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Patent Search Report

SEARCH TYPE: **INVALIDITY SEARCH**

TITLE: **US 8,282,966; US 8,293,284 and US 8,431,163**

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All References

Reference #	Title	Company	Authors	Pub / Issue Date
Ichinose et al	Review: Cardiovascular Drugs, Inhaled Nitric Oxide, A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential		Fumito Ichinose, Jesse D. Roberts Jr, Warren M. Zapol	2004

Reference Notes
Retrieved on May 12, 2014 from http //circ.ahajournals.org/content/109/25/3106.full

pg. 3109, col 1, para 8 to pg 3109, col 2, para 1 Inhaled NO has been demonstrated to be a selective pulmonary vasodilator in heart failure patients, although breathing NO was often accompanied by an elevation in LV filling pressure in patients with severe LV dysfunction.37,76 Investigators learned that the elevation in LV filling pressure that occurs with NO breathing is due to the augmentation of filling into a relatively noncompliant LV and is not caused by a negative inotropic effect.77,78 Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema.79

pg. 3107, col 2, para 2 to pg. 3108, col 1, para 1 pg. 3107-3108: In ventilated newborn animals with acute pulmonary hypertension, inhaled NO rapidly increases lung blood flow without causing systemic hypotension.19,20 Similar observations of selective pulmonary vasodilation induced by inhaled NO have been made in ventilated newborn animals with pulmonary hypertension caused by sepsis, lung hypoplasia, or inflammation.21–24 In severely hypoxemic babies with pulmonary hypertension, inhaled NO rapidly increases arterial oxygen tension without causing systemic hypotension 25,26 Randomized controlled studies demonstrated that NO inhalation safely improves arterial oxygen levels and decreases the need for ECMO therapy.27,28 On the basis of these data, the US Food and Drug Administration approved the use of inhaled NO for the treatment of newborns with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

Bernasconi et al	Inhaled nitric oxide applications in paediatric practice		A Bernasconi and M Beghetti	2002

Reference Notes
Retrieved on May 12, 2014 from http //www.ncbi.nlm.nih.gov/pmc/articles/PMC3232511/

pg. 6, para 4 The appropriate dose of iNO to assess pulmonary vascular resistance or treat pulmonary hypertension is not completely defined. Dose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN) and ARDS41–46 and in congenital heart disease.47,48 Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation perfusion mismatch and oxygenation.41 The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Recently, Tworetzky et al suggest an initial dose of 20 ppm for the treatment of PPHN, as it produced an improvement in the pulmonary to systemic arterial pressure ratio, even though 5 ppm iNO was enough to produce peak improvement in oxygenation.49 The exact dose required may indeed vary not only with the pathology but also with duration of therapy. Nelin et al. showed that the effective dose (the smallest dose effective to obtain a beneficial response) decreases as therapy continues.50

pg. 10, para 4-5 There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.103–108 Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.108 This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.103 Such a phenomenon has been confirmed by Rosales et al. in a patient with a small non compliant left atrium and ventricle after repair of total anomalous pulmonary venous return.109 Indeed several years ago, Wood already suggested that an elevation in pulmonary vascular resistance may protect the lungs from pulmonary oedema in severe mitral stenosis.110 A similar postulate may be applicable in patients with severe left ventricular dysfunction or poor left atrial and ventricular compliance. This pathophysiologic explanation has been confirmed, and a direct negative inotropic effect excluded by recent studies111,112 in pigs and in patients with normal left ventricular function.113 Loh et al.,114 in a canine model of cardiomyopathy, showed that iNO decreased pulmonary vascular resistance and increased left ventricular filling pressures, which was related to an increase in pulmonary venous return, without any effect on the contractile or relaxation properties of the left ventricular. This effect was further confirmed by Hayward et al. in patients with dilated cardiomyopathy,115

Even though iNO does not seem to have direct negative inotropic effects, these factors highlight the need for careful observation and intensive monitoring during NO inhalation in patients with left ventricular failure, if left ventricular afterload is not lowered concomitantly.

US5485827	Methods and devices for treating plumonary vasoconstriction and asthma	The General Hospital Corporation (Boston, MA)	Zapol; Warren M. (Concord, MA), Frostell; Claes (Danderyd, SE)	1/23/1996

col 3 ln 58-col 5 ln 9 The invention features methods for the prevention and treatment of asthma attacks or other forms of bronchoconstriction, of acute respiratory failure, or of reversible pulmonary vasoconstriction (i.e., acute pulmonary vasoconstriction or chronic pulmonary vasoconstriction which has a reversible component), in mammals (especially humans), whereby an affected mammal is identified (by, for example, traditional diagnostic procedures, or by the diagnostic method of the invention) and caused to inhale a therapeutically-effective concentration of gaseous nitric oxide or a therapeutically-effective amount of a nitric oxide-releasing compound. A bronchdilator treatment is herein said to be "therapeutically effective" in a given patient if it reduces the patient's airway resistance by 20% or more, as measured by standard methods of pulmonary mechanics. A pulmonary vasodilatory treatment is herein said to be "therapeutically effective" in a given patient if it can induce any one or more of the following: (1) prevention of the onset of pulmonary vasoconstriction following an injury (such as aspiration or trauma) that could be expected to result in pulmonary vasoconstriction; (2) a 20% or more decrease in the patient's .DELTA PVR (the difference between the patient's elevated PVR and "normal" PVR, with normal PVR assumed to be below 1 mmHg.min/liter for an adult human, unless found to be otherwise for a given patient); (3) a 20% or greater decrease in the patient's .DELTA PAP; (4) in adults with acute or chronic respiratory failure (e.g., due to asthma or pneumonia), an improvement in arterial oxygen tensions by at least 10 mm Hg; or (5) in an infant, improved transpulmonary O sub.2 transport, as measured by a 10% or greater increase of upper body (pre-ductal) arterial O sub.2 saturation. PVR is computed by subtracting the pulmonary capillary wedge pressure (PCWP) (or left atrial pressure when available) from the mean pulmonary artery pressure (PAP), and

dividing by the cardiac output (CO). PVR levels as high as 6-20 mmHg.min/liter have been observed in cases of severe ARDS (Zapol et al., N. Engl. J. Med. 296: 476-480, 1977).

The methods herein disclosed are useful for preventing (if given prior to the onset of symptoms) or reversing acute pulmonary vasoconstriction, such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia), as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia. Nitric oxide gas is preferably administered to a mammal with pulmonary vasoconstriction or asthma in accordance with one or more of the following:

(a) administration for at least three minutes (more preferably at least six minutes);

(b) administration in the absence of tobacco smoke;

(c) the inhaled concentration of nitric oxide is at least 1 ppm, more preferably at least 20 ppm, and most preferably at least 80 ppm, with the concentration not exceeding 180 ppm of nitric oxide (such concentration being monitored by a technique such as chemiluminescence);

(d) the nitric oxide is inhaled as a mixture including nitric oxide, oxygen (O.sub 2), and nitrogen (N.sub 2) gases, most preferably having an F.sub.I O.sub.2 (i e., proportion of sub.2 gas, by volume) of 0.21-0.99, the proportion of O.sub.2 in air being 0.21; and

(e) the concentration of NO.sub 2 is monitored and kept within safe limits (e g., less than 1 ppm). Inhalation of gaseous nitric oxide represents a major advance in asthma therapy, since the gas has no particles or droplets to disperse and transport to the respiratory tract. Gases have long free-diffusion pathways, bypass obstructions (such as constricted airways) readily, and dissolve directly in tissue without causing impaction bronchospasm. The beneficial effect of NO gas on bronchial smooth muscle tone is observed immediately following inhalation, making NO a useful first defense against bronchospasm that can be followed, if desired, by inhalation of longer-acting agents.

col 12 ln 44-61 Chronic pulmonary hypertension is characterized by the obstruction or structural narrowing of blood vessels in the lungs. To the extent that the chronic condition of a particular patient is caused or aggravated by spastic constriction of pulmonary vascular smooth muscle or bronchoconstriction, it may be at least partially ameliorated by inhalation of NO: such cases susceptible to treatment with NO, and potentially with systemic vasodilators, are readily identified by their response to a brief NO inhalation test (e.g., six minutes inhaling 80 ppm NO alternating with six minutes inhaling air without added NO, repeated for two to four cycles), while measuring PAP, PCWP, and cardiac output. Responsive cases (e.g., those in which the PVR is reduced by 20% or more) can then be treated either with portable NO inhalation therapy, with inhalation of NO-releasing compounds in solid or liquid form, or with NO-releasing systemic vasodilatory drugs such as glyceryl trinitrate or other non-specific systemic dilators (e g., calcium channel blockers).

Cardiovascular Physiology Concepts	Pulmonary Capillary Wedge Pressure		Richard E. Klabunde, Ph.D.	04/07/2007

Reference Notes
Retrieved on May 8, 2014 from http://web archive.org/web/20090602211655/http://www.cvphysiology com/Heart%20Failure/HF008.htm

pg. 1 t is important to measure PCWP to diagnose the severity of left ventricular failure and to quantify the degree of mitral valve stenosis. Both of these conditions elevate LAP and therefore PCWP. These pressures are normally 8-10 mmHg. Aortic valve stenosis and regurgitation, and mitral regurgitation also elevate LAP. When these pressures are above 20 mmHg, pulmonary edema are likely to be present, which is a life-threatening condition. Note that LAP is the outflow or venous pressure for the pulmonary circulation and increases in LAP are transmitted almost fully back to the pulmonary capillaries thereby increasing their filtration. By measuring PCWP, the physician can titrate the dose of diuretic drugs and other drugs that are used to reduce pulmonary venous venous and capillary pressure, and thereby reduce the pulmonary edema. Therefore, measurement of PCWP can help guide therapeutic efficacy.

Hoehn	Therapy of pulmonary hypertension in neonates and infants		Thomas Hoehn	2007

Reference Notes
Retrieved on May 8, 2014 from http://www.sciencedirect com/science/article/pii/S016372580700068X

pg. 322 9.1. Newborns
PPHN can be most easily diagnosed by echocardiography even by the less experienced echocardiographer. Should this expertise be unavailable, simultaneous (or rapid sequential) transcutaneous measurements of pre- and postductal oxygen saturation can be used. A 5% or greater saturation decrease from pre- to postductal values is highly suggestive of the presence of extrapulmonary right-to-left shunting (Macdonald & Yu, 1992). High oxygen requirements without radiographic evidence of parenchymal pulmonary disease in any newborn infant should lead the clinician to suspect the presence of PPHN.
9.2. Infants
Echocardiography is the most frequently used investigation to screen for PH or to confirm or refute clinically suspected PH. Not only can cardiac causes of PH be identified (if present), the measurement of tricuspid regurgitation velocity enables the estimation of right ventricular pressures (Tulloh, 2006). Cardiac catheterization remains the gold standard for measurement of pulmonary artery pressures. This investigation specifically allows the quantification of the effects of PVR-lowering medications like NO (Atz et al., 1999) or prostacyclin (Mikhail et al., 1997).

Wessel	Current and furture strategies in the treatment of childhood pulmonary hypertension		David L. Wessel	2001

Reference Notes
Retrieved on May 8, 2014 from http://www.sciencedirect com/science/article/pii/S1058981301000753

pg. 303 2.11.15.2. 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 210,211 . The attendant rise in left atrial pressure may produce pulmonary edema 212 . This is not likely to arise from any negative inotropic effect of NO 213 and may be ameliorated with vasodilators or diuretics.

pg. 290 Patients with congenital or acquired heart disease comprise a major diagnostic category for admissions in large pediatric intensive care units across the country, compromising 30ı40% or more of admissions in many centers. Obviously, assessment and treatment of pulmonary hypertension among patients with heart disease can be life saving. The principles of care that apply to this population may be extended to other acute pulmonary hypertension scenarios in intensive care. Table 1 lists the critical care strategies that are utilized for treatment of pulmonary hypertension, culminating in the selection of the most appropriate and specific vasodilators ŽTable 2..

pg. 297 2.11.2. Use in pulmonary hypertensive disorders
Inhaled NO has emerged as an important diagnostic and therapeutic agent in the critically ill patient with pulmonary hypertension. It is a selective pulmonary vasodilator with minimal adverse hemodynamic effects when administered and monitored in a judicious fashion ŽFig. 5.. It has a number of advantages compared with intravenous vasodilators, particularly the absence of systemic hypotension and the salutary effect on intrapulmonary shunting. Its hemodynamic effects have been demonstrated in patients with persistent pulmonary hypertension of the newborn, primary pulmonary hypertension, secondary pulmonary hypertension associated with cardiac disease, cardiac and lung transplantation, and pulmonary thromboemboli, among others.

EP0786264	DEVICES FOR TREAT NG PULMONARY VASOCONSTRICTION AND ASTHMA	GEN HOSPITAL CORP	ZAPOL WARREN M ; FROSTELL CLAES	07/30/1997

pg. 3 ln 39-pg. 4 ln 17 The invention features methods for the prevention and treatment of asthma attacks or other forms of bronchoconstriction, of acute respiratory failure, or of reversible pulmonary vasoconstriction (i.e., acute pulmonary vasoconstriction or chronic pulmonary vasoconstriction which has a reversible component), in mammals (especially humans), whereby an affected mammal is identified (by, for example, traditional diagnostic procedures, or by the diagnostic method of the invention) and caused to inhale a therapeutically-effective concentration of gaseous nitric oxide or a therapeutically-effective amount of a nitric oxide-releasing compound. A bronchdilator treatment is herein said to be "therapeutically effective" in a given patient if it reduces the patient's airway resistance by 20% or more, as measured by standard methods of pulmonary mechanics. A pulmonary vasodilatory treatment is herein said to be "therapeutically effective" in a given patient if it can induce any one or more of the following: (1) prevention of the onset of pulmonary vasoconstriction following an injury (such as aspiration or trauma) that could be expected to result in pulmonary vasoconstriction; (2) a 20% or more decrease in the patient's ?PVR (the difference between the patient's elevated PVR and "normal" PVR, with normal PVR assumed to be below 1 mmHg min/liter for an adult human, unless found to be otherwise for a given patient); (3) a 20% or greater decrease in the patient's ?PAP; (4) in adults with acute or chronic respiratory failure (e.g., due to asthma or pneumonia), an improvement in arterial oxygen tensions by at least 10mm Hg; or (5) in an infant, improved transpulmonary O2 transport, as measured by a 10% or greater increase of upper body (pre-ductal) arterial O2 saturation. PVR is computed by subtracting the pulmonary capillary wedge pressure (PCWP) (or left atrial pressure when available) from the mean pulmonary artery pressure (PAP), and dividing by the cardiac output (CO). PVR levels as high as 6-20 mmHg min/liter have been observed in cases of severe ARDS (Zapol et al., N. Engl. J. Med. 296: 476-480, 1977).
The methods herein disclosed are useful for preventing (if given prior to the onset of symptoms) or reversing acute pulmonary vasoconstriction, such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia), as well as those cases of chronic pulmonary vasoconstriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia. Nitric oxide gas is preferably administered to a mammal with pulmonary vasoconstriction or asthma in accordance with one or more of the following:
(a) administration for at least three minutes (more preferably at least six minutes);
(b) administration in the absence of tobacco smoke;
(c) the inhaled concentration of nitric oxide is at least 1 ppm, more preferably at least 20 ppm, and most preferably at least 80 ppm, with the concentration not exceeding 180 ppm of nitric oxide (such concentration being monitored by a technique such as chemiluminescence);
(d) the nitric oxide is inhaled as a mixture including nitric oxide, oxygen (O2), and nitrogen (N2) gases, most preferably having an FIO2 (i.e., proportion of O2 gas, by volume) of 0.21-0.99, the proportion of O2 in air being 0 21; and
(e) the concentration of NO2 is monitored and kept within safe limits (e.g., less than 1 ppm).

pg. 12 ln 49 - pg. 13 ln 15 The following is a description of an approved experimental protocol for the administration of NO to newborns at Massachusetts General Hospital. Selection of participants: [0070]
Ten patients with persistent pulmonary hypertension of the newborn (PPHN) will be enrolled in the study.
a. Inclusion criteria
infants under 1 week of age
infants with arterial blood sampling sites in the pre- and post-ductal distribution
infants requiring mechanical ventilatory support
respiratory failure as defined by criteria of Short, Clin. Perinatol. 14:737-748, 1987
infants may be receiving infusions of systemic vasodilators and/or buffers (bicarbonate)
b. Exclusion criteria
prematurity as defined by a gestational age <37 weeks by examination, maternal-fetal ultrasound and dates
birth weight <2500 g
pulmonary hypoplasia as suggested by a history of oligohydramnios, congenital diaphragmatic hernia, congenital scoliosis, or features consistent with asphyxiating thoracic dystrophy
unevacuated pneumothorax despite chest tube
pneumopericardium or pneumomediastinum with hypotension
fixed anatomic cardiac and vascular lesions (excluding isolated patent ductus arteriosus and patent foramen ovale)
active pulmonary hemorrhage or platelet count <50,000/mm3
cranial ultrasound within 24 hours of study entry providing evidence of intracranial hemorrhage
hyperviscosity as defined by a venous hematocrit =70% within 24 hours of birth
sepsis, as defined by positive blood cultures for pathogenic organisms
those who do not have informed consent from a parent or legal guardian

EP1516639	Use of NO for treating persistent pulmonary hypertension of the newborn	GEN HOSPITAL CORP	ZAPOL WARREN M ; FROSTELL CLAES	07/25/2007

para [0011] [0011] The invention relates to the use of a gaseous mixture consisting of NO and an insert gas, preferably N2, for the production of an inhalable medicament for treating persistent pulmonary hypertension of the newborn.

para [0013] [0013] The methods herein disclosed are useful for preventing (if given prior to the onset of symptoms) or reversing acute pulmonary vasoconstriction, such as may result from persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, or hypoxia. Nitric oxide gas is preferably administered to a mammal with pulmonary vasoconstriction in accordance with one or more of the following:
(a) administration for at least three minutes (more preferably at least six minutes);
(b) administration in the absence of tobacco smoke:
(c) the inhaled concentration of nitric oxide is at least 1 ppm, more preferably at least 20 ppm, and most preferably at least 80 ppm, with the concentration not exceeding 180 ppm of nitric oxide (such concentration being monitored by a technique such as chemiluminescence);
(d) the nitric oxide is inhaled as a mixture including nitric oxide, oxygen (O2), and nitrogen (N2) gases, most preferably having an FIO2 (i.e., proportion of O2 gas, by volume) of 0.21-0.99, the proportion of O2 in air being 0 21; and
(e) the concentration of NO2 is monitored and kept within safe limits (e.g., less than 1 ppm).

para [0049] [0049] First subject. Through compassionate use, nitric oxide was administered to an infant suffering from persistent pulmonary hypertension and congenital heart disease. As a result of prolonged ventilation, absence of a preductal arterial blood sampling site, and the existence of the atrial-ventricular (AV) canal, the patient was not included in the PPHN study mentioned above

para [0054] [0054] While in the intensive care unit, prostaglandin E1 was infused into the patient in an attempt to dilate the pulmonary vasculature. Despite a standard dosage of prostaglandin, nitric oxide could not be discontinued without the return of dangerously low oxygen saturations. The patient remained on nitric oxide until he could be placed on ECMO. This trial demonstrated the utility of nitric oxide in improving gas exchange in this patient with pulmonary hypertension and congenital heart disease. Subsequent subjects. Two more infants with PPHN have been treated by NO inhalation. Both had an excellent response to breathing NO at 20-80 ppm, showing increases in preductal oxygenation, and both survived longterm. One of the infants showed such rapid improvement with NO inhalation alone that ECMO was altogether avoided.

US5728705	Method of inducing vasorelaxation to treat pulmonary hypertension	The Trustees of Columbia University in the City of New York (New York, NY)	Lawson; Charles A. (Verona, NY), Pinsky; David J. (Riverdale, NY), Smerling; Arthur (New Rochelle, NY), Stern; David M. (Great Neck, NY)	3/17/1998

col 10 ln 35-57 A comparison of the pulmonary vasodilating effects between 8Br-cGMP and NO was performed in the thromboxane (n=3) and oleic acid (n=3) models. In the thromboxane model, NO reduced PVR by 46.8.+-.7 3% while inhaled 8Br-cGMP decreased PVR by 23.9% (p=NS). In the oleic acid model, 8-Br-cGMP tended to be more effective than NO at reducing PVR (-34.3.+-.8.0% for 8-Br-cGMP vs. -18.7.+-.4 5% for oleic acid, p=NS).

Although cardiac outputs increased slightly following 8-Br-cGMP (FIGS. 4A-4H), data of others (11-14) suggests that stimulation of the NO pathway may result in depression of myocardial contractility, which would be of clinical concern in patients with compromised ventricular function. The effect of inhaled 8-Br-cGMP on load-independent measures of cardiac contractility was investigated using a left ventricular conductance catheter and varying preload by controlling blood return via the inferior vena cava. To establish a control for this detection method, intravenous esmolol (40 mg) was given as a bolus injection, which demonstrated a clear-cut negative inotropic effect (FIG. 8C). In contrast, inhalation of 8Br-cGMP at a dose associated with a pulmonary vasodilator effect (30 mu.g/kg) did not alter ventricular performance (n=2) (FIG. 8B).

col 1 ln 64 - col 2 ln 10 This invention provides a method of decreasing pulmonary vascular resistance in a subject which comprises administering endotracheally or endobronchially an effective amount of a drug selected from the group consisting of cyclic nucleotides, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs, thereby decreasing pulmonary vascular resistance.

This invention provides a method of selectively decreasing pulmonary vascular resistance in a subject which comprises administering endotracheally or endobronchially an effective amount of a drug selected from the group consisting of cyclic nucleotides, phosphodiesterase inhibitors, nitric oxide precursors, nitric oxide donors, and nitric oxide analogs, thereby decreasing pulmonary vascular resistance.

WO1992010228	DEVICES FOR TREAT NG PULMONARY VASOCONSTRICTION AND ASTHMA	GEN HOSPITAL CORP [US]	ZAPOL WARREN M [US]; FROSTELL CLAES [SE]	6/25/1992

pg. 6 ln 14 - pg. 8 ln 23 The invention features methods for the prevention and treatment of asthma attacks or other forms of bronchoconstriction, of acute respiratory failure, or of reversible pulmonary vasoconstriction <RTI D=6.1>(i.e.,</RTI> acute pulmonary vasoconstriction or chronic pulmonary vasoconstriction which has a reversible component), in mammals (especially humans), whereby an affected mammal is identified (by, for example, traditional diagnostic procedures, or by the diagnostic method of the invention) and caused to inhale a therapeutically-effective concentration of gaseous nitric oxide or a therapeutically-effective amount of a nitric oxidereleasing compound.A bronchdilator treatment is herein said to be "therapeutically effective" in a given patient if it reduces the patient's airway resistance by 20% or more, as measured by standard methods of pulmonary mechanics. A pulmonary vasodilatory treatment is herein said to be "therapeutically effective" in a given patient if it can induce any one or more of the following: (1) prevention of the onset of pulmonary vasoconstriction following an injury (such as aspiration or trauma) that could be expected to result in pulmonary vasoconstriction; (2) a 20% or more decrease in the patient's <RTI D=7.1>APVR</RTI> (the difference between the patient's elevated PVR and "normal" PVR, with normal PVR assumed to be below 1 <RTI ID=7 2>mmHg#min/liter</RTI> for an adult human, unless found to be otherwise for a given patient); (3) a 20% or greater decrease in the patient's APAP; (4) in adults with acute or chronic respiratory failure (e.g., due to asthma or pneumonia), an improvement in arterial oxygen tensions by at least 10mm Hg; or (5) in an infant, improved transpulmonary <RTI ID=7 3>O2</RTI> transport, as measured by a 10% or greater increase of upper body (pre-ductal) arterial <RTI ID=7.4> 2</RTI> saturation PVR is computed by subtracting the pulmonary capillary wedge pressure (PCWP) (or left atrial pressure when available) from the mean pulmonary artery pressure (PAP), and dividing by the cardiac output (CO). PVR levels as high as 6-20 <RTI ID=7 5>TnmHg#min/liter -have</RTI> been observed in cases of severe ARDS (Zapol et al., N.

Engl. J. Med. 296: 476-480, 1977).

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