Inhaled nitric oxide versus aerosolized iloprost in secondary pulmonary hypertension in children with congenital heart disease: vasodilator capacity and cellular mechanisms

RIMENSBERGER, Peter, et al.

Abstract
Inhaled nitric oxide (iNO) has been used to assess the vasodilator capacity of the pulmonary vascular bed in children with congenital heart disease and elevated pulmonary vascular resistance. Inhaled iloprost is a pulmonary vasodilator for the long-term treatment of pulmonary hypertension (PHT). Because these 2 vasodilators act through different pathways (release of cGMP or cAMP, respectively), we compared the pulmonary vasodilator capacity of each.

Reference

DOI : 10.1161/01.CIR.103.4.544
PMID : 11157720
Inhaled Nitric Oxide Versus Aerosolized Iloprost in Secondary Pulmonary Hypertension in Children With Congenital Heart Disease

Vasodilator Capacity and Cellular Mechanisms

Peter C. Rimensberger, MD; Isabelle Spahr-Schopfer, MD; Michel Berner, MD; Edgar Jaeggi, MD; Afksendiyos Kalangos, PhD, MD; Beat Friedli, MD; Maurice Beghetti, MD

Background—Inhaled nitric oxide (iNO) has been used to assess the vasodilator capacity of the pulmonary vascular bed in children with congenital heart disease and elevated pulmonary vascular resistance. Inhaled iloprost is a pulmonary vasodilator for the long-term treatment of pulmonary hypertension (PHT). Because these 2 vasodilators act through different pathways (release of cGMP or cAMP, respectively), we compared the pulmonary vasodilator capacity of each.

Methods and Results—A total of 15 children with congenital heart disease and PHT who had elevated pulmonary vascular resistance (preoperative, n = 10; immediately postoperative, n = 5) were first given 20 ppm of iNO for 10 minutes; then, after baseline values were reached again, they were given aerosolized iloprost at 25 ng·kg⁻¹·min⁻¹ for another 10 minutes. Finally, iNO and iloprost were given simultaneously for 10 minutes. With iNO, the pulmonary vascular resistance and systemic vascular resistance ratio decreased from 0.48 ± 0.38 to 0.27 ± 0.16 (P < 0.001). Similarly, iloprost decreased the ratio from 0.49 ± 0.38 to 0.26 ± 0.11 (P < 0.05). The combination had no additional effect on the resistance ratio. Plasma cGMP increased from 17.6 ± 11.9 to 34.7 ± 21.4 nmol/L during iNO (P < 0.01), and plasma cAMP increased from 55.7 ± 22.9 to 65.1 ± 21.2 nmol/L during iloprost inhalation (P < 0.05).

Conclusions—In children with PHT and congenital heart disease, both iNO and aerosolized iloprost are equally effective in selectively lowering pulmonary vascular resistance through an increase in cGMP or cAMP, respectively. However, the combination of both vasodilators failed to prove more potent than either substance alone. Aerosolized iloprost might be an alternative to iNO for early testing of vascular reactivity and for the postoperative treatment of acute PHT. (Circulation. 2001;103:544-548.)

Key Words: hypertension, pulmonary heart defects, congenital vasodilatation nitric oxide prostaglandins

The assessment of pulmonary vascular reactivity plays an important role in the management of patients with pulmonary hypertension (PHT) and congenital heart disease (CHD). We and others have shown that the response to early testing with inhaled nitric oxide (iNO) seems to depend on the degree of established vascular disease and, thus, may be helpful in selecting patients for operation. Inhaled nitric oxide mediates vasodilatation through the stimulation of soluble guanylate cyclase to produce cGMP. Prostacyclin, an unstable arachidonic acid metabolite, is another endothelial-derived vasodilator that increases the concentration of cAMP in vascular smooth muscle cells. Recently, inhaled prostacyclin (PGI₂) was proven to act as a selective pulmonary vasodilator, and it has been proposed as an alternative to iNO for the treatment of adult respiratory distress syndrome and after repair of CHD. It has been demonstrated that iloprost, a stable prostacyclin analog, is as potent in its selective vasodilator effect as PGI₂.

We compared the hemodynamic effects and changes in plasma cGMP and cAMP levels induced by iNO and iloprost alone or in combination in patients with PHT and CHD preoperatively or postoperatively.

Methods

Study Population
Approval by the institutional ethics committee and written informed consent were obtained before recruiting 15 children (mean age, 5.4 ± 4.3 years) with PHT and CHD to participate in the study. Among the 15 children, 10 were studied in the catheterization laboratory preoperatively (group 1) and 5 were studied in the intensive care unit immediately after surgical repair (group 2). PHT was defined as a mean pulmonary pressure >30 mm Hg and an
indexed pulmonary vascular resistance >2.5 Wood U · m². Baseline demographic and hemodynamic data are given in Table 1.

### Study Design

The following protocol was used in all patients: (1) baseline measurements, (2) administration of 20 ppm iNO for 10 minutes, (3) return to baseline for 10 minutes, (4) administration of 25 ng · kg⁻¹ · min⁻¹ iloprost for 10 minutes, and (5) administration of iNO and iloprost for 10 minutes. Normoventilation (pH 7.38 to 7.42) and inspired oxygen concentration (21% in preoperative patients and 40% in postoperative patients) were kept constant throughout the study and was not measured during confounding factors. At the end of each step, hemodynamic changes were recorded, arterial blood gases were measured to ensure stable pH conditions, and blood samples were drawn from the left atrium or systemic artery for measurements of cGMP and cAMP.

Children in group 1 were premedicated with midazolam (Dormicum; 0.5 mg/kg PO; maximum dose 15 mg). For heart catheterization, the children were intubated and sedated using the following protocol: 10 μg/kg atropine as a single dose; 10 μg/kg alfentanil (Rapifen) as a single dose; 0.5 mg/kg atracurium as a single dose to facilitate intubation; and 2.5 to 3.5 mg/kg propofol (Disoprin) as a bolus, followed by 10 to 15 mg · kg⁻¹ · h⁻¹ propofol as a continuous infusion. Children in group 2, who were already intubated and ventilated, were sedated by a continuous infusion of morphine (40 to 80 μg · kg⁻¹ · h⁻¹) and midazolam (0.2 mg · kg⁻¹ · h⁻¹), as it is standard practice in our unit in the early postoperative period. Normoventilation was assured during the test protocol for both groups.

### Drug Administration

Medical-grade quality NO at 300 ppm in nitrogen was administered through a separate flowmeter into the inspiratory limb of the ventilator circuit, where it was volumetrically diluted to 20 ppm and monitored from a sampling port in the inspiratory limb close to the endotracheal tube connector. Peak NO and NO₂ concentrations were continuously measured with an electrochemical device during NO administration (PrinterNOx, Micro Medical Ltd).

Iloprost (Ilomedin, Schering AG, Schlieren, Switzerland) was prepared from a vial of 50 μg/0.5 mL and diluted to obtain a theoretical alveolar deposition of 25 ng · kg⁻¹ · min⁻¹. Dilution was calculated according the following formula: aerosol concentration/mL = (dose × body weight [kg]/nebulization rate [mL/min]) of the nebulizer. For nebulization, we used the Respigrard II (Marquest Medical Products) nebulizer connected to the inspiratory limb of the ventilator or to a modified Jackson-Rees system for bag ventilation, as described previously.¹ This jet nebulizer shows the following characteristics: mass median aerodynamic diameter, 2.1 μm; mass distribution, 80% of droplets were <6 μm, allowing a high intrapulmonary deposition in small children; and nebulization rate, ∼0.15 mL/min at a flow rate of 6 L/min.² Iloprost was continuously aerosolized at a flow rate of 6 L/min.

### Hemodynamic Assessment

Catheters were inserted femorally and placed in the superior vena cava, the pulmonary artery, the left atrium, and the aorta (or a peripheral systemic artery) to allow simultaneous measurements of pressure and blood gases and to avoid time-consuming and confounding measurements due to catheter manipulations. For patients with an atrial septal defect or a patent foramen ovale, a catheter was placed in a pulmonary vein instead of the left atrium. In the absence of an interatrial communication, pulmonary arterial wedge pressure was measured instead of left atrial pressure.

Intravascular pressures were measured with fluid-filled transducers, and oxygen content was calculated from hemoglobin concentrations and oxygen saturations. Blood gases were measured from systemic arterial blood at each level. Cardiac index and indexed pulmonary and systemic blood flow (Qp and Qs, respectively) calculations, based on the Fick principle, were obtained from assumed oxygen consumption. Systemic and pulmonary vascular resistances were calculated with standard formulas and indexed to body surface area. The pulmonary-to-systemic vascular resistance ratio (Rp/Rs) was then calculated. Oxygen consumption was assumed constant throughout the study and was not measured during

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**TABLE 1. Baseline Hemodynamics of All Patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age, y-mo</th>
<th>Weight, kg</th>
<th>Mean PAP</th>
<th>Mean PVR, U · m²</th>
<th>Rp/Rs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>VSD</td>
<td>5–7</td>
<td>17</td>
<td>78</td>
<td>69</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>AVSD</td>
<td>1–9</td>
<td>8</td>
<td>63</td>
<td>58</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>TGV corrected, VSD*</td>
<td>8–6</td>
<td>16</td>
<td>64</td>
<td>45</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>TGV corrected, VSD*</td>
<td>4–0</td>
<td>12</td>
<td>64</td>
<td>40</td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
<td>VSD</td>
<td>5–2</td>
<td>15</td>
<td>87</td>
<td>83</td>
<td>2.4</td>
</tr>
<tr>
<td>6</td>
<td>VSD, PDA</td>
<td>2–11</td>
<td>8</td>
<td>65</td>
<td>45</td>
<td>1.7</td>
</tr>
<tr>
<td>7</td>
<td>PDA, coarctation</td>
<td>6–5</td>
<td>10</td>
<td>85</td>
<td>61</td>
<td>2.9</td>
</tr>
<tr>
<td>8</td>
<td>VSD, PDA</td>
<td>11–10</td>
<td>17</td>
<td>70</td>
<td>40</td>
<td>2.6</td>
</tr>
<tr>
<td>9</td>
<td>ASD, PDA</td>
<td>14</td>
<td>27</td>
<td>85</td>
<td>71</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>ASD, VSD</td>
<td>1–1</td>
<td>8</td>
<td>47</td>
<td>46</td>
<td>0.54</td>
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</tbody>
</table>

**Postoperative**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age, y-mo</th>
<th>Weight, kg</th>
<th>Mean PAP</th>
<th>Mean PVR, U · m²</th>
<th>Rp/Rs</th>
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</thead>
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<tr>
<td>11</td>
<td>VSD closure</td>
<td>4–0</td>
<td>11</td>
<td>62</td>
<td>56</td>
<td>...</td>
</tr>
<tr>
<td>12</td>
<td>VSD closure</td>
<td>1–8</td>
<td>6</td>
<td>53</td>
<td>34</td>
<td>...</td>
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<tr>
<td>13</td>
<td>AVSD repair</td>
<td>1</td>
<td>5</td>
<td>51</td>
<td>29</td>
<td>...</td>
</tr>
<tr>
<td>14</td>
<td>VSD, PDA closure</td>
<td>1–11</td>
<td>7</td>
<td>71</td>
<td>34</td>
<td>...</td>
</tr>
<tr>
<td>15</td>
<td>VSD closure</td>
<td>11–11</td>
<td>17</td>
<td>86</td>
<td>31</td>
<td>...</td>
</tr>
</tbody>
</table>

VSD indicates ventricular septal defect; ASD, atrial septal defect; AVSD, atrioventricular septal defect; TGV, transposition of the great vessels; PDA, patent ductus arteriosus; SAP, systemic arterial pressure; and PAP, pulmonary arterial pressure.

*Post-Senning procedure with VSD left open.
drug administration, because the calculation of Rp/Rs avoids the influence of oxygen consumption changes. Hemodynamic parameters were measured at baseline and at the end of each period of drug exposure.

cGMP and cAMP Assays
Blood samples were collected in an EDTA vacutainer (Becton Dickinson Vacutainer systems) and immediately placed on ice. Plasma was obtained by centrifugation at 1600g for 10 minutes at 4°C and then stored at −70°C until analysis. cGMP and cAMP levels were determined in batches using a commercial radioimmunoassay kit (Immunotech catalog #1118 and 1117). The cGMP assay had a measurement range of 0.1 to 100 nmol/L and a sensitivity of 10 pmol/L. The cAMP assay had a measurement range of 5 to 50 nmol/L, and the sensitivity of the assay was 0.2 nmol/L. cGMP and cAMP levels are expressed in nmol/L.

Statistical Analysis
The data were computerized and analyzed using the GraphPad Prism Software package. Mean, median, SD, and lower and upper 95% confidence intervals were calculated for all parameters. Results are expressed as mean±SD. Analyses were performed for all patients and separately for groups 1 and 2. For each parameter, repeated measures ANOVA for normally distributed data or the Friedman’s test for non-normally distributed data were used, with post hoc corrections as appropriate, for all pairwise multiple comparisons (Tukey’s or Dunn multiple comparison test, respectively). P<0.05 was considered significant.

Results
Patient demographics and hemodynamic data are given in Table 1. Inhaled NO caused a selective pulmonary vasodilatation in 14 of 15 patients and an overall decrease in Rp/Rs from 0.48±0.38 (baseline 1) to 0.27±0.16 (P<0.001). Similarly, aerosolized iloprost resulted in a selective pulmonary vasodilatation in the same 14 patients, and Rp/Rs decreased from 0.49±0.38 (baseline 2) to 0.26±0.11 (P<0.05). The combination of both drugs did not result in an additional decrease of Rp/Rs (0.26±0.11 to 0.24±0.09).

One patient (patient 3 in Table 1), who had a ventricular septal defect after a previous palliative atrial switch procedure (Senning) for transposition of the great arteries, did not respond at all. One patient (patient 10 in Table 1), who had a ventricular septal defect and an atrial septal defect, presented with suprasystemic pulmonary arterial pressures and a right-to-left shunt (Qp/Qs, 0.54; Rp/Rs, 1.8) before testing. The intracardiac shunt diminished under iNO (Qp/Qs, 0.95) and inverted under aerosolized iloprost (Qp/Qs, 1.51) due to a decrease of Rp/Rs to 0.73 and 0.55, respectively. Rp/Rs decreased further to 0.43 when both substances were combined (Figure 1). When this patient was excluded from statistical analysis because of his very high initial pulmonary resistance, thus allowing for the testing of a more homogeneous group, results still remained significant. The Rp/Rs decreased from 0.39±0.11 (baseline 1) to 0.24±0.10 (P<0.001) under iNO and from 0.39±0.11 (baseline 2) to 0.24±0.08 (P<0.001) under aerosolized iloprost. The combination of both drugs did not further decrease Rp/Rs (0.24±0.08 to 0.22±0.08; Figure 2).

Plasma cGMP levels (Table 2) increased by 97%, from 17.6±11.9 nmol/L (baseline 1) to 34.7±21.4 nmol/L, during iNO (P<0.001) and normalized to baseline values after iNO was discontinued. During combined iNO and iloprost inhalation, cGMP increased from 17.4±14.1 nmol/L (on iloprost alone) to 36.1±15.2 nmol/L (P<0.001). Plasma cAMP levels (Table 2) remained stable under iNO (baseline, 55.7±22.9 nmol/L; during iNO, 54.0±21.8 nmol/L). During the 10-minute administration of iloprost, cAMP increased by 20%, from 54.0±21.8 to 65.1±21.2 nmol/L (P<0.05). It remained elevated, at 66.0±19.85 nmol/L, during the combined administration of iNO and iloprost (P<0.05 versus baseline and iNO). Subgroup analyses of preoperative or postoperative patients showed no differences in response when compared with all patients.

Discussion
In our study population, inhaled NO and aerosolized iloprost, at the concentration or doses used, were proven to be equipotent and equally selective in lowering pulmonary vascular resistance through an increase in either cGMP or cAMP, respectively. We observed no changes in systemic vascular resistance or in systemic arterial pressures during iloprost inhalation such as other investigators have reported, although we delivered slightly higher doses of 25 ng·kg⁻¹·min⁻¹ over a longer time (ie, over a total of 20 minutes when combining both substances) than those authors did. This may be explained by the use of a nebulizer, different characteristics of the aerosol spray, and the different intrapulmonary deposition characteristics between children and adults and between intubated and nonintubated patients.

Figure 1. Changes in Rp/Rs (○, solid line) and intracardiac shunt (Qp/Qs; ▽, dotted line) in patient 10, showing inversion of shunt with iNO and under iloprost aerosolization.

Figure 2. Individual responses from all patients in Rp/Rs to iNO and aerosolized iloprost (with exception of patient 10). Responders are indicated by ● and nonresponders by ○.
extracellular matrix, or plexiform obstructive vascular lesions may be responsible for the absent reaction. Although we did not see a synergistic effect of the combination of both vasodilators when statistical analysis were performed, there were a few patients who showed a further decrease in Rp/Rs when both substances were combined. One patient with both ventricular and atrial septal defects and a right-to-left shunt (Qp/Qs, 0.54) showed an impressive response to both iNO and iloprost alone, with inversion of the intracardiac shunt on aerosolized iloprost, and further improvement of Rp/Rs when both substances were combined (Figure 1). This observation suggests that there might be a subgroup of patients who will respond to a combined treatment better than to a single treatment.18 Whether this is of clinical or prognostic importance remains to be evaluated.

iNO increased cGMP and iloprost increased cAMP (Table 2). Both responses were highly selective, indicating different independent mediator pathways for the 2 vasodilators. Although initially different messenger pathways will be activated, the final pathway leading to smooth muscle cell relaxation is probably the same for both substances (ie, a decrease in the concentration of free intracellular cytosolic Ca2+).20,21 This might explain the lack of a synergistic effect when combining both pulmonary vasodilators. We found no evidence for an iloprost-induced endothelial cell release of NO, which would again stimulate soluble guanylate cyclase to produce cGMP, as has been postulated to be the case for PGI2.14,22

PGI2 has been proposed as an alternative to iNO after the repair of CHD.8 The nebulization of PGI2 or iloprost might have some advantages over the inhalation of NO, such as its lack of toxic reactions23,24 (which require monitoring NO2 and methemoglobin formation during NO inhalation) and its easy administration by conventional nebulizers compared with the more complicated delivery systems required for NO. Furthermore, possibly life-threatening rebound phenomena have been described with iNO25,26 but not with aerosolized PGI2 or iloprost withdrawal. These advantages might favor the use of iloprost for the treatment of PHT; however, because of the lack of well-documented studies with prostacyclin or prostacyclin analogs, it might be too early to recommend the use of iloprost instead of iNO for the postoperative management of patients with PHT and CHD. The use of iNO has been shown to be helpful for the assessment of pulmonary vascular reactivity in selecting patients for surgery.1–4 In this setting, the aerosolization of prostacyclin might offer a real alternative to iNO. However, as with any nebulizer device, some uncertainty will exist regarding the amount of prostacyclin effectively delivered into the alveolar space. This leads to a potential risk to falsely classify some patients as nonresponders. The problem may be more present in children, in whom aerosol deposition shows more variability and is less well studied than in adults.27,28

Our study has several limitations. First, iloprost was always given after iNO because of its longer half-life; iloprost has a documented hemodynamic effect of 1 to 2 hours,9,13 which would have excluded a 2-group study protocol with a randomized drug allocation. Such a protocol would have required a longer testing protocol, which we thought was not

### TABLE 2. Levels of cGMP and cAMP in Plasma Samples

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>iNO</th>
<th>Iloprost</th>
<th>iNO + Iloprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGMP, nmol/L</td>
<td>18 ± 12</td>
<td>35 ± 21†</td>
<td>17 ± 14</td>
<td>36 ± 15†</td>
</tr>
<tr>
<td>cAMP, nmol/L</td>
<td>56 ± 23</td>
<td>54 ± 22†</td>
<td>65 ± 21†</td>
<td>66 ± 19†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*P < 0.01 vs baseline; † P < 0.05 vs baseline or iNO (repeated measures ANOVA).

### TABLE 3. Hemodynamics and cGMP and cAMP Levels of Patient 3 (Nonresponder)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>iNO</th>
<th>Iloprost</th>
<th>iNO + Iloprost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SAP, mm Hg</td>
<td>64</td>
<td>65</td>
<td>70</td>
<td>67</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>45</td>
<td>47</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>Rp/Rs</td>
<td>0.35</td>
<td>0.32</td>
<td>0.37</td>
<td>0.37</td>
</tr>
<tr>
<td>cGMP, nmol/L</td>
<td>13.9</td>
<td>19.6</td>
<td>14.1</td>
<td>24.6</td>
</tr>
<tr>
<td>cAMP, nmol/L</td>
<td>34</td>
<td>35</td>
<td>56</td>
<td>58</td>
</tr>
</tbody>
</table>

SAP indicates systemic arterial pressure; PAP, pulmonary arterial pressure.
acceptable for ethical reasons. Furthermore, it would have been more difficult to insure stable conditions and a return to baseline over such a long period. Second, although we made sure of a return back to baseline hemodynamics after iNO inhalation before administering iloprost, a potential interaction between iNO-induced effects and the iloprost-induced vasodilator capacities on the endothelial cell cannot be excluded. However, the return to baseline of cGMP levels after iNO inhalation under iloprost makes this unlikely. Finally, dose-response studies were not performed. Therefore, we cannot exclude that higher doses of iloprost might have resulted in a dose-dependent additional decrease in pulmonary arterial resistance. However, this is unlikely on the basis of other reports.\[20\]\[29\].\[30\]

In children with PHT and CHD, both iNO and aerosolized iloprost are equally effective in selectively lowering pulmonary vascular resistance through a selective increase in cGMP or cAMP, respectively. However, the combination of both vasodilators failed to prove more potent than either substance alone. Although aerosolized iloprost may be an alternative to iNO for early testing of vascular reactivity and for the postoperative treatment of acute PHT, it may prove to be more useful for the prolonged treatment of PHT.

Acknowledgments

Supported by Schering AG, Schlieren, Switzerland. The authors thank Lazlo Vadás, PhD, Department of Medical Biochemistry, University of Geneva, Switzerland, for his assistance and for his measurements of cGMP and cAMP levels.

References

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_Circulation_. 2001;103:544-548
doi: 10.1161/01.CIR.103.4.544

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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