Inhaled Nitric Oxide in Congenital Heart Disease

Jesse D. Roberts Jr., MD; Peter Lang, MD; Luca M. Bigatello, MD; Gus J. Vlahakes, MD; and Warren M. Zapol, MD

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 vasodilatation 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 (FI(O2)) of 0.21–0.3 and 0.9 would reduce the pulmonary vascular resistance index (Rp). We then compared breathing oxygen with breathing NO. Inhaling 80 ppm NO at FI(O2) 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⁻² · m⁻² (mean±SD, both p<0.05). Increasing the FI(O2) 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 (Qp/Qs), primarily by increasing Qp (p<0.05). Breathing 80 ppm NO at FI(O2) 0.9 reduced mean pulmonary artery pressure and Rp to the lowest levels and increased Qp and Qp/Qs (all p<0.05). While breathing at FI(O2) 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 FI(O2) 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 vasodilatation. (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 flow¹ or cause pulmonary venous obstruction² may produce pulmonary artery smooth muscle hypertrophy and hyperplasia³ 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-arginine⁷ 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 vasoconstric-

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In lambs weighing 25–35 kg¹¹ and adult volunteers¹² and reduces pulmonary vascular resistance in adults with primary pulmonary hypertension¹³ 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.
TABLE 1. Patient Characteristics—Baseline Conditions

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Lesion</th>
<th>Medications</th>
<th>Other conditions</th>
<th>FiO₂</th>
<th>pHₐ</th>
<th>PacO₂</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3 Months</td>
<td>VSD</td>
<td>Digoxin, diuretics</td>
<td>Holt-Oram syndrome</td>
<td>0.21</td>
<td>7.42</td>
<td>41</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>3 Months</td>
<td>VSD, ASD</td>
<td>Digoxin</td>
<td>Trisomy 21</td>
<td>0.21</td>
<td>7.38</td>
<td>41</td>
<td>62</td>
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<tr>
<td>3</td>
<td>5 Months</td>
<td>AVC</td>
<td>Digoxin, diuretics</td>
<td>Trisomy 21</td>
<td>0.21</td>
<td>7.37</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>7 Months</td>
<td>AVC</td>
<td>Digoxin, diuretics</td>
<td>Trisomy 21</td>
<td>0.21</td>
<td>7.35</td>
<td>35</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>10 Months</td>
<td>VSD</td>
<td></td>
<td>Situs inversus totalis</td>
<td>0.21</td>
<td>7.37</td>
<td>32</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>14 Months</td>
<td>VSD</td>
<td>Digoxin</td>
<td>Trisomy 21</td>
<td>0.21</td>
<td>7.29</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>4.5 Years</td>
<td>PV stenosis</td>
<td></td>
<td></td>
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<td>7.36</td>
<td>45</td>
<td>75</td>
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<tr>
<td>8</td>
<td>6.5 Years</td>
<td>Small VSD, no shunt</td>
<td></td>
<td></td>
<td>0.21</td>
<td>7.35</td>
<td>41</td>
<td>137</td>
</tr>
<tr>
<td>9</td>
<td>3.5 Years</td>
<td>Mitral stenosis</td>
<td></td>
<td></td>
<td>0.21</td>
<td>7.35</td>
<td>45</td>
<td>73</td>
</tr>
<tr>
<td>10</td>
<td>5.5 Years</td>
<td>AVC-repaired MR severe</td>
<td>Digoxin, diuretics</td>
<td>Trisomy 21</td>
<td>0.30</td>
<td>7.40</td>
<td>59</td>
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</table>

Mean±SD: 7.36±0.03 45±9 71±27

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

Nitric Oxide Delivery System

NO gas (800–1,000 ppm in N₂, Airco, Riverton, N.J.) was mixed with N₂ using a standard low-flow blender (Bird Blender, Palm Springs, Calif.). The NO and N₂ 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 chemiluminescence¹⁷ (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·min⁻¹, which reduced the NO residence time within the breathing circuit and hence the time for oxidation of NO to NO₂. The stock NO gas contained up to 1% of the nitrogen oxides as NO₂ (e.g., 800 ppm NO stock gas contained less than 8 ppm NO₂); the inspired NO₂ 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 FiO₂ 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 PaO₂ 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 successful 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 FiO₂ 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 FiO₂ 0.9 was determined. In the last eight patients studied, the hemodynamic effects of inhaling 80 ppm NO at FiO₂ 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 FiO₂ 0.21 and at FiO₂ 0.9 with and without 80 ppm NO. Arterial blood was obtained for optical determination of methemoglobin levels²⁰ 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 AV (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 FiO₂ 0.30, nine patients were breathing room air. The baseline pHa and Paco₂ values were within the normal range (Table 1) and did not change during the study (p>0.05). Breathing at FiO₂ 0.9 increased Paco₂ to 292±83 mm Hg; breathing 80 ppm NO at FiO₂ 0.9 produced a Paco₂ of 287±119 mm Hg (p>0.05). Approximately three 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 FiO₂ 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 FiO₂ 0.9 significantly decreased Rp below both baseline and hyperoxic levels (p≤0.05). The maximum reduction of Rp was achieved by inhaling 80 ppm NO at FiO₂ 0.9. We therefore used 80 ppm NO to determine the hemodynamic effects of inhaled NO at FiO₂ 0.21–0.3 or 0.9.

Inhaling 80 ppm NO at FiO₂ 0.21–0.3 or 0.9 rapidly reduced mean pulmonary artery pressure and Rp below the baseline level (p≤0.05). 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 FiO₂ 0.21 modestly elevated pulmonary blood flow from 8.8±5.2 to 13.4±8.7 L · min⁻¹ · m⁻² (p>0.05). Breathing 80 ppm NO at FiO₂ 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 FiO₂ 0.21–0.30 in patients with high baseline levels of Rp, when breathing NO at FiO₂ 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 FiO₂ 0.21–0.90.

In contrast to inhaling NO, breathing at FiO₂ 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 FiO₂ 0.9 without added NO increased pulmonary blood flow from 8.8±5.2 to 15.7±7.8 L · min⁻¹ · m⁻² (p<0.05, Figure 2). For patients without an intracardiac shunt, breathing at FiO₂ 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 FiO₂ 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 FiO₂ (0.21–0.30) or at FiO₂ 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 FiO₂ 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 FiO₂ 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 vasconstriction 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 and pulmonary vascular resistance. Although only 5% of pediatric patients with congenital heart disease who undergo cardiac catheterization have Trisomy 21, approximately half of the pediatric patients with congenital heart disease and pulmonary hypertension have Trisomy 21.

Congenital heart lesions can produce pulmonary artery hypertension with vascular smooth muscle hyperplasia and hypertrophy. 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 is often desirable to determine the vasodilatory capacity of the pulmonary circulation during preparative 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 (PGL₃), tolazoline, prostaglandin E₁, and sodium nitroprusside may reduce the pulmonary vascular resistance. However, these intravenous agents are nonselective and dilate the systemic circulation. 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

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<th>PaO₂</th>
<th>PV</th>
<th>Ps</th>
<th>Rp</th>
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<th>Qo</th>
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<td>1,501±534</td>
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<tr>
<td>Mean±SD</td>
<td>292±83</td>
<td>48±19</td>
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<td>75±7</td>
<td>536±376</td>
<td>1,870±675</td>
<td>10.6±8.8</td>
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Fₚᵥ, mean pulmonary arterial pressure; Fᵥ, mean pulmonary venous pressure; Pₚₜ, mean aortic pressure; Rp, pulmonary vascular resistance index; Rpₛ, systemic vascular resistance index; Qₒ, pulmonary blood flow; Qₛ, systemic blood flow. The hemodynamic effects of inhaling 80 ppm NO at FIO₂ 0.21–0.9 by pediatric patients with congenital heart disease. Pressure units (P) are mm Hg, and resistance units (R) are dyne-sec/cm²-m²; Qₒ and Qₛ are in l/min-m².

*p<0.05 value differs from FIO₂ 0.21–0.3 without inhaled NO.
†p<0.05 value differs from FIO₂ 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 and congenital heart disease. Despite the differences in etiology of the pulmonary vascular hypertension in these two syndromes, inhaled NO produced more consistent pulmonary vasodilation than prostacyclin, without causing systemic vasodilation.

The pulmonary and systemic vasodilation produced by intravenous prostacyclin has been extensively studied in congenital heart disease. Bush et al. evaluated the pulmonary vasodilatory potency of intravenous PGfₐ 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 PGfₐ reduced Rp by 186 dyne·sec·cm⁻²·m² when the patients breathed at FIO₂ 0.21, and PGfₐ reduced Rp by 136 dyne·sec·cm⁻²·m² when the patients breathed at FIO₂ 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 FIO₂ 0.21–0.3 and 0.9, respectively, in contrast to PGfₐ. This indirect comparison suggests that inhaled NO may produce more potent and selective pulmonary vasodilation than prostacyclin 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. Inhaled NO diffuses directly into pulmonary vascular smooth muscle cells and activates guanylate cyclase 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); NO vasodilation was not altered by indomethacin treatment, suggesting prostacyclin production was not involved. 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.
reported that inhaled NO improved systemic oxygenation in many critically ill infants with persistent pulmonary hypertension of the newborn. Inhaled NO (10–80 ppm) reverses hypoxic pulmonary vasconstriction in normal human volunteers and patients with adult respiratory distress syndrome for periods up to 53 days. Pepke-Zaba et al 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.

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 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 1. Bar graph of effect on pulmonary vascular resistance index (Rp) of breathing 20–80 ppm NO at FIO2 0.9 by seven pediatric patients with congenital heart disease. *P<0.05 value differs from both baseline and FIO2 0.9 without inhaled NO. Increasing the FIO2 from baseline (0.21–0.3) to 0.9 did not change Rp. Adding 40 ppm NO reduced Rp below both baseline and FIO2 0.9 levels; the maximal pulmonary vasodilatory effect was obtained by breathing 80 ppm NO in oxygen.](image1)

![FIGURE 2. Bar graphs of hemodynamic effects of breathing at FIO2 0.9 and 80 ppm NO by six pediatric patients with congenital heart disease and an intracardiac shunt. Units for blood flow (\(Q\)) are l·min⁻¹·m⁻². *P<0.05 value differs from FIO2 0.21 without NO. †P<0.05 value differs from FIO2 0.21 with 80 ppm NO. Breathing 80 ppm NO at FIO2 0.9 increased pulmonary blood flow (\(Q_p\)). Inhaling 80 ppm NO at FIO2 0.21–0.3 and 0.9 did not alter systemic blood flow (\(Q_s\)). Breathing at FIO2 0.9 with or without 80 ppm NO increased \(Q_p/Q_s\). Maximum elevation of \(Q_p/Q_s\) occurred while inhaling 80 ppm NO at FIO2 0.9.](image2)
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FIGURE 3. Scatterplots of hemodynamic effects of breathing at FiO2 0.90 and 80 ppm NO by 10 pediatric patients with
congenital heart disease and pulmonary artery hypertension. The units of pulmonary vascular resistance index (Rp) are dyne · sec · cm−2 · m−2. The baseline Rp was measured while breathing at FiO2 0.21−0.30 without addition of NO gas. The Rp with treatment was during breathing at FiO2 0.21−0.90 with or without 80 ppm NO. ○, Values from patients with Trisomy 21; ●, values from patients without Trisomy 21. The stippled line is where the treatment would not change pulmonary pressure from baseline values. Inhaling NO at FiO2 0.21−0.90 reduced Rp in the many patients; those with a higher baseline pulmonary hypertension had greater pulmonary vasodilation. In all patients with Trisomy 21 (●), inhaling 80 ppm NO at FiO2 0.21−0.90 reduced Rp. Breathing at FiO2 0.90 without NO did not consistently reduce Rp.

tently reduced pulmonary artery pressure and an increased PaO2.14 Six of these patients survived, and there was no clinical evidence of additional lung injury due to NO inhalation. Methemoglobin levels can be increased by inhalation of NO but did not increase in either the patients with adult respiratory distress syndrome14 or our patients with congenital heart disease.

This study demonstrates that 40−80 ppm inhaled NO is a selective pulmonary vasodilator of pediatric patients suffering from congenital heart lesions complicated by pulmonary artery hypertension that does not dilate the systemic circulation. It is probable that inhaling NO at cardiac catheterization can assess pulmonary vasodilatory capacity in pulmonary hypertension and may safely allow the preoperative identification of children with a critically limited and restricted pulmonary vascular bed.

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