Inhaled Nitric Oxide-induced Closure of a Patent Foramen Ovale in a Patient with Acute Respiratory Distress Syndrome and Life-threatening Hypoxemia

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ACUTE respiratory distress syndrome (ARDS) is characterized by nonhemodynamic pulmonary edema, intrapulmonary shunting, arterial hypoxemia, and acute pulmonary hypertension that may induce acute right ventricular dysfunction.1,2 Autopsy studies indicate an incidence of patent foramen ovale (PFO) in the general population ranging from 25% to 35%.3 These PFOs are a potential source of right-to-left intracardiac shunt when the pressure gradient between right and left atrial pressure becomes positive as pulmonary hypertension develops. As a consequence, intracardiac shunt might contribute to the severe arterial hypoxemia observed in some patients with ARDS. In acute lung injury, inhaled nitric oxide selectively dilates pulmonary vessels in contact with gas-containing alveoli, thus diverting pulmonary blood flow from nonventilated to ventilated lung regions. As a consequence, arterial oxygenation improves via a reduction in intrapulmonary shunt.4,5 By reducing pulmonary arterial hypertension, inhaled nitric oxide may decrease the right-to-left atrial pressure gradient and reverse the right-to-left intracardiac shunt observed in neonates with persistent pulmonary arterial hypertension and congenital intracardiac shunt.6,7 A similar effect can be expected in adults with acute respiratory failure and PFO. We describe a case of severe ARDS in a patient with a PFO in which nitric oxide produced a dramatic improvement in arterial oxygenation by reducing intrapulmonary shunt and reversing right-to-left intracardiac shunt.

Case Report

After a car accident, a 64-year-old man with a history of dysrhythmia and chronic alcoholism was admitted to the emergency center of la Pitie Hospital in Paris. Initial lesions were a cervical fracture (C2) without neurologic injury treated by traction, a first rib fracture with a pulmonary contusion, and hemomediastinum secondary to a traumatic dissection of the right axillary artery, which required surgical repair. Postoperatively, he had rapidly worsening respiratory function...
that led to a cardiac arrest. After cardiopulmonary resuscitation, including tracheal intubation and ventilation, chest compression, and injection of epinephrine, the patient was transferred to the surgical intensive care unit. At this time, the clinical characteristics were significant for severe ARDS. The Murray score was 3.25. Within 24 h, radial and tibial pulmonary artery catheters were inserted, and the resulting hemodynamic and gas exchange data measured during intermittent positive pressure ventilation are listed in Table 1. Chest x-ray showed pulmonary bilateral infiltrates predominant on the right. Static respiratory compliance was 57 ml/cmH2O (slope of the pressure-volume curve between 500 and 1000 ml). High-resolution thoracic computed tomography scan showed extensive bilateral and nondependent hydropneumothorax extending to 70% of the lung parenchyma. Protected minihemothoracoscopic lavage samples were positive for Streptococcus pneumoniae and Neisseria meningitidis group B (>1,000 colony forming U/ml), and therapy with 100 mg/kg amoxicillin was given for 2 weeks.

Transesophageal echocardiography, performed within 24 h after admission to the surgical intensive care unit with a Sonos 1500 Hewlett-Packard (Andover, MA) using an omniplan 5-MHz transesophageal echocardiographic probe, showed a dilated right ventricle, a shift to the left and a paradoxical motion of the interventricular septum, and a severe tricuspid regurgitation. Left ventricular ejection fraction was normal with no evidence of myocardial contusion. Without nitric oxide, the interventricular septum was curved to the left (Fig. 1A), suggesting a positive pressure gradient between right and left atrial pressure. Pulmonary wedge pressure was equal to right atrial pressure. In addition, the color and pulsed-wave Doppler visualized a high-velocity, right-to-left intracardial shunt. Contrast echocardiography performed according to a previously described technique demonstrated an early opacification of the left atrium (Fig. 1B) consistent with a PFO.

Because of the severity of arterial hypoxemia (Pao2 56 mmHg, Fio2 1.0, zero end-expiratory pressure and Pao2 70 mmHg, Fio2 1.0, and PEEP 10 cmH2O) and pulmonary arterial hypertension, the patient was treated with 2 ppm inhaled nitric oxide. Nitric oxide was released from a tank of nitrogen with a nitric oxide concentration of 900 ppm (Air Liquide, Meudon-la-Forêt, France). Nitric oxide was delivered continuously within the inspiratory limb of the ventilator, before the Y piece. Endothelial concentration of nitric oxide and nitrous oxide were continuously measured using a chemiluminescence apparatus (NOX 2000 TM, Sèvres, Ix-En-Provence, France), calibrated in the range of 0–5,000 ppb using a tank of nitrogen containing 900 ppb nitric oxide (Air Liquide). Nitric oxide concentrations were measured using a continuous aspiration of tracheal gases (150 ml/min) through the proximal side port of a Mallinckrodt endotracheal tube (Argyle, NY). A concentration of 2 ppm was chosen according to the results of a previous study performed in hypoxic patients with pulmonary hypertension and severe acute respiratory failure.56 Hemodynamic and respiratory parameters were measured and recorded on a Gould ES 1000 recorder (Cleveland, OH) before and after nitric oxide administration and simultaneously with the transesophageal echocardiography procedure.

The respiratory and hemodynamic effects of inhaled nitric oxide are shown on Table 1. Nitric oxide decreased right ventricular chamber size and reduced tricuspid regurgitation and interventricular septal echocardiographic motion. It also changed intersegmental septal curvature to the right. This was associated with a negative gradient between right and pulmonary wedge pressures mainly related to an increased pulmonary wedge pressure. Contrast echocardiography showed the lack of opacification of the left atrium by bubbles, thereby demonstrating elimination of the right-to-left intracardiac shunt (Fig. 1C).

The patient continued to receive nitric oxide for 3 weeks. Serial echographic examinations showed persistent absence of right-to-left intracardiac shunt. A complete recovery of ARDS was obtained after 4 weeks, and the patient was progressively separated from mechanical ventilation and discharged from the surgical intensive care unit after 6 weeks.

Discussion

The ARDS described in the current case report was responsible for a life-threatening hypoxemia, associated with a major increase in pulmonary artery pressure. In patients with ARDS, pulmonary arterial hypertension usually results from several causes: hypoxic pulmonary vasoconstriction; disseminated occlusion of the pulmonary microvasculature; vascular compression of pulmonary vessels by edema or high alveolar pressure; increased release of vasoconstrictors, such as thromboxane A2 and endothelin; and decreased release of vasodilators, such as endogenous nitric oxide. It can cause right ventricular dysfunction and an increase in right cardiac filling pressures. When right atrial pressure exceeds that in the left atrium in the presence of a PFO, the opening of a right-to-left intracardiac shunt results in a further decrease in arterial oxygenation. Using contrast echocardiography and doppler echocardiographic study, Konstadt et al. found in a population of patients

![Table 1. Effects of Inhaled NO](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931826/ on 10/31/2018)

<table>
<thead>
<tr>
<th>NO = 0</th>
<th>NO = 2 ppm</th>
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</thead>
<tbody>
<tr>
<td>Pao2 (mmHg)</td>
<td>56</td>
</tr>
<tr>
<td>PpaO2 (mmHg)</td>
<td>42</td>
</tr>
<tr>
<td>VO2/VT (%)</td>
<td>35.6</td>
</tr>
<tr>
<td>Qg/Ql (%)</td>
<td>35</td>
</tr>
<tr>
<td>MPAP (mmHg)</td>
<td>48.6</td>
</tr>
<tr>
<td>PVR (%)</td>
<td>2.026</td>
</tr>
<tr>
<td>CL (L·min⁻¹·m⁻²)</td>
<td>1.6</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>7.6</td>
</tr>
<tr>
<td>PVWI (mmHg)</td>
<td>7.6</td>
</tr>
<tr>
<td>RVSWI (g·m⁻²)</td>
<td>11.7</td>
</tr>
<tr>
<td>LVEDA (cm²)</td>
<td>21.6</td>
</tr>
<tr>
<td>LVESA (cm²)</td>
<td>9.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>56</td>
</tr>
<tr>
<td>PFO</td>
<td>Open</td>
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</table>

*Voo/VT = alveolar dead space calculated as 1 – Paco2/PETCO2 (ETCO2 = end tidal carbon dioxide tension measured using a noninvasive infrared capnometer; O2 ET = right to left shunt; MPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance index calculated as MPAP – RAP/CI; CI = cardiac index; RAP = right atrial pressure; PWV = pulmonary wedge pressure; RVSWI = right ventricular stroke work index calculated as (MPAP – RAP) x CI; RVESA = left ventricular end-systolic area; RVEDA = left ventricular end-diastolic area; LVEDA = left ventricular end-diastolic area; LVEF = left ventricular ejection fraction calculated as LVEDA – LVEDA/ PFD – patent foramen ovale.*

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doppler echocardiographic measurements intraoperatively, Konstadt et al. found a high incidence of PFO in a population of patients undergoing cardiac surgery.10 Severe postoperative hypoxemia resulting from the opening of a PFO initially was described in cardiac patients whose lungs were mechanically ventilated.14-16 The additive effects of positive end-expiratory pressure also were outlined.16 The role played by PFO in the onset of severe hypoxemia in patients with ARDS is not known and remains to be evaluated in a large-scale study.

Estagnasinc et al. reported a case of reversal of right-to-left atrial positive pressure gradient and closure of a PFO by using inhaled nitric oxide in a concentration of 25 ppm in a patient with pulmonary embolism.17 The closure of the PFO was the consequence of a marked increase in pulmonary wedge pressure associated with a slight decrease in right atrial pressure after nitric oxide-induced decrease in pulmonary vascular resistance. In our patient, inhaled nitric oxide in a concentration of 2 ppm produced a major decrease in mean pulmonary artery pressure and pulmonary vascular resistance. Right atrial pressure slightly decreased, whereas pulmonary wedge pressure increased, reversing the atrial pressure gradient and resulting in functional closure of the foramen ovale. The increase in pulmonary wedge pressure was a direct consequence of inhaled nitric oxide-induced pulmonary vasodilation. The 50% reduction in pulmonary vascular resistance induced by nitric oxide was associated with an increase in cardiac index and left ventricular end-diastolic area, suggesting an increase in venous return to the left ventricle. Such a mechanism was reported in patients with left ventricular failure receiving inhaled nitric oxide.18-20 In cardiac patients with poor left ventricular function, inhaled nitric oxide-induced increase in left ventricle preload might induce pulmonary edema in the absence of a simultaneous reduction in left ventricular afterload.21 The reversal of right-to-left atrial pressure gradient promoted immediate closure of intracardiac right-to-left shunt and a dramatic improvement in arterial oxygenation. Using contrast
Echocardiography, inhaled nitric oxide-induced closure of the foramen ovale was demonstrated by the absence of bubbles crossing the septal wall. Echocardiographic changes in atrial septal position after nitric oxide administration were in accordance with changes in the pressure gradient between right atrial and capillary wedge pressures. The dramatic improvement in arterial oxygenation (from 56 to 318 mmHg) after inhaled nitric oxide administration was associated with a marked decrease in right-to-left shunt and allowed us to decrease the FIO2 to less than 0.6. Because of the lack of quantitative evaluation of the respective contribution of intrapulmonary and intracardiac shunting to the right-to-left shunt, it is impossible to know how significantly the PFO contributed to arterial hypoxemia. In all studies reporting the effects of inhaled nitric oxide on intrapulmonary shunt in patients with ARDS, right-to-left shunt decreases as a mean by 10–20%. In our patient, right-to-left shunt decreased by 46%, suggesting that the PFO was playing a role in hypoxemia. A slight decrease in PAO2 was also observed and associated with a marked decrease in alveolar dead space. In the absence of any change in minute ventilation, that decrease in alveolar dead space likely can be explained by the perfusion of ventilated lung areas previously nonperfused.

Based on the current case report, PFO should be systematically looked for in patients with ARDS and severe arterial hypoxemia. If present, a low concentration of inhaled nitric oxide may reverse the atrial pressure gradient, inducing a functional closure of the foramen ovale and a dramatic improvement in arterial oxygenation.

References


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