London, United Kingdom

2005 Plenary Speaker
"Recent Advances in Heart Failure and Pulmonary Hypertension", The Fourth World Congress of Pediatric Cardiology and Cardiac Surgery, Buenos Aires, Argentina.

2005 Invited Speaker
Controversy Session: "Inhaled Iloprost is the Best Pulmonary Vasodilator?", The Fourth World Congress of Pediatric Cardiology and Cardiac Surgery, Buenos Aires, Argentina.

2005 Invited Speaker
Chair, Oral Presentations: "Cardiac Intensive Care", The Fourth World Congress of Pediatric Cardiology and Cardiac Surgery, Buenos Aires, Argentina.

2006 Invited Faculty
"Outcomes of Heart Failure in the ICU: Mechanisms of Postoperative Dysfunction." Congress of Ventricular Dysfunction in Childhood, OPBG Cardiovascular International. Rome, Italy

2007 Invited Speaker
Multiple Oral Presentations and Panel Chair
Fifth World Congress on Pediatric Critical Care, Geneva, Switzerland

2007 Invited Speaker
"Cuidado perioperatorio del recién nacido con enfermedad cardiaca congénita", VI Annual Colombian Critical Care Congress, Medellín, Colombia

2007 Invited Speaker
"Postoperative Treatment of Pulmonary Hypertension,"& "Postoperative Care of Hypoplastic Left Heart: Comparing Norwood with BT Shunt vs. Sano from Birth through the Fontan."
International Cardiology Meeting, Avignon, France

2008 Invited Faculty
Plenary Lecture: "Pediatric Cardiac Intensive Care: Past, Present and Future"; "Dedicated Training Pathways in Pediatric Cardiac Intensive Care" & "How to plan a Research Study in ICU"
PCICS Europe Symposium, Monte Carlo, Monaco

2009 Invited Speaker
"Acute Heart Failure Pathophysiology", Treatment of Postoperative Acute Cardiac Failure", "Mechanical Support of Acute Cardiac Failure"
International Pediatric Cardiology Conference
Cartagena, Colombia

2010 Invited Faculty
Session Moderator: Pulmonary Hypertension, Right Ventricular Function and Congenital Heart Disease
3rd International Conference Neonatal and Childhood Pulmonary Vascular Disease
Banff, Alberta, Canada

2010 Invited Speaker
"Intraoperative Care and Perioperative Management for Transpostion"
The World Society for Pediatric and Congenital Heart Surgery
Antigua, Guatemala

10) GRANTS AWARDED

FUNDING INFORMATION

1987-89 The effects of ventilation on pulmonary vascular resistance in infants following cardiopulmonary bypass. Principal Investigator, American Society of Anesthesiologists Research Starter Grant.

1988-91 Infant heart surgery: CNS sequelae of circulatory arrest. Co-Investigator, National Institutes of Health. Grant No. HL41786.

1993-96 Ischemic neonatal brain injury: clinical and basic science. Co-investigator, National Institutes of Health. Grant No. P20 NS32570

1994-96 Inhaled nitric oxide for the treatment of pulmonary hypertension and acute respiratory failure in children. Principal Investigator, Clinical Research Grant-in-Aid Award, Children's Hospital, Boston, Massachusetts. Grant No. CH 89430.

1994-99 Pathogenesis of brain injury in infant heart surgery. Clinical advisor / mentor to Dr. Adre J. DuPlessis, National Institutes of Health. Grant No. K08 NS01721

1996-99 Dose response of inhaled nitric oxide in congenital heart disease. Principal Investigator, U.S. Food and Drug Administration. Grant No. FD R-001316.

1997-99 Neurodevelopmental follow up of patients with PPHN in a randomized trial of nitric oxide.Principal Investigator, Industry Sponsored.

1997-00 Echocardiographic assessment of right ventricular function in patients with pulmonary hypertension. Sponsor for Dr. Ricardo Munoz (MCAP), National Institutes of Health Grant No. M01 RR02172.

2000-01 Prophylactic use of Primacor® in pediatric patients at high risk of developing low cardiac output syndrome following cardiac surgery. Principal Investigator, Industry Sponsored.

2004-06 Principal Investigator (Boston) on three industry sponsored trials of sildenafil for treatment of pediatric pulmonary hypertension (see below).

2004-08 A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-16 Years, With Pulmonary Hypertension. Principal Investigator, Industry Sponsored

2004-08 Multicenter, Long-Term Extension Study to Assess Safety of Oral Sildenafil in the Treatment of Subjects Who Have Completed Study A1481131. Principal Investigator, Industry Sponsored

2004-06 7-Day, Open-Label, Multicenter, Pharmacokinetic Study (Part 1) of IV Sildenafil in the Treatment of Neonates With Persistent Pulmonary Hypertension of the Newborn (PPHN) or Hypoxic Respiratory Failure and at Risk for PPHN. Principal Investigator, Industry Sponsored

2006-08 Pilot Study of the Effects of Nesiritide on Hemodynamics and Urine Output Following Cardiopulmonary Bypass in Children. Co-investigator and mentor (John M. Costello); American Heart Association.

2006-10 Multinational Trial on the Efficacy and Safety of Clopidogrel in Infants with Cyanotic Congenital Heart Disease Palliated with a Systemic to Pulmonary Shunt (CLARINET). (Chair, Steering Committee, Institutional Co-investigator). Industry Sponsored (Sanofi-Aventis).

2009-14 Collaborative Pediatric Critical Care Research Network (CPCCRN). NIH-NICHD U10410HD049981. Principal Investigator; 20% effort. Base award over 5 years $925,000 direct costs plus annual awards for protocol funds (e.g. 2010 = $200,000)

- Critical Pertussis in US Children. Protocol #001
- The Critical Illness Stress-induced Immune Suppression Prevention Trial (CRISIS). Protocol #003
- Development of a Quantitative Functional Status Scale (FSS) for Pediatric Patients. Protocol #004
- Therapeutic Hypothermia after Pediatric Cardiac ArrestTrials (THAPCA). Protocol #010
- Cortisol Quantification Investigation. Protocol #012
- Measuring Opioid Tolerance Induces by Fentanyl (or Other Opioids). Protocol #026
- Physician's Perspectives on the Physician-Parent Follow-Up Conference.
- Pediatric Intensive Care Unit Bereavement Study
- CPCCRN Asthma Study

REPORT OF CURRENT RESEARCH ACTIVITIES

1. My primary current research activity involves designing and executing national and international pediatric clinical trials.

2. Safety and efficacy of type V phosphodiesterase inhibitors in children as selective pulmonary vasodilators and to augment vasodilatory potential of nitric oxide and attenuate rebound pulmonary hypertension. I was the overall primary scientific advisor in the development and execution of international multicenter randomized trials on type V inhibitors in pediatrics, Industry sponsored.Final publications in press.

3. Outcome studies evaluating ventilator management, inotropic agents, mechanical support of the circulation and new strategies in the critical care managementand perioperative care of
   a) premature newborns with congenital heart disease
   b) newborns after reparative surgery involving the right ventricle
   c) extracorporeal membrane oxygenation resuscitation of children with congenital heart disease.

4. Multinational Trial on the Efficacy and Safety of Clopidogrel in Infants with Cyanotic Congenital Heart Disease Palliated with a Systemic to Pulmonary Shunt(CLARINET). (Chair, Steering Committee, Institutional Co-investigator). Industry Sponsored.

5. I am the Principal Investigator (CNMC) and steering committee member for the NIH funded clinical research network with multiple active protocols listed above.

11) PUBLICATIONS

PAPERS IN REFEREED JOURNALS

1. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA. .Pulmonary and systemic hemodynamic responses to fentanyl in infants. Anesth Analg 1985;64:483-6.

2. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA. Blunting of stress responses in the pulmonary circulation by fentanyl. Anesth Analg 1985;64:1137-42.

3. Wessel DL, Keane JF, Fellows KE, Robichaud H, Lock JE. Fibrinolytic therapy for femoral arterial thrombosis after cardiac catheterization in infants and children. Am J Cardiol 1986;58:347-51.

4. Wessel DL, Lock JE. Transcatheter umbrella closure of congenital cardiac defects: technical considerations. Adv Bioeng (ASME). 1987;12:143-144.

5. Wessel DL, Keane JF, Parness I, Lock JE. Outpatient closure of the patent ductus arteriosus. Circulation 1988;77:1068-1071.

6. Castaneda AR, Mayer JE, Jonas RA, Lock JE, Wessel DL, Hickey PR. The neonate with critical congenital heart disease: repair - a surgical challenge. J Thorac Cardiovasc Surg 1989;98:869-75.

7. DiDonato RM, Wernovsky G, Walsh EP, Colan SD, Lang P, Wessel DL, Jonas RA, Mayer JE Jr, Castaneda AR. Results of the arterial switch operation for transposition of the great arteries with ventricular septal defect: Surgical considerations and midterm follow-up data. Circulation 1989;80:1689-1705.

8. Wernovsky G, Jonas RA, Colan SD, Sanders SP, Wessel DL, Castaneda AR, Mayer JE: Results of the arterial switch operation in patients with transposition of the great arteries and abnormalities of the mitral valve or left ventricular outflow tract. J Am Coll Cardiol 1990;16:1446-1454.

9. Bellinger DC, Wernovsky G, Rappaport LA, Mayer JE Jr, Castaneda AR, Farrell DM, Wessel DL, Lang P, Hickey PR, Jonas RA, Newburger JW. Cognitive development of children following early repair of transposition of the great arteries using deep hypothermic circulatory arrest. Pediatrics 1991;87:701-707.

10. Chang AC, Wernovsky G, Kulik TJ, Jonas RA, Wessel DL. Management of the neonate with transposition of the great arteries and persistent pulmonary hypertension. Am J Cardiol 1991;68:1253-1256.

11. Chang AC, Hanley FL, Weindling SN, Wernovsky G, Wessel DL. Left heart support with a ventricular assist device in an infant with acute myocarditis. Crit Care Med 1992;20:712-715.

12. Hickey PR, Wessel DL, Streitz SL, Fox ML, Kern FH, Bridges, ND, Hansen, DD. Transcatheter closure of atrial septal defects: Hemodynamic complications and anesthetic management. Anesth Analg 1992;74:44-50.

13. Wernovsky G, Giglia TM, Jonas RA, Mone SM, Colan SD, Wessel DL. Course in the intensive care unit after 'preparatory' pulmonary artery banding and aortopulmonary shunt placement for transposition of the great arteries with low left ventricular pressure. Circulation 1992;86[suppl II]II133-139.

14. Wong PC, Barlow CF, Hickey PR, Jonas RA, Castaneda AR, Farrell DM, Lock JE, Wessel DL. Factors associated with choreoathetosis after cardiopulmonary bypass in children with congenital heart disease. Circulation 1992;86[suppl II]:II118-II126.

15. Chang AC, Wernovsky G, Wessel DL, Freed MD, Parness IA, Perry SB, O'Brien P, Van Praagh R, Hanley FL, Jonas RA, Castaneda AR, Mayer JE. Surgical management for late right ventricular failure after Mustard or Senning repair. Circulation 1992;86[suppl II]:II-140-II-149.

16. Chang AC, Kulik TJ, Hickey P, Wessel DL. Real-time gas exchange measurement of oxygen consumption in neonates and infants after cardiac surgery. Crit Care Med 1993;21:1287-1295.

17. Irazuzta J, Pearlman N, Pascucci R, Wessel DL. Effects of fentanyl administration on respiratory system compliance in infants. Crit Care Med 1993;21:1001-1004.

18. Chang AC, Hanley FL, Wernovsky G, Rosenfeld H., Wessel DL, Jonas RA, Mayer JE, Castaneda AR. Early bidirectional cavopulmonary shunt in young infants: postoperative course and early results. Circulation 1993; 86[suppl II]:II-149-II158.

19. Hanley FL, Heinemann MK, Jonas RA, Mayer JE, Cook NR, Wessel DL, Castaneda AR. Repair of truncus arteriosus in the neonate. J Thorac Cardiovasc Surg 1993;105:1047-1056.

20. Wessel DL. Hemodynamic responses to perioperative pain and stress in infants. Crit Care Med 1993; 21[suppl]:S361-S362.

21. Newburger JW, Jonas RA, Wernovsky G, Wypij D, Hickey PR, Kuban KCK, Farrell DM, Holmes GL, Helmers SL, Constantinou J, Carrazana E, Barlow JK, Walsh AZ, Lucius KC, Share JC, Wessel DL, Hanley FL, Mayer, JE, Castaneda AR, Ware JH. A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med 1993;329:1057-1064.

22. Wessel DL. Inhaled nitric oxide for the treatment of pulmonary hypertension before and after cardiopulmonary bypass. Crit Care Med 1993;21[suppl]:S344-S345.

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2. Wessel DL; Session Chair, Inhaled nitric oxide therapy in newborns: reaching a European consensus. ESPNIC, Rome 2002. CD-ROM.

3. Kinsella J, Steinhorn R, Clark R, Wessel D, ed. Hypoxic respiratory failure in the neonate: diagnosis and treatment. . CD-ROM and Slide Kit. iNO 2003.

4. Wessel DL; editor. Proceedings from the World Congress in Pediatric Critical Care Symposium on "New strategies in the treatment of pulmonary hypertension." Monograph and CD-ROM. University of Colorado Continuing Medical Education.

EXHIBIT 7

Exhibit 7

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 of Research and Development at INO Therapeutics LLC ("INO"), which is a wholly-owned subsidiary of Ikaria, Inc. 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. I have been shown a Non-Final Office Action issued by the United States Patent and Trademark Office (USPTO) on June 8, 2011 in a pending patent application having US serial number 12/820,866. This Non-Final Office Action rejected the pending claims of 12/820,866 as "obvious" based on clinical interpretations presented by the USPTO regarding the teaching and disclosure of Atz & Wessel. (Seminars in Perinatology 1997, 21(5), 441-455), Kinsella et al. (Lancet 1999, 354 1061-1065) and Loh et al. (Circulation 1994, 90, 2780-2785). Below is my professional opinion and interpretation of the arguments and clinical interpretations presented by the USPTO within the Non-Final Office Action of June 8, 2011, for 12/820,866 (the "Office Action).

8. On page 7 of the Office Action, the Examiner states:

> *"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)."*

A more complete excerpt from Atz & Wessel, p. 452, left column is as follows:

> "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 ...." (emphasis added)

Thus, although Atz & Wessel warns that "[c]aution should be exercised when administering nitric oxide (NO) to patients with severe left ventricular dysfunction and pulmonary hypertension[,]" this caution is specifically limited to two populations of patients. In the first population, the statement in Atz & Wessel p. 452, left column, is directed to adult patients with ischemic cardiomyopathy who also exhibit severe left ventricular dysfunction and pulmonary hypertension. This patient population is clearly different from the neonatal population that is the object of the teaching of the present claims.

9. Further in the same paragraph, Atz & Wessel specifically refers to a second patient population, which is also distinct from that of the present patent application, to whom inhaled NO should not be administered, namely, neonates depending on right-to-left shunting of blood:

> "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." (emphasis added)

For this second patient population, Atz & Wessel state that these patients exhibit a "different but related phenomenon" from that observed in adults with ischemic cardiomyopathy. This second population of patients consists of newborn patients with congenital heart disease and left ventricular dysfunction who are **dependent on a right-to-left shunt through a ductus arteriosus** in order to maintain peripheral circulation necessary to survive. In these patients, a patent ductus provides the only alternate pathway for blood being pumped by the right ventricle to **bypass the dysfunctional left ventricle** and thereby substitute for the dysfunctional left ventricle in providing life-sustaining blood flow to the peripheral circulation. Blood emerging

from the right ventricle has only two possible pathways, either through the pulmonary circulation and then back to the dysfunctional left ventricle, or to pass through the patent ductus arteriosus in a right-to-left shunt to reach the systemic circulation. Inhaled NO dilates the pulmonary circulation, and therefore would divert blood to the lungs at the expense of the patent ductus arteriosus and systemic circulation, causing systemic vascular collapse and death. Again, this second patient population described by Atz & Wessel is also completely different from the patient population addressed in the present claims, which is term or near term neonates with left ventricular dysfunction who are **NOT dependent upon right-to-left shunting.**

10. The risk of circulatory collapse in the subset of newborns with congenital heart disease and severe left ventricular dysfunction **who are dependent upon a right-to-left shunt** through a patent ductus arteriosus was well known in this field long before the Atz & Wessel publication, as evidenced by the contraindication stated in the US Food and Drug Administration (FDA) prescribing information for INOMAX® (nitric oxide) for inhalation from the time of its initial approval by the FDA in 1999: **"CONTRAINDICATIONS:** Neonates known to be dependent on right-to-left shunting of blood".

11. As a result of the INOT22 study, it was recognized that a second population of neonates existed, distinct from the population described in Atz & Wessel, that had an increased risk of adverse events when inhaled NO was administered, namely: pediatric patients with left ventricular dysfunction **who are not dependent upon right-to-left shunting of blood.** In view of this newly identified risk, the FDA imposed the addition of a distinct and separate precaution to the prescribing information for INOMAX specifically cautioning about an additional risk of pulmonary edema for patients with left ventricular dysfunction (see paragraph 15). It is important to note that patients covered in the pre-existing contraindication (specifically neonates known to be dependent on right-to-left shunting of blood) were completely excluded from INOT22 by virtue of the labeled contraindication. The newly discovered risk of adverse events in neonates and children with left ventricular dysfunction **who are not dependent on right-to-left shunting** was not addressed, suggested or otherwise inferred from the teachings of Atz & Wessel, because when Atz and Wessel recommend that inhaled NO should be used with caution

"if at all", that warning relates to neonates **who are dependent upon right-to-left shunting of blood** – a completely different population of patients than the population that is addressed in the present claims.

12. On page 7 of the Office Action, the Examiner further states:

> *"Since pulmonary hypertension is instantly claimed, then the subject intrinsically has hypoxic respiratory failure."*

This statement is not medically accurate. Pulmonary hypertension occurs in many conditions other than hypoxic respiratory failure, such as congenital heart disease, maternal use of serotonin reuptake inhibitors, idiopathic pulmonary hypertension, etc.

13. On page 7 and 8 of the Office Action, the Examiner states:

> *"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.' (p. 452, left column) (emphasis differing from original)."*

This statement merely reiterates the "caution" delivered by Atz & Wessel for the second population of patients identified in that publication, namely neonates **dependent upon a right-to-left shunt** at the ductus arteriosus. In this statement, Atz & Wessel simply teach that patients with severe left ventricular dysfunction dependent upon an exclusively right-to-left shunt at the ductus arteriosus often have coexistent predominantly left-to-right shunt at the foramen ovale. This additional left-to-right shunt at the foramen ovale, upstream from the dysfunctional left ventricle, permits blood to bypass the dysfunctional left ventricle and enter the right side of the heart, thereby enhancing the ability of the right ventricle to pump sufficient blood through the ductus arteriosus to maintain the systemic circulation. The population of patients dependent upon right-to-left shunting of blood (with or without shunting at the foramen ovale) was already excluded by the pre-existing FDA-mandated contraindication for inhaled NO, and is distinct from the patient population addressed in the present claims.

14. On page 8 of the Office Action, the Examiner states:

> *"Atz 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."*

This statement misinterprets the teaching of Atz & Wessel. Specifically, "if at all" refers to the second patient population, wherein no treatment is allowed in the population of newborn "patients dependent upon right-to-left shunting of blood" who are at risk for circulatory collapse. Because these patients were already contraindicated in the drug labeling for inhaled NO prior to INOT22 (see paragraph 10 above), they were excluded from INOT22 and more importantly, are distinct from the patients identified in the new inhaled NO safety warnings mandated by the FDA in view of the risk that was newly identified as a result of the INOT22 study.

15. On February 25, 2009, INO Therapeutics LLC (owner of NDA 20845) submitted a label supplement to the FDA seeking to amend the prescribing information (i.e., the "label") for INOMAX® (nitric oxide) for inhalation, to include a new warning statement based on the unexpected outcome of the INOT22 study 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 by Health Authorities in Japan, Europe, Canada and Australia. The FDA (and it's counterparts in foreign nations) would

not add new warnings and precautions to the label of an approved drug that merely 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 & Wessel, with respect to neonates dependent on right-to-left shunt.

16. On page 8 and 9 of the Office Action, the Examiner states:

> *"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 p. 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 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 then treatment with NO is performed thereby reducing the risk of adverse events associated with the treatment."*

Based on these statements, it is clear that the Examiner fails to understand several critical aspects of the study of Kinsella et al.

17. First and foremost, the patients included in the Kinsella et al. trial were premature neonates who have severe respiratory failure due to immature lungs and surfactant deficiency, rather than term and near-term neonates suffering from pulmonary hypertension. In addition, none of the premature neonates enrolled in Kinsella et al. suffered from pulmonary hypertension. Thus, the patients included in Kinsella et al. were clinically differentiated, by age, etiology and pathophysiology, from the term and near-term neonates addressed in the present claims.

18. Secondly, exclusion of patients from a particular study may occur for a variety of reasons. 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.

19. 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.

20. 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).

21. On page 9 of the Office Action, the Examiner states:

> *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 18mm Hg had a greater effect of inhaled NO due to the greater degree of reactive pulmonary hypertension present in such patients (p. 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 (p. 2784, left column).

The Examiner apparently neglects to consider that the acute hemodynamic effect of inhaled NO was studied by Loh et al. only in **adult** patients with New York Heart Association Class III or IV congestive failure due to coronary artery disease or dilated cardiomyopathy, not in term or near-term neonates who were not dependent upon right-to-left shunting. Thus, their observations do not teach, or even suggest, the risk of inhaled NO in neonates or children with pulmonary hypertension and left ventricular dysfunction who are not dependent on right-to-left shunting of blood, the population that is addressed in the present claims.

22. 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.

23. On page 10 of the Office Action, the Examiner states:

> *"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."*

24. Atz & Wessel do not recommend exercising "caution" when treating term or near-term neonates who are not dependent upon right-to-left shunting, but rather refer to two **other** patient populations, namely (i) neonatal patients whose systemic circulation is dependent upon right-to-left shunting of blood and who therefore might suffer from systemic circulatory collapse if given inhaled NO (a well-known contraindication for inhaled NO) and (ii) adult patients with New York Heart Association Class III-IV heart failure due to ischemic or dilated cardiomyopathy and increased neuro-humorally-mediated pulmonary vascular resistance might be hemodynamically at risk for pulmonary edema if given inhaled NO (the same population discussed by Loh et al.).

25. On page 10 of the Office Action, the Examiner states:

> *"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."*

The conclusion presented by the Examiner is not clinically accurate, nor does it accurately reflect the expectations or motivations of a clinician of ordinary skill in the art at the time of the invention. Their expectation would have been quite the opposite. It is by no means "*1) ... 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.*" Firstly, inhaled NO would have no utility in healthy neonates, and is safely used in very severely ill neonates on a routine basis. Secondly, Atz & Wessel teach "using extreme caution or not using NO at all" only in neonates dependent upon right-to-left shunting of blood in order to avoid systemic circulatory collapse, and makes no statement regarding neonates with left ventricular dysfunction **who are not dependent upon right-to-left shunting**. Kinsella et al. do not teach about the safe or unsafe use of inhaled NO in neonates or children, let alone term or near-term neonates not dependent upon right-to-left shunting, but merely noted that they had excluded premature babies with fatal malformations or congenital heart disease from a clinical trial of inhaled NO in premature babies suffering from the respiratory distress of prematurity. Loh et al. teach about the effect of inhaled NO on hemodynamic measurements in adults with advanced heart failure and secondary neuro-humorally-mediated increased pulmonary vascular resistance, and speculate that these adults may be at increased risk for pulmonary edema, but do not teach anything about the use of inhaled NO in term or near-term neonates not dependent upon right-to-left shunting.

26. On page 11 of the Office Action, the Examiner states:

> "*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 is obvious given the teachings above.*" (emphasis in original)

It is inaccurate to represent Loh et al as "*serving as a guidepost for alerting the artisan to adverse events from inhaled NO,*" as Loh et al. reported no adverse events during administration of inhaled NO for 10 minutes to 19 stable patients with advanced heart failure. Rather, Loh et al. speculated that a finding of an elevation in PCWP in a subgroup of such patients could pose an increased risk of pulmonary edema in adults with congestive heart failure due to ischemic or dilated cardiomyopathy. As discussed above, extrapolation of that theoretical risk to neonates and children with different forms of heart disease, different cardiovascular hemodynamics, and different pulmonary vasculature physiology, pathophysiology and pathology was not obvious , as evidenced by the fact that the members of the INOT22 Screening Committee (including Dr. Wessel) who designed the INOT22 study protocol, the approximately 18 Institutional Review Boards and/or Independent Ethics Committee, and 5 National Health Authorities (FDA and national Health Authority for United Kingdom, France, Netherlands and Spain) who reviewed and approved the INOT22 study protocol prior to its initiation, all failed to predict that any untoward effects would be caused by the administration of inhaled NO within a pediatric patient population having left ventricular dysfunction who are not dependent on right-to-left shunting of blood.. Only after being informed of the present invention did the FDA mandate a change to the drug labeling for inhaled NO to include a new warning (separate and distinct from the pre-existing contraindication pertaining to neonates dependent on right-to-left shunting of blood) concerning the use of inhaled NO in patients with pre-existing left ventricular dysfunction.

27. On page 12 of the Office Action the Examiner states:

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."

The arguments by which this conclusion is supported are both medically and scientifically unsound. To summarize, the teaching of Atz & Wessel is inaccurately portrayed by the Examiner due to his confusion of the known risk of systemic vascular collapse if inhaled NO is administered to neonates dependent upon right-to-left shunting of blood, and the opposite case of adults where inhaled NO may be less effective than in children. The Examiner misconstrues Kinsella et al.'s clinical trial inclusion/exclusion criteria as a teaching of risk associated with inhaled NO administration, rather than as a routine practical measure in the design of clinical trials to minimize confounding factors and heterogeneity in the study population. Lastly, the Examiner grossly over-interprets the hemodynamic findings of Loh et al. in adults with ischemic or dilated cardiomyopathy and congestive heart failure (a disease process differing in etiology, physiology, pathophysiology and pathology from childhood congenital heart disease) as "*a guidepost to the artisan*" regarding the use of inhaled NO in children and neonates with pulmonary hypertension and left ventricular dysfunction, but not dependent on right-to-left shunting of blood. These inaccurate and erroneous interpretations of all three supporting publications cited by the Examiner lead the Examiner to draw incorrect conclusions regarding what is or is not taught or suggested by the prior art.

28. On June 28, 2011, I met with Dr. David L. Wessel, the chair of the INOT22 Steering Committee and the senior author of *Atz & Wessel (Seminars in Perinatology 1997, 21(5), pp 441-455.* During our discussion, I informed Dr. Wessel of the 12/820,866 and 12/820,980 patent applications, and the fact that in both pending patent applications, the Examiner was citing Atz & Wessel to allege that it would have been obvious to predict the adverse events and outcomes of the INOT22 study that lead to the inventions claimed in 12/820,866 and 12/820,980.

29. Dr. Wessel disagreed with the Examiner's allegation and found it ironic that his own publication would be cited to suggest the obviousness of the unexpected outcomes of the INOT22 study, when Dr. Wessel himself, the senior author of Atz & Wessel, failed to predict that neonatal and child patients with left ventricular dysfunction who are not dependent on right-to-left shunting of blood would be at increased risk of adverse events when administered inhaled NO. A copy of a June 29, 2011 letter from Dr. Wessel to me stating this opinion is attached hereto as Exhibit 2.

30. 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.

Dated: 7/7/11

Douglas A. Greene, M.D.

EXHIBIT 1

(curriculum vitae)

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 President, Chief Medical Officer, Sanofi-Aventis, Bridgewater, NJ. Overseeing medical, regulatory, pharmacovigilance, 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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Peer-Reviewed Publications (Selected from over 170 peer-reviewed articles):

1. Greene DA, DeJesus PV, Winegrad AI: Effect of insulin and dietary Myo-Inositol on impaired peripheral motor nerve conduction velocity in acute streptozotocin diabetes. *J. Clin. Invest.* 55:1326-1336, 1975.

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.

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diacylglycerol in cultured human retinal pigment epithelial cells. *J. Clin. Invest.* 93:2718-2724, 1994.

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51. The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 287:2563-2569, 2002.

EXHIBIT 2

(June 29, 2011, letter from Dr. David Wessel to Dr. Douglas Greene)

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Children's National
Medical Center

David L. Wessel, MD
Senior Vice President
Center for Hospital-Based Specialties
Ikaria® Distinguished Professor of
Critical Care Medicine

June 29, 2011

Douglas Greene, M.D.,
Executive Vice President and Head of Research & Development
Ikaria, Inc.
Perryville III Corporate Park
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RE: USSN 12/820,866 and 12/820,980
Atz et al., Seminars in Perinatology 1997,21(5), pp 441-455

Dear Doug:

In 2005, I chaired the Steering Committee of the Sponsor, INO Therapeutics LLC (INOT), to establish, design and oversee the INOT22 Study. Presently, I am Chief, Division of Critical Care Medicine and Senior Vice President, Children's National Medical Center, Washington, D.C.[1]

In addition to being the Chair of the INOT22 Steering Committee, I also am the senior author of *Atz et al., Seminars in Perinatology 1997,21(5), pp 441-455* (Atz et al.).

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.

Neither the Atz et al. article that I co-authored, nor the medical literature or medical experience of which I was aware at the time, predict this risk. Instead, Atz et al describes two distinct, independent precautions with respect to the use of iNO. First, with respect to adults, Atz et al. stated that iNO may be more effective in newborns than in older patients, and noted that it

[1] In the interest of full disclosure, I formerly served as a consult for INO Therapeutics LLC, I currently serve without remuneration as a member of the Ikaria Scientific Board of Advisors. In 2010 I was appointed by my institution as the Ikaria Distinguished Professor of Critical Care Medicine.

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Medical Center

should be used with caution in adults with ischemic cardiomyopathy in whom a risk of pulmonary edema is a consideration (see page 462, left column). Second, with respect to neonates, we stated the well-known contraindication (currently found in the INOMAX® prescribing information) that iNO should not be used in newborns dependent upon right-to-left shunting of blood across a patent ductus arteriosus to avoid circulatory collapse. What we did not disclose or predict was 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.

It is ironic that my own publication 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 et al., 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.

Sincerely,

David L. Wessel, M.D.

EXHIBIT 8

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 JAMES S. BALDASSARRRE, M.D.
UNDER 37 C.F.R. § 1.132

I, James S. Baldassarre, do hereby declare the following:

1. I currently hold the position of Vice President of Clinical Research at INO Therapeutics LLC ("INO"), which is a wholly-owned subsidiary of Ikaria, Inc. A copy of 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. In 2004, I was the Medical Monitor responsible for the design and execution of the INOT22 study.

4. 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 a randomized, multi-center study having an expected

enrollment of 150 patients, aged four weeks to 18 years, in approximately 18 study sites over approximately 2 years.

5. The INOT22 study was established and designed by the study sponsor, INO Therapeutics LLC and a Steering Committee comprising international 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

6. The Steering Committee consisted of:

a. David L. Wessel, MD, presently Senior Vice President, The Center for Hospital based Specialties, and Division Chief, Pediatric Critical Care Medicine at Children's National Medical Center, Washington, DC;
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, UK.

7. The original INOT22 study protocol designed by INO and the Steering Committee did not exclude study patients with pre-existing left ventricular dysfunction who were not dependent on right-to-left shunting of blood.

8. After the INOT22 study protocol design, but prior to study initiation and enrollment, the original INOT22 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. In addition, prior to study initiation and enrollment, the original INOT22 study protocol was reviewed by the US Food and

Drug Administration (FDA) and separately reviewed by each national Health Authority (European equivalent to FDA) within the four European countries participating in the INOT22 trial (United Kingdom, France, Netherlands and Spain). In addition, INO regularly requested input and scientific guidance on clinical trials from its own Scientific Advisory Board At no time did any member of the Steering Committee, INOT, an IRB, IEC, individual principal investigator, Advisory Board member, FDA or European Health Authority appreciate, recognize or otherwise suggest that subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt should be excluded from the INOT22 study or that such subjects would be anticipated or predicted to have an increased risk of adverse events or serious adverse events arising from the administration to them of inhaled nitric oxide.

9. Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects. The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as subjects in the research. To accomplish this purpose, IRBs use a group process to review research protocols to ensure protection of the rights and welfare of human subjects of research. An IRB must have at least five members and each member must have enough experience, expertise and diversity to make an informed decision on whether the research is ethical, informed consent if sufficient and the appropriate safeguards have been put in place (see 21 CFR Part 56).

10. In Europe, an Ethics Committee is an independent body in a Member State consisting of healthcare professionals and non-medical members whose responsibility is to protect the rights, safety and well being of human subjects involved in a clinical trial and to provide public assurance of that protection by expressing an opinion on a proposed clinical trial protocol, the suitability of the investigators and adequacy of facilities involved in a trial (see Directive 2001/20/EC).

11. In total, at least 115 individuals experienced in, and responsible for, the review of clinical trial protocols for patient safety, in addition to the FDA and four European Health Authorities reviewed the original INOT22 protocol prior to initiating the INOT22 study. Again, not a single individual or authority suggested, predicted or raised a concern about an increased risk associated with the use of inhaled nitric oxide in study subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt.

12. On the contrary, it was only after unexpected serious adverse events (including at least one death) occurred during the course of the INOT22 study that the study protocol was amended to exclude study subjects with pre-existing left ventricular dysfunction who are not dependent on right-to-left shunt. In particular, the exclusion criteria of the INOT22 study was amended to exclude subjects having an elevated pulmonary capillary wedge pressure greater than 20 mm Hg.

13. 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.

Dated: 7 July 2011

James S. Baldassarre, M.D.

CURRICULUM VITAE

James S. Baldassarre, MD

HOME ADDRESS:	145 Pebble Woods Dr Doylestown, Pa 18901	**PHONE:** 215-348-2835
PERSONAL:	Married (Susan Cohen-Baldassarre) Children Alyssa (18), Julia (16) and Andrew (10) Citizenship: USA	
BUSINESS ADDRESS:	Ikaria/ INO Therapeutics 6 Route 1173 Clinton, NJ 08809	**PHONE:** 908-238-6363
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

PUBLICATIONS:

1. Levison M E and Baldassarre J S: Intra-Abdominal Infections. *Current Practice of Medicine* 1993.
2. Baldassarre J S and Abrutyn E: Antibiotic-Resistant Streptococcus pneumoniae. Infectious Disease Practice 1993; 17 (9).
3. Baldassarre J S and Abrutyn E: Genital Ulcer Disease. *Infectious Disease Practice* 1992; 16 (9); 1-7.
4. Levison M E and Baldassarre J S: Community Acquired Pneumonia: Time to Reassess Treatment Strategies. *Modern Med* 1992; 60:12 86-91.
5. Levison M E and Baldassarre J S: Community Acquired Pneumonia: Keys to Making the Diagnosis. *Modern Med* 1992; 60: 11 42-58.
6. Baldassarre J S, Ingerman M J, Nansteel J, and Santoro J: Development of Listeria Meningitis during Vancomycin Therapy: A Case Report. *J Infect Dis* 1991; 164: 221-222.
7. Baldassarre J S, Update on the Management of Sexually Transmitted Diseases. *Phila Med* 1991; 87-5 230-233.
8. Baldassarre J S and Kaye D: Special Problems in Urinary Tract Infection in the Elderly. *Med Clin North Am* 1991; 75:2 375-390.
9. Baldassarre J S, Johnson CC and Levison M E: Peritonitis: Update on Pathophysiology, Clinical Manifestations and Management. *Clinical Infectious Diseases* 1997; 24(6); 1035-47.

10. Baldassarre JS and Levison ME: Intra-abdominal Infections *Current Practice of Medicine* 1999, vol 2 (4)591-605

11. Baldassarre JS and Pledger GW Clinical Trial Design for New Antiepileptic Drugs: Determination of Dose and Titration Schedules *Rev Contemp Pharmacother* 1999: 10

12. E. Potapov, D. Meyer, M. Swaminathan, M. Ramsay, A. El Banayosy, C. Diehl et al. Use of Inhaled Nitric Oxide After Left Ventricular Assist Device Placement: Results of a Prospective, Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial *J Heart Lung Transplant* 2010 accepted

13. Mercier JC, Hummler H, Durrmeyer X, Sanchez-Luna M, Carnielli V, Field D, Greenough A, Van Overmeire B, Jonsson B, Hallman M, Baldassarre J; EUNO Study Group. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet.* 2010 Jul 31;376(9738):346-54.

14. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel DL; NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension *Pediatr Cardiol.* 2010 Jul;31(5):598-606.

Book Chapters

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.

Abstracts

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.

5. Doose DR, Walker SA, Baldassarre J. The effect of food on the oral bioavailability of topiramate from an investigational paediatric sprinkle formulation. Epilepsia 1997; 38(suppl 3):147.

6. Glauser TA, Olberding L, Clark P, Reife R, Baldassarre J, Conover D. Topiramate monotherapy substitution in children with partial epilepsy. Epilepsia 1996; 37(suppl 4):98.

7. JC Mercier, H. Hummler, X Durrmeyer, M. Sanchez-Luna, V Carnielli, D Field, A. Greenough, B. Van Overmeire, B Jonsson, M Hallman, J Baldassarre, for the EUNO Study Group. The effects of inhaled nitric oxide on the development of bronchopulmonary dysplasia (BPD) in preterm infants: the 'EUNO' multicentre randomised clinical trial. European Academy of Pediatrics; Nice, France October 2008

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]

9. EV Potapov; D Meyer; M Swaminathan; M Ramsay; A El Banayosy; C Diehl; B Veynovich; ID Gregoric; J Baldassarre; M J Zucker; R Hetzer Use of Inhaled Nitric Oxide After Left Ventricular

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

EXHIBIT 9

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

HOME ADDRESS:	145 Pebble Woods Dr Doylestown, Pa 18901	**PHONE:** 215-348-2835
PERSONAL:	Married (Susan Cohen-Baldassarre) Children Alyssa (18), Julia (16) and Andrew (10) Citizenship: USA	
BUSINESS ADDRESS:	Ikaria/ INO Therapeutics 6 Route 1173 Clinton, NJ 08809	**PHONE:** 908-238-6363
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

PUBLICATIONS:

1. Levison M E and Baldassarre J S: Intra-Abdominal Infections. *Current Practice of Medicine* 1993.
2. Baldassarre J S and Abrutyn E: Antibiotic-Resistant Streptococcus pneumoniae. Infectious Disease Practice 1993; 17 (9).
3. Baldassarre J S and Abrutyn E: Genital Ulcer Disease. *Infectious Disease Practice* 1992; 16 (9); 1-7.
4. Levison M E and Baldassarre J S: Community Acquired Pneumonia: Time to Reassess Treatment Strategies. *Modern Med* 1992; 60:12 86-91.
5. Levison M E and Baldassarre J S: Community Acquired Pneumonia: Keys to Making the Diagnosis. *Modern Med* 1992; 60: 11 42-58.
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14. Barst RJ, Agnoletti G, Fraisse A, Baldassarre J, Wessel DL; NO Diagnostic Study Group. Vasodilator testing with nitric oxide and/or oxygen in pediatric pulmonary hypertension *Pediatr Cardiol.* 2010 Jul;31(5):598-606.

Book Chapters

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.

Abstracts

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.

5. Doose DR, Walker SA, Baldassarre J. The effect of food on the oral bioavailability of topiramate from an investigational paediatric sprinkle formulation. Epilepsia 1997; 38(suppl 3):147.

6. Glauser TA, Olberding L, Clark P, Reife R, Baldassarre J, Conover D. Topiramate monotherapy substitution in children with partial epilepsy. Epilepsia 1996; 37(suppl 4):98.

7. JC Mercier, H. Hummler, X Durrmeyer, M. Sanchez-Luna, V Carnielli, D Field, A. Greenough, B. Van Overmeire, B Jonsson, M Hallman, J Baldassarre, for the EUNO Study Group. The effects of inhaled nitric oxide on the development of bronchopulmonary dysplasia (BPD) in preterm infants: the 'EUNO' multicentre randomised clinical trial. European Academy of Pediatrics; Nice, France October 2008

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]

9. EV Potapov; D Meyer; M Swaminathan; M Ramsay; A El Banayosy; C Diehl; B Veynovich; ID Gregoric; J Baldassarre; M J Zucker; R Hetzer Use of Inhaled Nitric Oxide After Left Ventricular

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

EXHIBIT 10

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

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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 40 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

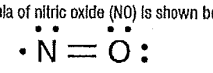
Overdosage with INOmax will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or 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.

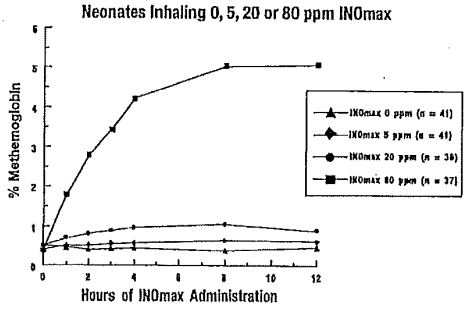
12.4 Pharmacokinetics: Uptake and Distribution

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.

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EXHIBIT 11

Acute pulmonary hypertension in infants and children: cGMP-related drugs

Alain Fraisse, MD, PhD; David L. Wessel, MD

Pharmacologic strategies to reduce pulmonary vascular tone and to treat pulmonary hypertension originally aimed to enrich vascular smooth muscle cyclic adenosine monophosphate levels. Alternatively, increasing cyclic guanosine monophosphate (cGMP) also reduces pulmonary vascular tone. 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. However, not all patients respond to inhaled nitric oxide and withdrawal is sometimes problematic. This has prompted investigation of alternative methods to increase intracellular vascular smooth muscle cGMP. Phosphodiesterase type 5 is particularly abundant in the lung vasculature of patients with severe pulmonary hypertension. Its inhibition with the sildenafil class of drugs is now commonplace. Drugs that affect cGMP metabolism in children with acute pulmonary hypertension are the subject of this review and consensus statement. Oral sildenafil is recommended in postoperative pulmonary hypertension after failed withdrawal of inhaled NO (class I, level of evidence B). The effectiveness of prolonged treatment with sildenafil in documented postoperative pulmonary hypertension is not well established (class IIb, level of evidence C). Sildenafil is indicated in idiopathic pulmonary hypertension, although data have been extrapolated mainly from adult trial (class I, level of evidence A, extrapolated). Recently, completed pediatric trials have seemed to support this recommendation. Longer-acting and intravenous forms of phosphodiesterase type 5 inhibitors, brain natriuretic peptides, and direct soluble guanylate cyclise activators all have appeal, but there is insufficient experience in children with acute pulmonary hypertensive disorders for recommendations on treatment. (Pediatr Crit Care Med 2010; 11[Suppl.]:S37–S40)

Key Words: inhaled nitric oxide; sildenafil; congenital heart disease; postoperative pulmonary hypertension.

In children with pulmonary arterial hypertension (PAH), endothelial dysfunction results in an imbalance of endogenous vasoconstrictors (e.g., endothelin-1) and vasodilators (e.g., nitric oxide [NO]), leading to vascular constriction, *in situ* thrombosis, and vascular remodeling (1–3). Postoperative PAH and endothelial dysfunction are further exacerbated by the effects of cardiopulmonary bypass.

Strategies to reduce pulmonary vascular tone aim to enrich vascular smooth muscle cyclic adenosine monophosphate levels through β agonists (isoproterenol) or with phosphodiesterase type III inhibitors (e.g., milrinone). Alternatively, increasing cyclic guanosine monophosphate (cGMP) with nitro-vasodilators (sodium nitroprusside, nitroglycerin, inhaled NO) also reduces pulmonary vascular tone. Inhaled NO is extremely efficacious in selectively reducing mean pulmonary arterial pressure (PAP) in cardiac patients and is considered standard treatment in most centers. However, not all patients respond to inhaled NO. Its application is limited as it is cumbersome and expensive to consider administering chronically and there is a withdrawal response seen in some postoperative patients. Withdrawal of inhaled NO can lead to significant rebound PAH.

Sildenafil and other phosphodiesterase type 5 (PDE5) inhibitors may play a role in the management of PAH as an alternative or adjunct to current therapies by preferentially inhibiting PDE5. Sildenafil acts by inhibiting the breakdown of cGMP through PDE5, an enzyme that metabolizes intracellular cGMP to inactive 5′-GMP. Other cGMP-related drugs may act through direct guanylate cyclase activation.

Pharmacology of Sildenafil

PDE5 is particularly abundant in the lung vasculature of patients with severe PAH. The main pharmacologic mechanism by which sildenafil achieves its clinical effect is by preferential inhibition of PDE5 that is present in penile tissue, platelets, skeletal muscle, and vascular and visceral smooth muscle, thereby slowing the degradation of cGMP, resulting in lower levels of intracellular calcium and relaxation of vascular smooth muscle. In PAH, this results ultimately in a reduction of PAP and pulmonary vascular resistance (3). However, other factors may play a significant role, such as atrial natriuretic peptide and NO up-regulation (4). One potential contraindication for sildenafil therapy is postcapillary hypertension. When left atrial pressure is elevated, sildenafil could worsen heart failure by increasing pulmonary blood flow through its vasodilator effect, as has been reported with inhaled NO. Although with sildenafil, this might be counterbalanced by its peripheral vasodilator properties (5). Furthermore, sildenafil may be an important regulator for contraction and stress remodeling pathways. Studies in surgical specimens and in rat hypertrophied right ventricular myocardium demonstrated that PDE5 is markedly up-regulated there. Consequently, administration of PDE5 inhibitors increases right

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ventricular inotropy and decreases right ventricular afterload, making them potentially ideal for the treatment of diseases affecting the right ventricle like PAH (6).

Clinical Studies With Oral Sildenafil in Adult PAH

Four randomized, controlled trials have been performed to evaluate sildenafil in patients with "chronic" PAH (7–10), with inclusion of few pediatric patients in one (10). They all reported positive results, primarily based on improvement with exercise, using the 6-min walk test. Following the results of the pivotal study from Galiè and colleagues, the U.S. Food and Drug Administration approved oral sildenafil for therapy for PAH (7). More recently, combination therapy was evaluated in a double-blind, randomized trial in which either oral sildenafil or placebo was given to patients already receiving intravenous epoprostenol. The primary end point (6-min walk test) significantly improved in treated patients relative to placebo, along with secondary end points (hemodynamics, quality of life, and time to clinical worsening) (11).

Experience is very limited in adults with the use of sildenafil in acute PAH after cardiac surgery. Beside anecdotal case reports of oral sildenafil in cardiac surgical patients, only one small, retrospective study demonstrated significantly decreased mean PAP and pulmonary vascular resistances in eight postoperative patients after mitral valve surgery or left ventricular assist device placement (12).

Indications and Clinical Applications of Oral Sildenafil in Pediatric PAH

The first human use of sildenafil for the purpose of treating PAH was more than a decade ago in infants with postoperative PAH after failure to wean inhaled NO. The administration of sildenafil blunted rebound PAH during inhaled NO withdrawal (13). From this first experience, there have been growing anecdotal evidence and widespread adoption of the use of sildenafil to treat PAH in pediatric patients. Studies in support of chronic administration of oral sildenafil in children are only now appearing. In a 12-month open-label, clinical trial, Humpl and colleagues demonstrated significant improvement with hemodynamics and exercise capacity (6-min walk test) in 14 children with idiopathic or secondary PAH (14). More recently, results of a large, prospective, double-blind, placebo-controlled trial in children have been announced (R. J. Barst and D. L. Wessel, personal communication). Improvement in exercise capacity and secondary outcome variables was observed.

In acute PAH, the use of oral sildenafil has been studied during the early postoperative period, mainly to prevent rebound PAH during inhaled NO withdrawal (13, 15). Of particular interest is the prospective, randomized, double-blind, placebo-controlled study of Namachivayam and colleagues. They demonstrated in 15 postoperative infants and children who were receiving inhaled NO after cardiac surgery that a single dose of enteral sildenafil effectively prevented the development of rebound PAH after NO withdrawal, as compared with 14 children allocated to placebo. Sildenafil also reduced the subsequent duration of mechanical ventilation (15). This raises potential interest in the prophylactic administration of sildenafil in such patients with elevated pulmonary vascular resistance and failure to wean inhaled NO. This concept of the prophylactic use of sildenafil to facilitate weaning from NO was further enhanced by Lee and colleagues, who succeeded with oral sildenafil in withdrawing inhaled NO in seven postoperative cardiac children with PAH who had previously failed attempts at inhaled NO weaning (16). In this study, the sildenafil was continued for an average duration of 28 days.

Beside postoperative PAH, sildenafil has been studied in persistent pulmonary hypertension of the newborn, another acute form of PAH. In a placebo-controlled, randomized study in infants >35.5 wks' gestation and <3 days old with severe persistent pulmonary hypertension of the newborn and oxygenation index >25, sildenafil was given at a dose of 1 mg/kg. Oxygenation index improved in all infants within 6 hrs to 30 hrs. All the patients demonstrated a steady improvement in pulse oxygen saturation over time, and none had noticeable effect on blood pressure (17).

Currently, the optimal dose of oral sildenafil in children remains undetermined, but is likely to be in the range of 0.3–1.0 mg/kg three times per day. Bioavailability in a postoperative child may be significantly impaired. Few serious adverse events have been reported in patients on sildenafil, most frequently dizziness, tachycardia, erythema, and drowsiness (18). Of concern is the report of cases of nonarteritic anterior ischemic optic neuropathy in adult patients using sildenafil for erectile dysfunction. This suggests a possible causal relationship with sildenafil, although such population with erectile dysfunction also often presents with generalized endothelial disease, which also constitutes a risk factor for nonarteritic anterior ischemic optic neuropathy. In children, a single case of ischemic optic neuropathy was reported (19). In pediatric PAH, no significant effect on systemic arterial and central venous pressures was seen after incremental doses of 0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, and 2.0 mg/kg (20). Even accidental ingestions of adult pills of Viagra (Pfizer, New York, NY) did not result in significant nor sustained hemodynamic compromise (21).

Guidelines are as follows:

1. Sildenafil is recommended in postoperative PAH after failed withdrawal of inhaled NO (class I, level of evidence B). There are several case reports and small cohort studies (13, 16) as well as one small prospective, randomized, double-blind, placebo-controlled study in 30 patients (15).
2. The effectiveness of prolonged treatment with sildenafil in documented postoperative PAH is not well established (class IIb, level of evidence C). There are limited data on prolonged use of sildenafil in such indication. In the study by Lee and colleagues, sildenafil was continued for an average duration of 28 days (16). Sildenafil may be reasonable for more prolonged perioperative treatment if PAH is hemodynamically significant. Preliminary review of a large, randomized, pediatric trial suggested a good safety profile and potential mid-term benefit. This will likely raise the class of evidence to IIa.
3. Sildenafil is indicated in idiopathic PAH, although data are extrapolated mainly from adult trials (7–10) (class I, level of evidence A, extrapolated). Completed pediatric trials seem to support this recommendation, but final review and publication are pending.

Intravenous Sildenafil

When sildenafil is administered enterally, its bioavailability is only about 40% in healthy subjects (22). In critically ill, postoperative children with even more unpredictable enteral absoption, the intravenous form of sildenafil seems more appropriate. Several preliminary studies in children with intravenous sildenafil have reported encouraging results to lower PAP and pulmonary vascular resistances after cardiac surgery or during cardiac catheterization (23–25). In a recent work investigating the pharmacologic properties of three different doses of intravenous sildenafil on postoperative PAH, the use of a bolus followed by maintenance dose for a maximal duration of 72 hrs was specifically designed for treating PAH in the early postoperative course. Beside the ability for the three doses of intravenous sildenafil to decrease PAP effectively, patients experienced a shorter time to extubation and a shorter intensive care unit length of stay compared with placebo (25). This preliminary and underpowered study cannot be used for recommendations regarding this unapproved form of the drug.

Whereas the majority of animal and human studies on intravenous sildenafil did not document any clinically significant hemodynamic and respiratory side effects (25–28), Schulze-Neick and colleagues reported significant intrapulmonary shunting in postoperative children with PAH after cardiac surgery, although no patient experienced significant hypoxemia (23). In another study, systemic hypotension and impaired oxygenation were observed after 0.35 mg/kg IV of sildenafil in postoperative infants at risk but not suffering from PAH (24). In a dose-finding trial of intravenous sildenafil for newborns with persistent pulmonary hypertension of the newborn, the drug was associated with improved oxygenation and, in some patients, may have prevented the need for standard therapy (inhaled NO) (29).

Second-Generation PDE Inhibitors (Tadalafil, Vardenafil)

With a longer plasma half-life and a more specific and potent PDE inhibition, the new PDE inhibitors are of potential interest in heart failure. To date, no studies in children have been completed and published. In an animal model of persistent pulmonary hypertension of the newborn, tadalafil improves oxygenation (30).

Direct Soluble Guanylate Cyclase Activators

The limitation of NO donors, such as nitroprusside, includes development of tolerance and lack of selectivity for the pulmonary circulation. This has prompted investigation into a new promising class of compounds that directly activate soluble guanylate cyclase. The so-called BAY compounds (e.g., cinaciquat) have been shown to selectively activate the oxidized/heme free enzyme, causing marked vasodilation in diseased organs. Phase II trials are ongoing and no experience in children has been reported.

Nesiritide

The natriuretic hormone system is an important regulator of neurohormonal activation, cardiac diastolic function, and fluid balance, as well as vascular tone. Furthermore, brain natriuretic peptide seems to be a useful marker to monitor disease severity in pediatric PAH (31). Nesiritide (synthetic B-type natriuretic peptide) may have a hemodynamic profile that is comparable with milrinone as a rather nonspecific pulmonary vasodilator. It reduces PAP in adults and improves diuresis and fluid balance in children after congenital surgery but no study has been conducted in acute PAH children (32).

Conclusion

Over the last decade, oral sildenafil has played a growing role in the treatment of acute PAH, emerging as an effective first-line therapeutic agent. Selective pulmonary vasodilation and antiremodeling properties played an important role in its clinical efficacy, whereas very few serious adverse events were associated with its administration in children. Future well-designed trials are needed to clarify the efficacy of sildenafil in acute PAH. Other cGMP-related agents are of potential interest but they require more specific studies to provide information on their therapeutic use in acute PAH.

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(x) Related Proceedings Appendix

There are no decisions in related proceedings.