Successful Use of Inhaled Nitric Oxide for Treatment of Severe Hypoxemia in an Infant with Total Anomalous Pulmonary Venous Return

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INFANTS with total anomalous pulmonary venous return (TAPVR) often present with heart failure or cyanosis or both. These infants become severely cyanotic and acidic, and their condition may deteriorate rapidly. Mechanical ventilation, along with sedatives and muscle relaxants, is often used to stabilize the children's condition preoperatively. However, urgent operation usually is necessary. Nitric oxide (NO) has been identified as an endothelium-derived relaxing factor, and the addition of low-dose NO to inspired gas has been shown to provide selective pulmonary vasodilation both in animals and in humans.

We describe an infant with TAPVR in whom inhalation of low-dose NO was used successfully to treat life-threatening hypoxemia.

Case Report

A 4-month-old, 6,210 g boy was admitted to the hospital with a 6-day history of cyanosis after an upper respiratory tract infection. He had been born at full term and had no history of previous illnesses. At the time of admission he was tachypneic but not hypotensive. Arterial blood gas values were pH 7.36, carbon dioxide tension 43 mmHg, oxygen tension 37 mmHg, and base excess 0 mmol/L while he breathed room air. A chest radiograph showed a dilated heart with hypervascular lungs. Oxygen therapy and mechanical ventilation were commenced, but the patient's condition did not improve. He was transferred to our intensive care unit 2 days later.

On admission to intensive care unit, echocardiography demonstrated an atrial septal defect, marked enlargement of the right atrium and ventricle, and tricuspid regurgitation. Doppler ultrasound by the tricuspid gradient method estimated the systolic pressure gradient between the right ventricle and right atrium at 40 mmHg, indicating the presence of pulmonary arterial hypertension. Although the sites of the entry of the individual pulmonary veins into the systemic venous circulation were not clearly identified, TAPVR was suggested.

Mechanical ventilation with a SERVO 900C ventilator (Siemens-Elema, Stockholm, Sweden) was started with an inspired oxygen fraction (FIO2) of 1.0, a tidal volume of 60–70 ml, and 3–5 cmH2O positive end-expiratory pressure while fentanyl, midazolam, and vecuronium were administered. However, the child exhibited cyanosis and increasing metabolic acidosis.

Seventeen hours after admission (on day 2), peripheral cyanosis became severe. Arterial blood gas values were pH 7.11, carbon diox-

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ide tension 69 mmHg, oxygen tension 43 mmHg, and base excess -8 mEq/l with FIO2 1.0. Blood lactate concentration increased to 5.7 mm. A chest radiograph showed an increase in pulmonary vascular markings. Because the patient's condition was worsening, manual ventilation by a Mapleson D system with an FIO2 of 1.0 was started. Three hours later, the Doppler-estimated systolic pressure gradient increased to 60 mmHg, suggesting the presence of severe pulmonary arterial hypertension at greater than systemic blood pressure. The signs of hypoxia, including peripheral cyanosis and coldness of the extremities, did not improve. With permission of the parents and institutional human studies approval, inhalation of NO was started by a Mapleson D system with an efficient scavenging system (2-A, Igarashi-Ika, Tokyo, Japan).

NO (Nihon Sanso, Oyama, Japan) was obtained as a mixture of 800 ppm in pure nitrogen. The NO concentration of the stock tank was certified by the gas company with a chemiluminescence analyzer (CLM-201, Shimadzu, Kyoto, Japan). NO was administered at 0.2 l/min via a Y-piece into a 10l/min continuous stream of fresh gas flow just proximal to the patient's tracheal tube connection. The flow rate of NO was regulated by a flow meter (RX1200, Kojima, Tokyo, Japan). The calculated concentration of NO of the breathing mixture was 16 ppm. The nitric oxide (NO2) concentration of the breathing mixture was chemically analyzed with a toxic gas detector (9L, Gastec, Yokohama, Japan) just before NO inhalation was started. The detector showed the presence of less than 0.1 ppm NO2; an infrared analyzer (270-30, Hitachi, Tokyo, Japan) showed the presence of less than 10 ppm NO2 in the NO stock gas.

Improvement was immediate, with an increase of peripheral arterial hemoglobin oxygen saturation (SpO2) from 85% to 96% within 1 min. The extremities became warm, and cyanosis disappeared. The changes in hemodynamics, blood gases, Doppler-estimated systolic pressure gradient, and methemoglobin level associated with NO inhalation are presented in Table 1. NO inhalation was discontinued for 30 min because of concern over potential toxicity associated with prolonged NO inhalation. SpO2 remained adequate thereafter with an FIO2 of 0.7-1.0. Three hours after discontinuation of NO inhalation, the Doppler-estimated systolic pressure gradient remained low, at 18 mmHg.

Eighteen hours after the discontinuation of NO (on day 3), because of a decrease of SpO2 from 90% to 65%, a second 30-min trial of NO inhalation was started. Improvement again was immediate, with an increase of SpO2 from 65% to 98% within 1 min. The arterial blood gas values before and 30 min after inhalation of NO with an FIO2 of 1.0 during manual ventilation were pH 7.31 and 7.40, carbon dioxide tension 53 and 39 mmHg, oxygen tension of 52 and 83 mmHg, and base excess -1 and 0 mEq/l, respectively. Methemoglobin after 30 min of NO inhalation was 0.2%. One hour later, a third trial of NO inhalation was required because of a sudden decrease in SpO2 from 91% to 58%. Again, improvement was immediate. A chest radiograph showed development of mild pulmonary edema. The positive end-expiratory pressure was increased to 6 cmH2O, and the amount of fluid administration was restricted. Intravenous furosemide (1 mg) was started and repeated every 8 h. Dobutamine (2 μg/kg) was also started. Pulmonary edema improved gradually.

On day 5, the patient was transferred to a children's hospital, where surgery was performed successfully the next day. At surgery, a mixed type of TAPVR, atrial septal defect, and patent ductus arteriosus were found. The common pulmonary vein from the left pulmonary veins and right lower pulmonary vein joined the portal vein (intrahepatic type), and the pulmonary vein from the right upper and middle lobes drained into the uppermost part of the superior vena cava (supracardiac type). An anastomosis was performed between the retrocardiac common pulmonary vein and the left atrium; the atrial septal defect was closed; and the patent ductus arteriosus was ligated. Correction of the pulmonary vein draining into the superior vena cava was not performed because it was associated with too great a risk.

The patient's postoperative course was uneventful, and he was discharged 50 days after operation.

**Discussion**

The only effective treatment for TAPVR is surgical correction of the defect. The aims of medical treatment are to stabilize the patient's general condition while

### Table 1. Changes of Systolic and Diastolic Blood Pressure, Heart Rate, Blood pH, Blood Gases, Hemoglobin Oxygen Saturation with Pulse Oximetry, Estimated Systolic Pressure Gradient between Right Ventricle and Right Atrium, and Methemoglobin Level before, during, and after Nitric Oxide Inhalation

<table>
<thead>
<tr>
<th></th>
<th>Before NO</th>
<th>NO 5 Min</th>
<th>NO 10 Min</th>
<th>NO 20 Min</th>
<th>NO 30 Min</th>
<th>5 Min after NO</th>
<th>10 Min after NO</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
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<td>77</td>
<td>95</td>
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<td>86</td>
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<td>DBP (mmHg)</td>
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<td>49</td>
<td>53</td>
<td>61</td>
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<td>57</td>
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<tr>
<td>HR (beats/min)</td>
<td>188</td>
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<td>186</td>
<td>179</td>
<td>182</td>
<td>198</td>
<td>191</td>
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<tr>
<td>SpO2 (%)</td>
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<td>99</td>
<td>97</td>
<td>98</td>
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<td>94</td>
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<td>FIO2</td>
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<td>PaO2 (mmHg)</td>
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<td>77</td>
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<td>-0.7</td>
<td>-0.6</td>
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<td>0.2</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<td>ΔP (mmHg)</td>
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<td>35</td>
<td>-18</td>
<td>-18</td>
<td>-20</td>
<td>-18</td>
<td>-18</td>
</tr>
</tbody>
</table>

NO = nitric oxide; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; SpO2 = hemoglobin oxygen saturation with pulse oximetry; FIO2 = inspired oxygen fraction; PaO2 = arterial oxygen tension; PaCO2 = arterial carbon dioxide tension; BE = base excess; Met-Hb = methemoglobin level; ΔP = estimated systolic pressure gradient between right ventricle and right atrium.

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he or she awaits operation. Severe hypoxia due to the marked reduction of pulmonary blood flow and the development of pulmonary edema should be avoided, and the interatrial right-to-left shunt flow should be maintained for systemic perfusion.\textsuperscript{1,7}

The reduction of pulmonary blood flow is produced by an increase in pulmonary vascular resistance and subsequent right heart failure.\textsuperscript{1,7} Thus, the magnitude of pulmonary blood flow, and therefore the ratio of oxygenated to unoxgenated blood that returns to the right atrium, are a function of pulmonary vascular resistance.\textsuperscript{1} In this condition, in other words, arterial oxygen saturation is inversely related to pulmonary vascular resistance.\textsuperscript{1}

Pulmonary vascular resistance increases because of anatomic pulmonary venous obstruction, pulmonary vascular pathologic changes secondary to prolonged pulmonary arterial hypertension (Eisenmenger's phenomenon), functional pulmonary vasoconstriction, or a combination of these.\textsuperscript{1,7} There is no effective medical therapy for anatomic pulmonary venous obstruction or Eisenmenger's phenomenon. However, medical therapy is available for functional pulmonary vasoconstriction.

Currently used vasodilator agents such as prostainglandin E\textsubscript{1}\textsuperscript{8} and tolazoline\textsuperscript{9} may be used to dilate pulmonary vasculature. However, these agents are nonselective and also dilate systemic blood vessels. Inhaled NO is a recently discovered rapidly acting pulmonary vasodilator that does not significantly dilate the systemic circulation.\textsuperscript{4} A dose-dependent reduction of hypoxic pulmonary vasoconstriction through the use of inhaled NO has been reported in the newborn lamb.\textsuperscript{10} Roberts et al.\textsuperscript{11} demonstrated that inhaling NO increased pulmonary blood flow in infants and children with congenital heart disease. In addition, short-term inhalation of NO increased postductal oxygenation\textsuperscript{12} in newborns with persistent pulmonary hypertension and may improve outcome.\textsuperscript{13} In the current case, NO inhalation resulted in dramatic improvement in oxygenation and decreased pulmonary hypertension. The disappearance of peripheral cyanosis and coldness suggested improvement of systemic perfusion by NO inhalation. On the other hand, the early decrease in systemic blood pressure with inhaled NO was inconsistent with the findings of the previous reports.\textsuperscript{5,11-13} Seldén et al.\textsuperscript{14} reported a case of sustained reduction of pulmonary hypertension with short-term NO inhalation after cardiac surgery in an infant, a finding that is consistent with that of our case.

Eighteen hours after the discontinuation of NO, we noted development of mild pulmonary edema. Although the precise mechanism of pulmonary edema is unclear, its development may be attributed to an increase in pulmonary blood flow and to an increase in the left-to-right shunt flow via a patent ductus arteriosus after NO inhalation. In this case, pulmonary edema was successfully managed by the combined use of positive end-expiratory pressure, fluid restriction, diuretic agents, and dobutamine.

Finally, the risks and benefits of NO inhalation for treatment of the severe hypoxia of TAPVR need careful consideration. The potential dangers of administering NO are methemoglobinemia and spontaneous formation of NO\textsubscript{2} in the presence of oxygen.\textsuperscript{4} The methemoglobinemia in this infant did not exceed 0.3%. The rate of NO\textsubscript{2} formation depends on the concentration of NO, R\textsubscript{NO}, and the contact time with oxygen.\textsuperscript{15} In this case, only 16 ppm NO was used, for the limited time of 30 min. The contact time of NO and oxygen was kept as short as possible by mixing both just proximal to the patient's tracheal tube.

In summary, in a hypoxic infant with TAPVR, inhalation of 16 ppm NO produced immediate improvement in oxygenation and a lasting reduction of pulmonary hypertension. The patient's general condition improved dramatically after the start of NO inhalation. We believe that NO inhalation may be a useful method for treating severely hypoxic infants who have TAPVR while awaiting operation.

References

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