Inhaled Nitric Oxide in Congenital Heart Disease

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Background. **Congenital heart lesions may be complicated by pulmonary arterial smooth muscle hyperplasia, hypertrophy, and hypertension. We assessed whether inhaling low levels of nitric oxide (NO), an endothelium-derived relaxing factor, would produce selective pulmonary vasodilation in pediatric patients with congenital heart disease and pulmonary hypertension. We also compared the pulmonary vasodilator potencies of inhaled NO and oxygen in these patients.**

Methods and Results. **In 10 sequentially presenting, spontaneously breathing patients, we determined whether inhaling 20–80 ppm by volume of NO at inspired oxygen concentrations (F_{IO_2}) of 0.21–0.3 and 0.9 would reduce the pulmonary vascular resistance index (Rp). We then compared breathing oxygen with inhaling NO. Inhaling 80 ppm NO at F_{IO_2} 0.21–0.3 reduced mean pulmonary artery pressure from 48±19 to 40±14 mm Hg and Rp from 658±421 to 491±417 dyne · sec · cm^{-5} · m^{-2} (mean±SD, both $p<0.05$). Increasing the F_{IO_2} to 0.9 without adding NO did not reduce mean pulmonary artery pressure but reduced Rp and increased the ratio of pulmonary to systemic blood flow ($\dot{Q}_p/\dot{Q}_s$), primarily by increasing $\dot{Q}_p$ ($p<0.05$). Breathing 80 ppm NO at F_{IO_2} 0.9 reduced mean pulmonary artery pressure and Rp to the lowest levels and increased $\dot{Q}_p$ and $\dot{Q}_p/\dot{Q}_s$ (all $p<0.05$). While breathing at F_{IO_2} 0.9, inhalation of 40 ppm NO reduced Rp ($p<0.05$); the maximum reduction of Rp occurred while breathing 80 ppm NO. Inhaling 80 ppm NO at F_{IO_2} 0.21–0.9 did not alter mean aortic pressure or systemic vascular resistance. Methemoglobin levels were unchanged by breathing up to 80 ppm NO for 30 minutes.**

Conclusions. **Inhaled NO is a potent and selective pulmonary vasodilator in pediatric patients with congenital heart disease complicated by pulmonary artery hypertension. Inhaling low levels of NO may provide an important and safe means for evaluating the pulmonary vasodilatory capacity of patients with congenital heart disease without producing systemic vasodilation. (*Circulation* 1993;87:447–453)**

KEY WORDS • **hypertension, pulmonary artery • congenital heart disease • endothelium-derived relaxing factor • nitric oxide**

Congenital heart lesions that increase pulmonary blood flow[1] or cause pulmonary venous obstruction[2] may produce pulmonary artery smooth muscle hypertrophy and hyperplasia[3] and pulmonary vasoconstriction. Current drug therapies for pulmonary artery hypertension are nonselective and dilate systemic blood vessels. Unless surgical correction of the underlying congenital heart lesion occurs early in life, pulmonary vasoconstriction may persist, progress to vascular obliteration, and produce a high morbidity.[4]

Nitric oxide (NO), which has identical activity as endothelium-derived relaxing factor,[5,6] is produced from L-arginine[7] by endothelial NO synthase.[8] NO diffuses into subjacent vascular smooth muscle and mediates vasodilation by stimulating soluble guanylate cyclase to produce cyclic GMP (cGMP).[9,10] Inhaling low levels of NO reverses hypoxic pulmonary vasoconstriction in lambs weighing 25–35 kg[11] and adult volunteers[12] and reduces pulmonary vascular resistance in adults with primary pulmonary hypertension[13] and the adult respiratory distress syndrome.[14] We have reported that inhaling 80 ppm NO for 30 minutes increases preductal and postductal oxygenation in infants with persistent pulmonary hypertension of the newborn.[15] NO diffuses into the intravascular space, where it rapidly binds to hemoglobin, becoming inactivated and thereby prohibiting systemic vasodilation. This reaction leads to the formation of methemoglobin.[16]

In the present study, we demonstrate that inhaling NO for brief periods selectively reduces pulmonary vasoconstriction in pediatric patients with congenital heart disease complicated by pulmonary artery hypertension. We also compare the pulmonary vasodilatory effectiveness of low concentrations of inhaled NO with oxygen breathing in pediatric patients with congenital heart disease undergoing cardiac catheterization.

Methods

These investigations were performed with approval by the subcommittees for human studies of the Massachusetts General Hospital and an IND approval by the US Food and Drug Administration. Informed consent was obtained from the parents of our patients.

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TABLE 1. Patient Characteristics—Baseline Conditions

Patient	Age	Lesion	Medications	Other conditions	F_{IO_2}	pHa	P_{aCO_2}	P_{aO_2}
1	3 Months	VSD	Digoxin, diuretics	Holt-Oram syndrome	0.21	7.42	41	57
2	3 Months	VSD, ASD	Digoxin	Trisomy 21	0.21	7.38	41	62
3	5 Months	AVC	Digoxin, diuretics	Trisomy 21	0.21	7.37	53	56
4	7 Months	AVC	Digoxin, diuretics	Trisomy 21	0.21	7.35	35	49
5	10 Months	VSD		Situs inversus totalis	0.21	7.37	32	97
6	14 Months	VSD	Digoxin	Trisomy 21	0.21	7.29	54	48
7	4.5 Years	PV stenosis	Digoxin, diuretics		0.21	7.36	45	75
8	6.5 Years	Small VSD, no shunt			0.21	7.35	41	137
9	3.5 Years	Mitral stenosis			0.21	7.35	45	73
10	5.5 Years	AVC-repaired MR severe	Digoxin, diuretics	Trisomy 21	0.30	7.40	59	60
Mean±SD						7.36±0.03	45±9	71±27

VSD, ventricular septal defect; ASD, atrial septal defect; AVC, complete atrioventricular canal; PV, pulmonary vein; MR, mitral regurgitation.

Nitric Oxide Delivery System

NO gas (800–1,000 ppm in N_2, Airco, Riverton, N.J.) was mixed with N_2 using a standard low-flow blender (Bird Blender, Palm Springs, Calif.). The NO and N_2 gas mixture was then mixed with varying quantities of air and oxygen shortly before introduction into the 1-l reservoir of a pediatric nonrebreathing mask (Baxter Healthcare Corp., Valencia, Calif.) worn by the patient. This system allowed separate regulation of the inspired concentrations of NO as quantified by chemiluminescence[17] (model 14A, ThermoEnvironmental Instruments Inc., Franklin, Mass.) and oxygen (Hudson Oxygen Meter 5590, Temecula, Calif.). The total gas flow rate was maintained above 8 $l \cdot min^{-1}$, which reduced the NO residence time within the breathing circuit and hence the time for oxidation of NO to NO_2. The stock NO gas contained up to 1% of the nitrogen oxides as NO_2 (e.g., 800 ppm NO stock gas contained less than 8 ppm NO_2); the inspired NO_2 concentration did not exceed 5% of the NO level. Exhaled gases, as well as those discharging from the chemiluminescence instrument, were scavenged.

Patient Studies

During diagnostic cardiac catheterization, we investigated separately the hemodynamic effects of inhaling low levels (20–80 ppm) of NO and a high F_{IO_2} by 10 successively studied, spontaneously breathing pediatric patients with congenital heart disease complicated by pulmonary hypertension. After sedation and placement of vascular catheters under local anesthesia, the specific cardiac lesions were defined with standard hemodynamic measurements and angiographic techniques. Pulmonary and femoral arterial blood pressures were determined with indwelling catheters and fluid-filled transducers (model 1280C, Hewlett-Packard, Palo Alto, Calif.). In patients with intracardiac shunting (patients 1–6; Tables 1 and 2), pulmonary and systemic blood flows were determined by measuring oxygen consumption (MRM-2, Waters Instruments, Rochester, Minn.),[18] calculating pulmonary artery and pulmonary vein oxygen content from P_{aO_2} and hemoglobin oxygen saturation (Radiometer, Copenhagen), and using the Fick principle. In patients without an angiocardiographically demonstrated intracardiac shunt, cardiac output was determined in triplicate utilizing the thermodilution technique of injecting 3-ml aliquots of 0°C normal saline (COM-2, Baxter, Irvine, Calif.). Vascular resistance and central shunt were determined with standard formulae, and resistance was indexed to body surface area.[19]

In the 10 successive patients with pulmonary artery hypertension defined by an initial peak pulmonary artery pressure of more than half the systolic arterial pressure, the hemodynamic response to 10-minute periods of breathing at F_{IO_2} 0.9 with or without inhaling low levels of NO was determined. In the first seven patients treated (excluding patients 2, 3, and 6), the response of the pulmonary circulation to 10-minute periods of sequentially inhaling 0, 20, 40, and 80 ppm NO at F_{IO_2} 0.9 was determined. In the last eight patients studied, the hemodynamic effects of inhaling 80 ppm NO at F_{IO_2} 0.21 were determined. In the six patients with an intracardiac shunt (patients 1–6), pulmonary and systemic blood flows were determined while breathing at F_{IO_2} 0.21 and at F_{IO_2} 0.9 with and without 80 ppm NO. Arterial blood was obtained for optical determination of methemoglobin levels[20] before and at the completion of the study.

All values are presented as mean±SD. ANOVA with repeated measures was utilized; a posteriori testing was performed using a Fisher's protected least significant difference test.[21] In comparing the patients with Trisomy 21 with others, a one-tailed Student's *t* test was used.[21] Significance is judged at a 5% level.

Results

A total of 10 patients (age range, 3 months to 6.5 years) were studied (Table 1). Six patients (patients 1–6) had increased pulmonary blood flow due to a ventricular septal defect (VSD) or complete atrioventricular canal (AVC), and two patients had pulmonary venous hypertension. One patient had pulmonary hypertension after repair of a VSD and pulmonary vein stenosis, and one had pulmonary hypertension associ-

ated with a hemodynamically insignificant VSD. Of the five patients with Trisomy 21, three had a complete AVC (one of which was corrected), and two had a VSD. All 10 patients had pulmonary hypertension with a baseline mean pulmonary artery pressure of 48±19 mm Hg and pulmonary vascular resistance index (Rp) of 658±421 dyne · sec · cm^{-5} · m^{-2} (Table 2). The mean pulmonary artery pressure of the five patients with Trisomy 21 was 60±19 mm Hg and higher than that of the other five patients whom we studied ($p<0.05$). In the six patients with an intracardiac shunt, the pulmonary-to-systemic blood flow ratio was 2.0±0.8. Except for patient 10, who chronically breathed at F_{IO_2} 0.30, nine patients were breathing room air. The baseline pHa and P_{aCO_2} values were within the normal range (Table 1) and did not change during the study ($p>0.05$). Breathing at F_{IO_2} 0.9 increased P_{aO_2} to 292±83 mm Hg; breathing 80 ppm NO at F_{IO_2} 0.9 produced a P_{aO_2} of 287±119 mm Hg ($p>0.05$). Approximately two thirds of the patients were chronically treated with digoxin; daily diuretic therapy was given to half of the patients. The baseline hematocrit was 37±5%.

The dose-response of pulmonary hemodynamics to 0–80 ppm inhaled NO at F_{IO_2} 0.9 was determined in seven patients. Adding NO to the hyperoxic gas mixture decreased Rp in a dose-dependent manner (Figure 1). Breathing 40 ppm NO at F_{IO_2} 0.9 significantly decreased Rp below both baseline and hyperoxic levels ($p\leq0.05$). The maximum reduction of Rp was achieved by inhaling 80 ppm NO at F_{IO_2} 0.9. We therefore used 80 ppm NO to determine the hemodynamic effects of inhaled NO at F_{IO_2} 0.21–0.3 or 0.9.

Inhaling 80 ppm NO at F_{IO_2} 0.21–0.3 or 0.9 rapidly reduced mean pulmonary artery pressure and Rp below the baseline level ($p\leq0.05$). However, pulmonary artery hypertension returned within minutes of cessation of NO inhalation. In patients with an intracardiac shunt (patients 1–6), inhaling 80 ppm NO at F_{IO_2} 0.21 modestly elevated pulmonary blood flow from 8.8±5.2 to 13.4±8.7 0.9 l · min^{-1} · m^{-2} ($p>0.05$). Breathing 80 ppm NO at F_{IO_2} 0.9 significantly elevated pulmonary blood flow to 15.7±7.8 l · min^{-1} · m^{-2} and pulmonary-to-systemic blood flow ratio from 2.0±0.8 to 4.7±2.5 (both $p<0.05$) (Figure 2). Although the greatest reduction in Rp occurred while inhaling 80 ppm NO at F_{IO_2} 0.21–0.30 in patients with high baseline levels of Rp, when breathing NO at F_{IO_2} 0.90, eight of 10 patients exhibited a reduction in Rp (Table 2 and Figure 3). Each of the patients with Trisomy 21 had reduced mean pulmonary artery pressure and Rp values when measured during NO inhalation at F_{IO_2} 0.21–0.90.

In contrast to inhaling NO, breathing at F_{IO_2} 0.9 without added NO did not reduce mean pulmonary artery pressure but did reduce Rp to 535±379 dyne · sec · cm^{-5} · m^{-2} ($p<0.05$). In patients with an intracardiac shunt, breathing at F_{IO_2} 0.9 without added NO increased pulmonary blood flow from 8.8±5.2 to 15±7.8 l · min^{-1} · m^{-2} ($p\leq0.05$, Figure 2). For patients without an intracardiac shunt, breathing at F_{IO_2} 0.9 without added NO only modestly elevated pulmonary blood flow (Table 2).

Although inhaled NO was a potent pulmonary vasodilator in eight of 10 pediatric patients with pulmonary hypertension, inhaling 80 ppm NO at both F_{IO_2} 0.21 and 0.9 did not produce systemic vasodilation and did not alter mean aortic pressure, systemic blood flow, or systemic vascular resistance index (Rs). Inhaling up to 80 ppm NO for 30 minutes did not change the circulating methemoglobin levels (0.7±0.7% before NO, 0.7±0.4% after NO; $n=7$, $p=0.53$).

Discussion

In our studies of 10 pediatric patients with congenital heart disease and pulmonary artery hypertension, inhaling 80 ppm NO at either the baseline F_{IO_2} (0.21–0.30) or at F_{IO_2} 0.9 reduced pulmonary vascular resistance and pulmonary artery pressure within 1–3 minutes without decreasing systemic arterial pressure or resistance (Table 2). In each of our patients, within minutes after cessation of NO inhalation, pulmonary vascular resistance and pulmonary artery pressure returned to baseline levels. We found that inhaling 80 ppm NO at F_{IO_2} 0.9 produced the maximum reduction of Rp in eight of our 10 patients and increased pulmonary blood flow in all six patients with an intracardiac shunt (Figures 2 and 3). In contrast, breathing at F_{IO_2} 0.9 without NO did not reduce mean pulmonary artery pressure below baseline values and produced only a modest decrease of Rp compared with baseline measurements (Figure 3). Thus, inhaling NO can dilate pulmonary vasoconstriction that is not caused by hypoxia in congenital heart disease.

The patients in our study with the greatest level of pulmonary hypertension or pulmonary vascular resistance had the most consistent reduction of mean pulmonary artery pressure and Rp with NO inhalation. Many of these patients also had Trisomy 21. Other investigators have reported that patients with Trisomy 21 and congenital heart disease exhibit the highest levels of pulmonary hypertension[22,23] and that 90% of patients with Trisomy 21 presenting for diagnostic cardiac catheterization will have significant pulmonary hypertension.[22] Although only 5% of pediatric patients with congenital heart disease who undergo cardiac catheterization have Trisomy 21,[23] approximately half of the pediatric patients with congenital heart disease and pulmonary artery hypertension have Trisomy 21.[22,24]

Congenital heart lesions can produce pulmonary artery hypertension with vascular smooth muscle hyperplasia and hypertrophy.[3] After corrective cardiac surgery, the pulmonary vascular bed in some patients with congenital heart diseases may not regress sufficiently to accommodate the postoperative hemodynamic changes. It often is desirable to determine the vasodilatory capacity of the pulmonary circulation during preoperative cardiac catheterization to attempt to predict the postoperative pulmonary vascular resistance. Hyperoxic breathing has been used to determine the vasodilatory capacity of the lung. Currently used vasodilator agents such as prostacyclin (PGI_2),[25] tolazoline,[26] prostaglandin E_1,[27] and sodium nitroprusside[27] may reduce the pulmonary vascular resistance. However, these intravenous agents are nonselective and dilate the systemic circulation.[25,27–29] Thus, we chose to compare the pulmonary vasodilator potency of inhaled NO with oxygen as it is the only other pulmonary vasodilator in widespread use that does not cause systemic vasodilation. This study demonstrates that inhaled NO is a selective pulmonary vasodilator that exhibits a far greater vasodilatory effect than

TABLE 2. Physiological Responses to Inhaling NO Without and With High Oxygen Concentrations

	0 ppm NO							
Patient	PaO_2	$P_{\overline{PA}}$	$P_{\overline{PV}}$	$P_{\overline{Ao}}$	R_p	R_s	$\dot{Q}_p$	$\dot{Q}_s$
FIO_2 0.21–0.30								
1	57	47	5	55	419	767	8.0	5.2
2	62	52	7	70	782	1,830	4.6	2.8
3	56	66	3	68	883	1,558	5.7	3.3
4	49	70	5	72	321	975	16.2	5.5
5	97	31	4	72	151	1,135	14.3	4.8
6	48	80	2	80	1,558	1,358	4.0	4.6
7	75	25	2	70	707	2,117	2.6	2.6
8	137	37	4	82	1,014	2,429	2.6	2.6
9	73	35	15	55	410	1,079	3.9	3.9
10	60	32	15	70	485	1,758	2.8	2.8
Mean±SD	71±27	48±19	6±5	69±9	673±411	1,501±534	6.5±4.9	3.8±1.1
FIO_2 0.90								
1	391	45	6	67	243	1,183	12.8	4.4
2	225	60	7	68	347	1,838	12.2	2.5
3	311	55	7	70	215	2,437	17.8	2.1
4	148	55	3	72	236	1,286	17.6	4.1
5	357	25	2	70	64	1,206	28.6	4.5
6	184	89	0	90	1,229	1,822	5.2	4.0
7	346	24	2	80	732	3,324	2.4	2.4
8	315	35	4	78	854	2,069	2.9	2.9
9	376	67	18	82	870	1,350	4.5	4.5
10	266	33	16	75	566	2,181	2.4	2.4
Mean±SD	292±83	48±19	7±6	75±7	536±376†	1,870±675	10.6±8.8	3.4±1.0

$P_{\overline{PA}}$, mean pulmonary artery pressure; $P_{\overline{PV}}$, mean pulmonary venous pressure; $P_{\overline{Ao}}$, mean aortic pressure; R_p, pulmonary vascular resistance index; R_s, systemic vascular resistance index; $\dot{Q}_p$, pulmonary blood flow; $\dot{Q}_s$, systemic blood flow. The hemodynamic effects of inhaling 80 ppm NO at FIO_2 0.21–0.9 by pediatric patients with congenital heart disease. Pressure units (P) are mm Hg, and resistance units (R) are dyne · sec · cm^{-5} · m^{-2}; $\dot{Q}_p$ and $\dot{Q}_s$ are in l · min^{-1} · m^{-2}.

*$p<0.05$ value differs from FIO_2 0.21–0.3 without inhaled NO.

†$p<0.05$ value differs from FIO_2 0.9 without inhaled NO.

hyperoxic breathing. A much larger study correlating the effects of preoperative inhaled NO with postoperative hemodynamic course should be performed in the future.

Our study demonstrates that inhaled NO is a potent pulmonary vasodilator. There are two recent reports comparing the pulmonary vasodilatory effects of intravenous prostacyclin with inhaled NO in two adult patient populations: adults with primary pulmonary hypertension[13] and adult respiratory distress syndrome.[14] Despite the differences in etiology of the pulmonary vascular hypertension in these two syndromes, inhaled NO produced more consistent pulmonary vasodilation than PGI_2, without causing systemic vasodilation.

The pulmonary and systemic vasodilation produced by intravenous prostacyclin has been extensively studied in congenital heart disease. Bush et al[25] evaluated the pulmonary vasodilatory potency of intravenous PGI_2 in 20 pediatric patients with congenital heart disease and a Rp ($p=0.65$, unpaired t test) and mean pulmonary artery pressure ($p=0.98$) similar to those of the patients whom we studied. Bush and coworkers reported that intravenous infusions of 20 ng · kg^{-1} · min^{-1} PGI_2 reduced Rp by 186 dyne · sec · cm^{-5} · m^{-2} when the patients breathed at FIO_2 0.21, and PGI_2 reduced Rp by 136 dyne · sec · cm^{-5} · m^{-2} when the patients breathed at FIO_2 1.0. In comparison with this study of intravenous prostacyclin, we found 24% and 70% greater reduction of Rp when 80 ppm NO was breathed at FIO_2 0.21–0.3 and 0.9, respectively, in contrast to PGI_2. This indirect comparison suggests that inhaled NO may produce more potent and selective pulmonary vasodilation than PGI_2 in pediatric patients with congenital heart disease.

Studies of patients with pulmonary hypertension following congenital heart surgery reported a reduction of mean pulmonary artery pressure during treatment with intravenous nitroprusside, a NO donor compound.[29] Inhaled NO diffuses directly into pulmonary vascular smooth muscle cells and activates guanylate cyclase[9,10] to produce vasodilation. NO that diffuses into the pulmonary circulation is rapidly inactivated by combination with hemoglobin, thereby preventing systemic vasodilation. Our laboratory has reported selective pulmonary vasodilation by NO inhalation in sheep weighing 25–35 kg with pulmonary vasoconstriction produced by hypoxia or infusion of a stable thromboxane analogue (U46619)[11]; NO vasodilation was not altered by indomethacin treatment, suggesting prostacyclin production was not involved.[30] Recently, we reported that inhaled NO is a pulmonary vasodilator that rapidly and completely reverses hypoxic pulmonary vasoconstriction without producing systemic hypotension in the newborn lamb with a transitional circulation.[31,32] We also re-

TABLE 2. Continued

Patient	80 ppm NO							
	PaO_2	$P_{\overline{PA}}$	$P_{\overline{PV}}$	$P_{\overline{Ao}}$	R_p	R_s	$\dot{Q}_p$	$\dot{Q}_s$
FIO_2 0.21–0.30								
1	69	30	7	65	67	1,199	27.6	4.2
2	76	42	7	58	411	1,838	6.8	2.4
3	53	47	6	63	372	1,606	8.8	2.9
4	59	50	2	72	195	1,462	19.7	3.8
5	76	25	1	65	153	1,422	12.5	3.6
6	58	65	0	75	1,018	1,175	5.1	5.1
7	73	22	2	72	571	2,269	2.8	2.8
8	127	40	4	78	1,199	2,533	2.4	2.4
9								
10								
Mean±SD	74±23	40±14*†	4±3	69±7	498±412*	1,688±494	10.7±8.9	3.4±1.0
FIO_2 0.90								
1	457	32	10	75	91	1,694	19.4	3.4
2	409	45	8	68	137	2,597	21.6	2.0
3	298	42	7	63	148	2,213	18.9	2.1
4	113	55	7	70	192	927	20.1	5.5
5	358	27	2	72	60	1,334	33.3	4.2
6	177	52	0	85	561	1,047	7.4	6.5
7	279	18	2	72	492	2,741	2.6	2.6
8	337	37	4	72	879	1,838	3.0	3.0
9	327	30	18	85	240	1,702	4.0	4.0
10	111	35	25	85	285	2,045	2.8	2.8
Mean±SD	287±119	37±11*†	8±8	75±8	308±260*	1,814±607	13.3±10.7*	3.6±1.5

ported that inhaled NO improved systemic oxygenation in many critically ill infants with persistent pulmonary hypertension of the newborn.[15] Inhaled NO (10–80 ppm) reverses hypoxic pulmonary vasoconstriction in normal human volunteers[12] and patients with adult respiratory distress syndrome for periods up to 53 days.[14] Pepke-Zaba et al[13] reported that Rp decreased in eight adult patients with chronic PA hypertension breathing 80 ppm NO but did not report PA pressure or cardiac output. NO inhalation has recently been reported to be a bronchodilator of the methacholine-constricted guinea pig.[33]

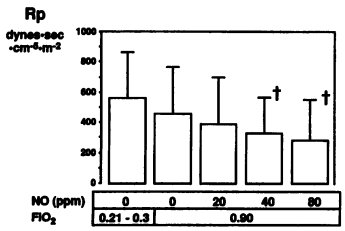

FIGURE 1. *Bar graph of effect on pulmonary vascular resistance index (Rp) of breathing 20–80 ppm NO at FIO_2 0.9 by seven pediatric patients with congenital heart disease. †p<0.05 value differs from both baseline and FIO_2 0.9 without inhaled NO. Increasing the FIO_2 from baseline (0.21–0.3) to 0.9 did not change Rp. Adding 40 ppm NO reduced Rp below both baseline and FIO_2 0.9 levels; the maximal pulmonary vasodilatory effect was obtained by breathing 80 ppm NO in oxygen.*

It is likely that there is no toxicity associated with breathing 20–80 ppm NO for the brief period of a cardiac catheterization. No pulmonary injury, which is more likely to be associated with NO_2 inhalation, was apparent in our patients. Recently, seven patients with severe adult respiratory distress syndrome were treated by inhaling 20 ppm NO for 11–53 days with a consis-

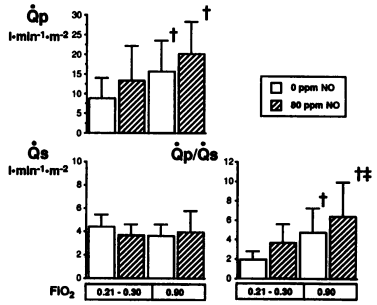

FIGURE 2. *Bar graphs of hemodynamic effects of breathing at FIO_2 0.9 and 80 ppm NO by six pediatric patients with congenital heart disease and an intracardiac shunt. Units for blood flow ($\dot{Q}$) are $l \cdot min^{-1} \cdot m^{-2}$. †p<0.05 value differs from FIO_2 0.21 without NO. ‡p<0.05 value differs from FIO_2 0.21 with 80 ppm NO. Breathing 80 ppm NO at FIO_2 0.9 increased pulmonary blood flow ($\dot{Q}_p$). Inhaling 80 ppm NO at FIO_2 0.21–0.3 and 0.9 did not alter systemic blood flow ($\dot{Q}_s$). Breathing at FIO_2 0.9 with or without 80 ppm NO increased $\dot{Q}_p/\dot{Q}_s$. Maximum elevation of $\dot{Q}_p/\dot{Q}_s$ occurred while inhaling 80 ppm NO at FIO_2 0.9.*

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