Claims 1-30 of the '284 patent are unpatentable under 35 U.S.C. § 103(a) as Obvious Over *Ichinose* in View of *Macrae*, *Germann*, *Neonatal Group*, *Loh*, and *Goyal*.

U.S. Pat. No. 8,293,284	*Ichinose*, *Macrae*, *Germann*, *Neonatal Group*, *Loh*, and *Goyal*
CLAIM 1	
A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:	See Sections (a)-(c) of Claim 1 below.
(a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the patient is not dependent on right-to-left shunting of blood;	*Ichinose* teaches 20 ppm inhaled nitric oxide ("iNO") is a known treatment. Although early studies of inhaled NO in the treatment of pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been realized that concentrations >20 ppm provide little additional hemodynamic benefit in most patients. Ex. 1009 at 3106. At higher inhaled NO_2 doses, pulmonary edema is the major toxicological effect[70] and can result in death.[71] In a simulation using a model lung and commercially available ventilators, production of NO_2 during NO inhalation at 20 ppm appears to be minimal (<0.7 ppm) even with an FiO_2 of 95%.[72] Ex. 1009 at 3109. *Neonatal Group* teaches using echocardiography to identify neonates suffering from hypoxic respiratory failure caused by persistent pulmonary hypertension of the newborn ("PPHN") and in need of iNO treatment and also teaches treating these identified neonates with 20 ppm iNO.

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	Methods Infants born after a gestation of ⩾34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements were eligible for the study. infants were randomly assigned to receive nitric oxide at a concentration of 20 ppm or 100 percent oxygen (as a control). Ex. 1011 at Abstract. Infants born at 34 or more weeks of gestation who required assisted ventilation for hypoxic respiratory failure and had an oxygenation index of at least 25 on two measurements made at least 15 minutes apart were eligible for the trial. Hypoxic respiratory failure was caused by persistent pulmonary hypertension, meconium aspiration, pneumonia or sepsis, respiratory distress syndrome, or suspected pulmonary hypoplasia associated with oligohydramnios and premature rupture of the membranes. [illegible] infants were required to have an indwelling catheter and to undergo echocardiography before randomization. Ex. 1011 at 598. *Macrae* teaches that iNO can be harmful to babies with congenital heart disease, such as those with severe left ventricular dysfunction ("LVD") with right-to-left ductal shunting. It teaches the use of echocardiography to exclude those patients prior to administering iNO. The major randomised, controlled trials of iNO in term or near-term babies have used echocardiography to exclude congenital heart disease as a cause of hypoxaemia prior to exposure to iNO. Babies with such lesions are at best unlikely to benefit from iNO, as cyanosis is due to extra-pulmonary shunting. Inhaled NO exposure may even be harmful in some babies with congenital heart disease, such as those with obstructed total anomalous pulmonary venous drainage or severe left ventricular dysfunction with right-to-left ductal shunting Ex. 1008 at 373-374.
(b) determining that the patient identified in (a) has a	*Ichinose* teaches that there may be negative effects such as pulmonary edema upon administering iNO to a patient.

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pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and	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] Ex. 1009 at 3109. *Loh* teaches measuring a baseline wedge pressure prior to administering iNO. (Wedge pressure may also be called pulmonary capillary wedge pressure ("PCWP"), pulmonary arterial wedge pressure ("PAWP"), or merely "wedge." All the terms refer to the same concept). *Loh* further teaches that patients with LVD have a baseline wedge pressure that is greater than 20 mm Hg. 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. Ex. 1006 at 2780. To establish baseline conditions, patients inhaled room air (F_{IO_2}, 21%; N_2, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (F_{IO_2}, 21%; N_2, 79%) Ex. 1006 at 2781.

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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.

Ex. 1006 at Table 1.

Additionally, *Goyal* teaches measuring wedge pressure in infants.

During cardiac catheterization study, baseline heart rate, systolic, diastolic and mean systemic as well as PA pressures, right atrial pressure and pulmonary capillary wedge pressure (PCWP) were recorded for all the patients

Ex. 1007 at 209.

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	Table 1 Patient characteristics. Data are expressed as median (range) or absolute numbers. BSA, body surface area; Hb, haemoglobin; VSD, ventricular septal defect Age (months) 33 (8–54) M:F 12:7 Weight (kg) 11 (5–17) Height (cm) 89(64–115) BSA (m^2) 0.52 (0.29–0.75) Hb (gm dl^{-1}) 11.2 (10–14) Type of VSD Perimembranous 15 Muscular 2 Multiple muscular 1 Perimembranous with muscular 1 Ex. 1007 at Table 1.
(c) excluding the patient from inhaled nitric oxide treatment based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.	*Ichinose* teaches that there may be negative effects, such as pulmonary edema, upon administering iNO to a patient that has LVD. 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] Ex. 1009 at 3109. *German* teaches that treatment with iNO can be dangerous in patients with LVD. iNO decreases PVR but potentially increases left ventricular preload which may be dangerous in left ventricular dysfunction. In the presence of left heart dysfunction it is increasingly recognised that iNO testing should be performed only after optimising heart failure therapy immediately prior to testing. Ex. 1010 at 1033.
CLAIM 2	
The method of claim 1, wherein step (b) comprises performing echocardiography.	**All the elements of the independent claim from which this claim depends are disclosed in Ichinose, Macrae, Germann, Neonatal Group, Loh, and Goyal as outlined above in Claim 1.**

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