Claims 1, 2, 4, 6-14, 17-23, 31, 32, 34, 35, 37-40, and 42-44 of the '741 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over *Bernasconi* in view of *Loh* and *Goyal*.

U.S. Pat. No. 8,795,741	*Bernasconi, Loh*, and *Goyal*
CLAIM 1	
A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:	*Bernasconi* teaches that there may be negative effects such as pulmonary edema upon administering inhaled nitric oxide ("iNO") to a patient. 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] Ex. 1004 at 8. *Bernasconi* teaches the FDA recommended dose for neonates with hypoxic respiratory failure is 20 ppm iNO. 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 ARDS[41–46] and in congenital heart disease.[47,48] Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Ex. 1004 at 3. Additionally, *Loh* teaches measuring a baseline wedge pressure prior to administering iNO by having patients inhale room air and then performing measurements. (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 and that the wedge pressure increases upon treatment with iNO.

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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.

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 2781, Table 1.

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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.

Ex. 1006 at 2782.

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).

Ex. 1006 at 2782, Table 2.

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	Goyal teaches that wedge pressure may be measured in infants and children. 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. **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. *See also* parts (a)-(e)
(a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;	*Bernasconi* teaches that echocardiography may be used to confirm whether a patient has a condition which may be helped by iNO. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO. Ex. 1004 at 8. *Bernasconi* teaches that a condition that may be helped by iNO treatment is neonatal hypoxic respiratory failure and that the FDA recommended dose for treating neonatal hypoxic respiratory failure is 20 ppm iNO.

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	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 ARDS[41–46] and in congenital heart disease.[47,48] Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Ex. 1004 at 3.
(b) determining that a first patient of the plurality does not have left ventricular dysfunction;	*Bernasconi* teaches that echocardiography may be used to confirm a diagnosis and conduct therapy with iNO, as well as to exclude structural congenital heart disease that may contraindicate the use of iNO. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential. Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO. Ex. 1004 at 8. *Bernasconi* teaches that there are reports of negative effects of iNO treatment in patients with left ventricular dysfunction ("LVD"), specifically pulmonary edema. 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] Ex. 1004 at 8.
(c) determining that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;	*Bernasconi* teaches that there are negative effects of iNO in patients with LVD including a risk of causing pulmonary edema. 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] Ex. 1004 at 8. Additionally, *Loh* teaches measuring a baseline wedge pressure

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