Very-low-dose inhaled nitric oxide: A selective pulmonary vasodilator after operations for congenital heart disease

Inhaled low-dose nitric oxide (2, 10, 20 ppm), together with high inspired oxygen concentration (0.80), was administered after corrective operations 13 times to 10 infants (median age 6 months) who were at risk of postoperative pulmonary hypertension because of their congenital heart disease and left-to-right shunt. Inhaled nitric oxide, even in a very low dose (2 ppm), caused selective pulmonary vasodilatation. The pulmonary/systemic artery pressure ratio was a predictor of the response to nitric oxide, with a greater response being seen in those with a high ratio ($\geq$0.50). In children with a high pulmonary/systemic pressure ratio, the mean pulmonary vascular resistance index fell by 37% to 42%, accompanied by only a 10% fall in the systemic vascular resistance index but a 14% to 16% rise in mean cardiac index. No toxicity was seen in any subject. This exciting new therapy may prove to be an important adjunct in the management of postoperative pulmonary hypertension in the child with congenital heart disease. (J THORAC CARDIOVASC SURG 1994;108:487-94)

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Pulmonary vascular disease remains a significant cause of morbidity and mortality in children with congenital heart disease.[1] In addition, children with certain types of congenital heart disease[2] and potentially reversible pulmonary vascular disease may still have life-threatening reactive pulmonary hypertensive crises in the immediate postoperative period,[3] despite a technically successful corrective operation.[4] Conventional management involves the administration of a high fractional inspired oxygen concentration, lung volume recruitment, hyperventilation, inotropic drugs, and vasodilators.[5-7] Unfortunately, because currently available vasodilators lack specificity for the pulmonary vascular bed, their administration may further compromise outcome by inducing systemic hypotension. Inhaled nitric oxide (NO) diffuses from the alveolus to act directly on pulmonary vascular smooth muscle causing vasodilation, and because inhaled NO is inactivated on exposure to hemoglobin,[8] it should not theoretically cause systemic vasodilation.

In clinical studies, inhaled NO has been shown to be a selective pulmonary vasodilator in adults with primary pulmonary hypertension,[9] neonates with persistent pulmonary hypertension,[10] and children with uncorrected heart disease and elevated pulmonary vascular resistance.[11]

We[12] have previously described a safe and effective method for the administration of inhaled NO to infants receiving ventilatory support. We now report the effect of inhaled NO, administered by this method, on children at risk of postoperative pulmonary hypertension after correction of congenital heart lesions associated with high preoperative pulmonary flow or pressure, or both.

Methods

Patients. Patients undergoing a corrective operation for a left-to-right shunt lesion, who were considered at high risk for postoperative pulmonary hypertension, were recruited prospectively. Inclusion was based on preoperative studies that revealed

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Table I. *Baseline characteristics in 10 subjects who received inhaled NO (two exposures in three patients)*

Patient	*Sex*	*Age (mo)*	*Diagnosis*	*Hours postop.*	*PAP initial (mm Hg)*	*PAP/SAP initial*	*PVR/SVR initial*	*Dopamine (μg/kg/min)*	*GTN (μg/kg/min)*
Subjects with high PAP/SAP ≥0.50									
1	M	2	AVSD†	3	32	0.57	0.53	6	2
1*	M	2	AVSD†	48	46	0.82	0.98	4	—
2	M	2	TAPVD	3	44	0.61	0.59	—	—
3	F	13	TAPVD	12	36	0.69	0.65	15	3
4	F	6	AVSD	6	43	0.53	0.52	12	8
4*	F	10	AVSD	6	29	0.60	0.50	6	8
5*	F	21	VSD†	20	32	0.50	0.41	—	—
Mean		8.0			37.4	0.62	0.60		
SEM		2.7			2.6	0.04	0.07		
Subjects with low PAP/SAP <0.50									
6	M	11	Truncus	3	23	0.31	0.22	10	—
7	F	3	TAPVD	18	18	0.45	0.29	—	—
8	M	6	VSD	6	23	0.49	0.30	6	—
5	F	21	VSD†	7	28	0.48	0.40	5	—
9	M	7	AVSD†	10	25	0.35	0.23	8	—
10	M	2	DORV/APW	4	21	0.32	0.18	—	3
Mean		8.3			23	0.41	0.27		
SEM		2.9			1.4	0.03	0.03		

NO, Nitric oxide; *PAP*, mean pulmonary artery pressure *SAP*, mean systemic artery pressure; *PVR*, pulmonary vascular resistance; *SVR*, systemic vascular resistance; *GTN*, glyceryl trinitrate; *AVSD*, atrioventricular septal defect; *TAPVD*, total anomalous pulmonary venous drainage; *VSD*, ventricular septal defect; *DORV*, double-outlet right ventricle; *APW*, aortopulmonary window; *SEM*, standard error.

*Second exposure in same patient.

†Down syndrome.

a high pulmonary artery pressure (PAP), greater than half the systemic arterial pressure (SAP), and/or high pulmonary blood flow (pulmonary/systemic shunt ratio greater than 2:1) when evaluated by echocardiography or cardiac catheterization, or both. Ten consecutive children were recruited and 13 studies were done. All 10 patients were studied on the first postoperative day during a period of hemodynamic stability, regardless of the PAP/SAP ratio, at a time when the SAP had been constant (±10%) for at least 60 minutes and the difference between the peripheral and core temperatures was less than 2° C. In addition, three patients were studied twice. Patient 4 was restudied after reoperation for left atrioventricular valve incompetence, 4 months after an initial study following repair of atrioventricular septal defect. Patient 5 was studied on successive days, the first study on the day of the operation when the PAP/SAP was low and subsequently on the second postoperative day, because the PAP/SAP ratio rose to 0.50 or more. Patient 1 was studied routinely on the first postoperative night and again 2 days later during an acute pulmonary hypertensive crisis.

The subjects had the following cardiac lesions: atrioventricular septal defect ($n = 3$), perimembranous ventricular septal defect ($n = 2$), nonobstructive total anomalous pulmonary venous drainage ($n = 3$), truncus arteriosus ($n = 1$), and double-outlet right ventricle with aortopulmonary window ($n = 1$). Three children (five studies) had Down syndrome (Table I). None had evidence of parenchymal lung disease or major extracardiac abnormality. The group comprised six boys and four girls, aged 2 to 21 months (median age 6 months). Institutional ethical approval had been received and informed consent was obtained in each case from the parent(s).

Surgery and intensive care. Surgical repair and anesthetic practice were unchanged for the study and the use of inotropic agents or vasodilators was not restricted (see Table I). At the completion of the surgical repair, a 3F double-lumen thermodilution catheter (model 94-011-3F, Baxter Healthcare Corporation, Irvine, Calif.) was positioned under direct vision in the proximal main pulmonary artery for pressure monitoring and cardiac output measurement.

Systemic arterial, pulmonary arterial, right atrial, and left atrial pressures were continuously monitored via indwelling catheters, high-pressure tubing, and fluid-filled transducers with the Merlin Component Monitoring System (Hewlett-Packard, Boeblingen, Germany). After postoperative echocardiography had excluded residual intracardiac shunting, cardiac output was measured, before and after each NO exposure, by triplicate thermodilution (1 ml normal saline 0° to 4° C) and computed by means of the Hewlett-Packard system. Pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) were calculated from standard equations. Vascular resistance was expressed in Wood units (Um^2, where Um^2 = mm Hg/L/min · m^2).

All subjects were intubated, given vecuronium (1 to 2 μg/kg per minute) for muscle relaxation, sedated with morphine (20 to 40 μg/kg per hour), and their lungs mechanically ventilated with a continuous-flow, time-cycled, pressure-limited infant ventilator (Babylog 8000, Drägerwerk Aktiengellschaft, Lübeck, Germany) and standard disposable ventilator circuit (Intersurgical, Surrey, England). The fractional inspired oxygen concentration was preset and maintained at 0.80 throughout the study. Oxygen analysis was performed immediately proximal to the endotracheal tube.

NO dosage and administration. All studies used a protocol

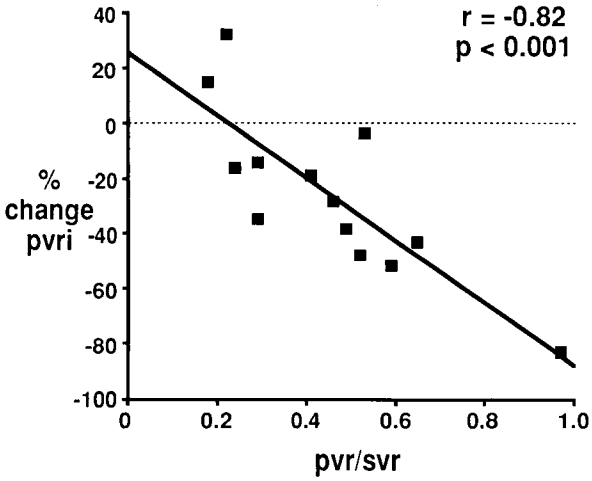

Fig. 1. Correlation of initial PVR/SVR ratio and maximal percentage change after exposure to inhaled NO ($r = -0.82$, $p < 0.001$).

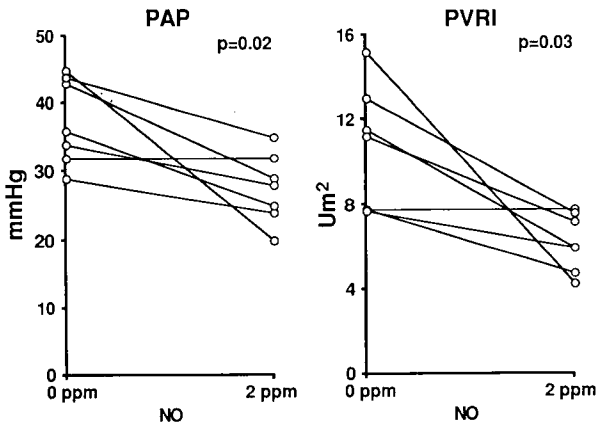

Fig. 2. Responses in PAP and PVRI for the seven patients with an initial PAP/SAP ratio ≥ 0.50, on exposure to inhaled NO at 2 ppm. Both parameters fell significantly: PAP ($p = 0.02$) and PVRI ($p = 0.03$), see text.

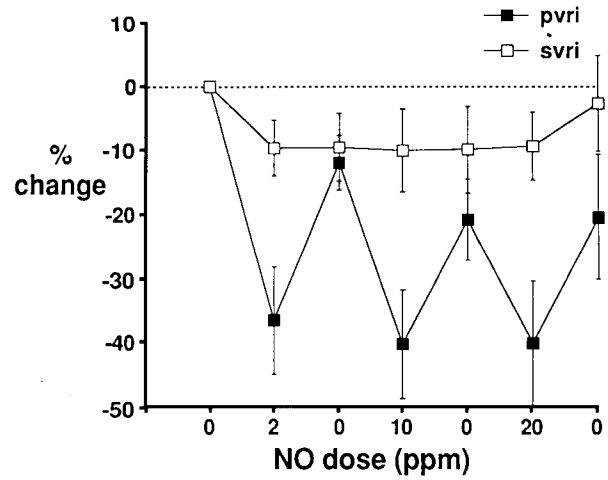

Fig. 3. Mean percentage change in PVRI and SVRI after exposure to increasing doses of inhaled NO (2, 10, and 20 ppm), with intervening 0-exposure control periods, in seven subjects with PAP/SAP ratio ≥ 0.50.

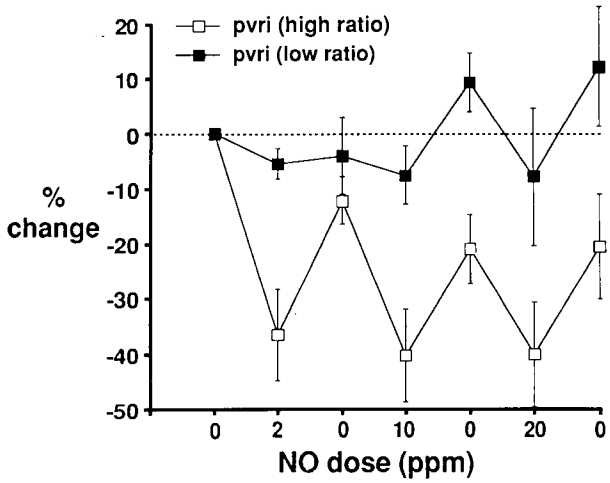

Fig. 4. Percentage change in PVRI for both the low and high PAP/SAP ratio groups after exposures to increasing doses of inhaled NO (2, 10, and 20 ppm) with intervening control periods.

of three NO doses (2, 10, and 20 ppm), each for 10 minutes, with intervening 0-exposure control periods of 10 minutes. NO gas, obtained in a mixture with nitrogen (N_2) at 1000 ppm NO (BOC-Special Gases, Surrey, England), was titrated via a calibrated N_2 flowmeter (KDG Instruments, Surrey, England) and added directly into the inspiratory limb of the ventilator circuit 25 cm proximal to the endotracheal tube. The concentrations of inspired NO and its toxic oxidative product nitrogen dioxide (NO_2) were analyzed by chemiluminescence on samples of circuit gas that were continuously aspirated from a site 25 cm distal to the patient. A commercially available device, originally designed for environmental monitoring (model 42H, Thermo Environmental Instruments, Franklin, Mass.), was used. The analyzer was calibrated at 0 and 10 ppm NO before each study. Because exposure to high-dose NO may also lead to an elevation in the methemoglobin,[13] arterial blood gases and methemoglobin percentage (IL-1306 blood gas analyzer, IL-482 Co-Oximeter, Instrumentation Laboratory, Lexington, Mass.) were analyzed at the beginning and end of each NO exposure.

Statistical analysis. The clinical syndrome of postoperative pulmonary hypertension was diagnosed when the mean PAP was greater than half the mean SAP. According to this clinical definition, subjects were allocated either to a high ratio group (PAP/SAP ≥ 0.50) or a low ratio group (PAP/SAP < 0.50). Hemodynamic parameters for each group, before and after each NO exposure, were described as mean $\pm$ standard error of the mean. The effects of nitric oxide at 2 ppm on PAP, PVRI,

Table II. *Hemodynamic parameters for each subject at baseline 0 exposure and after 2, 10, and 20 ppm inhaled NO*

	PAP (mm Hg)				*SAP (mm Hg)*				*HR (beats/min)*			
Patient	*0*	*2*	*10*	*20*	*0*	*2*	*10*	*20*	*0*	*2*	*10*	*20*
Subjects with high PAP/SAP ≥0.50												
1	32	32	31	33	56	54	58	55	152	146	144	141
1*	46	20	17	14	56	54	50	56	168	151	146	135
2	44	35	33	33	72	78	80	77	132	146	152	157
3	36	25	24	22	52	52	60	56	136	138	140	140
4	43	29	28	26	81	71	71	56	210	204	204	187
4*	29	24	26	26	48	51	46	54	188	185	181	187
5*	32	28	28	27	67	67	69	72	142	134	134	145
Mean	37.4	27.6	26.7	25.9	61.7	61.0	62.0	60.9	161	157	157	156
SEM	2.6	1.9	2.0	2.5	4.5	4.1	4.6	3.6	11.0	9.9	9.7	8.4
Subjects with low PAP/SAP <0.50												
6	23	23	22	22	74	70	70	68	157	155	155	151
7	18	18	15	17	40	40	37	39	105	101	98	99
8	23	22	23	22	47	57	58	52	153	155	166	162
5	28	28	29	35	57	61	71	72	134	135	148	170
9	25	23	21	20	62	57	49	51	187	183	179	186
10	21	21	19	21	66	70	65	59	145	142	144	142
Mean	23.0	22.5	21.5	22.8	57.7	59.2	58.3	56.8	146	145	148	151
SEM	1.4	1.3	1.9	2.5	5.1	4.5	5.4	4.9	11.1	11.1	11.3	12.2

PAP, Mean pulmonary artery pressure; *SAP*, mean systemic artery pressure; *HR*, heart rate; *LAP*, left atrial pressure; *PVRI*, pulmonary vascular resistance index; *SVRI*, systemic vascular resistance index; *SEM*, standard error.

*Second exposure in same patient.

and SVRI were compared to baseline by means of the Student's *t* test for paired samples. To investigate whether a dose-response relationship exists between NO dose over the range 2 to 20 ppm and the change in PVRI, we performed an analysis of variance for repeated measures. The relationship between initial PVR/SVR ratio and percentage change in PVRI after NO inhalation was calculated by linear regression. Statistical significance was inferred at a p value less than 0.05.

Results

In this study, inhaled NO at a dose of 2 to 20 ppm acted as a selective pulmonary vasodilator, and the initial PVR/SVR ratio for each subject correlated well with the maximal pulmonary vasodilator response (Fig. 1). Hemodynamic data for all patients before and after exposure to inhaled NO at 2, 10, and 20 ppm are summarized in Table II.

For the group as a whole, exposure to 2 ppm inhaled NO resulted in a significant fall in PAP ($p = 0.02$) and PVRI ($p = 0.03$) when compared with the baseline (0 ppm) exposure. The SVRI at 2 ppm, however, was not significantly different from baseline ($p = 0.09$). In those with an initially high PAP/SAP ratio ($n = 7$), the results were similar, with significant falls in PAP and PVRI (Fig. 2) but not SVRI ($p = 0.12$) after administration of inhaled NO at 2 ppm. In the low ratio group, however, inhaled NO did not cause any significant changes in any of these parameters.

PVRI was lower than baseline for each exposure to inhaled NO in the group as a whole; however, there was no dose-response relationship between inhaled NO and fall in PVRI, and analysis of variance for repeated measures revealed no significant difference in the PVRI values at all three NO doses ($p > 0.80$).

No clinical evidence of toxicity was seen during any administration of inhaled NO. In all subjects the methemoglobin level was always less than 2% and the NO_2 always less than 2 ppm. (Occupational exposure guidelines issued by the Centers for Disease Control[14] recommend an upper exposure limit to NO_2 of 5 ppm over an 8-hour period.)

Group A: PAP/SAP 0.50 or more. Seven subjects had a high postoperative PAP/SAP ratio (mean 0.62 ± 0.04; range 0.51 to 0.82), a mean PAP of 37.4 ± 2.6 mm Hg; range 29 to 46 mm Hg), and a mean PVRI of 10.2 ± 1.8 Um^2 (range 7.6 to 15.0 Um^2). The mean SVRI was 17.7 ± 3.0 Um^2 (range 14.6 to 22.1 Um^2) and the mean PVR/SVR ratio was 0.60 ± 0.07 (range 0.41 to 0.98). After inhalation of NO at 2, 10, and 20 ppm, the mean decreases from baseline in the PVRI were −37%, −41%, and −42% and in the SVRI −10%,

LAP (mm Hg)				*PVRI (Um²)*				*SVRI (Um²)*			
0	*2*	*10*	*20*	*0*	*2*	*10*	*20*	*0*	*2*	*10*	*20*
8	8	8	9	7.8	7.8	7.5	7.8	15	14	15	14
5	5	4	5	15	4.3	3.5	2.6	16	13	12	14
8	8	8	7	13	7.6	6.3	7.6	22	18	17	19
6	5	5	5	4.5	2.9	2.9	2.7	7	7	8	8
2	2	1	1	17	7.9	9.3	7.1	33	33	30	16
11	11	14	13	7.6	4.8	4.1	3.7	16	16	12	12
8	8	8	7	6.8	5.7	5.2	5.5	17	17	16	18
6.9	6.7	6.9	6.7	10.2	5.9	5.5	5.3	18.0	16.9	15.7	14.4
1.1	1.1	1.5	1.4	1.8	0.7	0.9	0.9	3.0	3.0	2.6	1.4
9	9	9	7	3.1	3.2	3.3	4.4	14	14	15	17
9	8	7	10	2.3	2.3	1.8	1.5	8	8	7	6
12	11	11	10	3.5	3	3.2	3.3	12	13	12	11
9	10	11	9	6.3	5.7	5	5.9	16	16	17	14
12	10	9	10	4.9	4.5	4.1	3.1	21	15	12	12
11	11	10	11	2	1.7	2.2	2.3	11	10	13	11
10.3	9.8	9.5	9.5	3.7	3.4	3.3	3.4	13.7	12.7	12.7	11.8
0.6	0.5	0.6	0.6	0.7	0.6	0.5	0.6	1.8	1.3	1.4	1.5

−10%, and −9%, respectively (Fig. 3). The mean PVR/SVR ratio fell by −31%, −34%, and −33% and the mean cardiac index increased 14%, 16%, and 14%. The maximal response was seen in patient 1, a 2-month-old boy with Down syndrome, after repair of an atrioventricular septal defect. Despite continued paralysis, mechanical ventilation, and a high fractional inspired oxygen concentration, the boy had a pulmonary hypertensive crisis (mean PAP 46 mm Hg, PVR/SVR ratio 0.97) on the third postoperative evening after cessation of intravenous vasodilators. Administration of inhaled NO according to the described protocol resulted in dramatic clinical improvement. The PAP dropped to 20, 17, and 14 mm Hg after exposure to 2, 10, and 20 ppm NO, respectively (see Table II), representing an 83% decrease in PVRI after the largest dose. The SVRI fell by up to 24% (at 10 ppm) and the cardiac index increased 30%.

Group B: PAP/SAP less than 0.50. Six subjects had an initial PAP/SAP ratio of less than 0.50. The mean PAP in this group was 23 ± 1.4 mm Hg (18 to 28 mm Hg), the mean PAP/SAP ratio was 0.41 ± 0.03 (0.31 to 0.49), the mean PVRI was 3.7 ± 0.7 Um^2 (2.0 to 6.3 Um^2), the mean SVRI was 13.7 ± 1.8 Um^2 (7.9 to 20.8 Um^2), and the mean PVR/SVR ratio was 0.27 ± 0.03 (0.18 to 0.41). Exposure to inhaled NO at 2, 10, and 20 ppm resulted in a modest response with a mean decrease from baseline in PVRI of −5%, −7%, and −8% (Fig. 4). The SVRI fell −5%, −1%, and −9%, the PVR/SVR ratio −12%, −3%, and 0%, and the cardiac index increased 12%, 9%, and 16%, respectively.

Discussion

Inhaled NO in very low doses (2 to 20 ppm), when used as an adjunct to routine postoperative intensive care and high fractional inspired oxygen concentration, caused selective pulmonary vasodilatation in infants with congenital heart disease and raised PVR after corrective operations, especially in those with a high PAP/SAP ratio.

In 1980 Furchgott and Zawadzki[15] demonstrated the importance of an intact endothelium in controlling vasomotor tone. A labile endothelium-derived relaxing factor has been subsequently identified as endogenous NO.[16-18] NO activates guanylate cyclase in the smooth muscle cell, leading to an elevation of cyclic guanosine monophosphate and consequently smooth muscle relaxation.[19] Basal release of NO appears to be fundamental for constant active vasodilation.[20, 21] In the lung, pulmonary endothelial damage is an early histologic event in children with congenital heart disease and pulmonary hypertension,[22, 23] and children with prolonged high pressure and flow in the pulmonary circulation exhibit physiologic evidence of impaired endothelial function by having a reduced pulmonary vasodilator response to acetylcho-

line.[24] Endothelial dysfunction may therefore be an important contributing factor in postoperative pulmonary hypertension, with a consequent loss of local endothelium-derived relaxing factor–NO vasodilator activity.[25] In this setting, exogenous NO is theoretically attractive. Arteries with endothelial damage are particularly sensitive to exogenous NO,[26] and vasodilation after NO inhalation is expected to be selective for the pulmonary vasculature because of the rapid inactivation of NO by hemoglobin in the pulmonary capillaries.

The clinical application of inhaled NO began after publication of lamb studies,[27, 28] which demonstrated pulmonary vasodilation with NO doses in the range 5 to 180 ppm after hypoxia- or pharmacologically induced pulmonary vasoconstriction. Inhaled low-dose NO has been used as a selective pulmonary vasodilator after operations for acquired heart disease in adult patients with chronic pulmonary hypertension,[29] and preliminary case reports by us[30, 31] and others[32] have suggested that inhaled NO has a role in the management of perioperative and postoperative pulmonary hypertension in children with congenital heart disease.

We have now extended these observations by using low-dose inhaled NO in 10 children (13 cases) with a perceived high risk of postoperative pulmonary hypertension. The major findings are, first, that the magnitude of response to inhaled NO is associated with the initial ratio of pulmonary-to-systemic resistance; the higher the ratio the greater the response. Second, our subjects responded equally well to very-low-dose NO (2 ppm) and to a higher dose of NO (20 ppm). This lack of a clear dose-response relationship is surprising given the previous reports of a reproducible dose response in earlier animal and human studies.[11, 28, 33] We chose doses of NO based on pilot data suggesting efficacy in the dose range 2 to 10 ppm. Other workers[9-11, 34] have reported selective pulmonary vasodilation in human beings using 20 to 80 ppm, and Kinsella and associates[35] reported a good response to NO at 6 ppm in neonates with persistent pulmonary hypertension but have not commented on infants with congenital heart disease. In our study of a small number of children in the postoperative setting, we have observed important pulmonary vasodilation at an even lower dose (2 ppm); however, the statistical power of the study is insufficient to exclude a dose-response relationship between 2 and 20 ppm NO. Firm conclusions therefore regarding a dose response at very low doses will require further study.

The effectiveness of inhaled NO in a dose of 2 ppm in this study is important, because the combination of high inspired oxygen and high NO dose may lead to toxic production of NO_2, and current guidelines advise the avoidance of NO_2 above 5 ppm.[14, 36] Some investigators have recently suggested that even lower levels of NO_2 (1 to 2 ppm) may affect pulmonary immune cells.[37, 38] To ensure accurate measurement, the chemiluminescence analyzer was carefully calibrated (10 ppm NO/balance N_2, BOC-Special Gases, Surrey, England) before each study and is of the same type or model used in previous reports. The hemodynamic effect of inhaled NO at each dose was first measured after a 10-minute exposure period. The analyzer readings were stable and the hemodynamic measurement technique was unchanged for each condition. The dosage protocol was not randomized. The lowest dose (2 ppm) was always applied first, and therefore carry-over effect from a higher exposure cannot be invoked as an explanation for this significant effect at the very low dose.

In the group with a higher PAP/SAP ratio, the response to inhaled NO was dramatic, relatively selective for the pulmonary circulation, and therefore likely to be clinically important. Although inhaled NO should theoretically be selective for the pulmonary circulation, exposure to inhaled NO in subjects with a high PAP/SAP ratio led to an initial fall in SVR, which then remained stable with successive NO exposures (see Fig. 3). In our study, SVRI is a derived value, with the thermodilution-measured cardiac output used as the denominator ((Systemic artery pressure − Left atrial pressure)/Cardiac Index). The small observed reduction in SVRI may therefore be real or an artifact, as any augmentation in pulmonary artery flow was read as an increase in cardiac output. A demonstrable increase in pulmonary artery flow resulting from a reduction in right ventricular afterload may represent a true increase in cardiac output or may just reflect an increased left-to-right shunt through a previously undetected residual septal defect, which only becomes apparent after pulmonary vasodilation. The change in cardiac output may also simply reflect the error inherent in the thermodilution technique. Alternatively, and contrary to current understanding, inhaled NO may have downstream systemic effects. In any case, the change in SVRI was small and further studies in a similar population may clarify whether systemic vasodilation is a common occurrence.

The use of inhaled NO in infants with a PAP/SAP ratio less than 0.50 led to only a modest response compared with those of infants with high PAP/SAP ratios (see Fig. 4). Previous investigations in normal adult volunteers have shown similar findings: that inhaled NO has no effect at rest, when PAP is low, but does cause a selective reduction in PVR after hypoxia-induced pulmonary vasoconstriction.[39]

An impressive response (−83% change in PVRI) to inhaled NO seen during a life-threatening pulmonary

hypertensive crisis in patient 1* contrasted with a poor response (−4% change in PVRI) in the same infant seen in the first NO trial. This difference may be explained by the lower initial PAP/SAP ratio in the first study.

Conclusion

Infants with pulmonary hypertension after cardiac operations show marked selective pulmonary vasodilation in response to inhaled NO in the dose range 2 to 20 ppm. The effectiveness of very-low-dose inhaled NO (2 ppm) may be important in minimizing toxicity. Others[35, 40] have reported safe and effective prolonged administration of inhaled NO in the setting of neonatal pulmonary hypertension and the adult respiratory distress syndrome, without noting important adverse effects. This novel therapy may therefore prove important in the management of postoperative pulmonary hypertension in the child with corrected congenital heart disease.

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