of eosinophils in the BAL, and negative investigations for other causes of eosinophilia, the diagnosis of CEP was made.

The patient responded rapidly to treatment with IV methylprednisolone, 1 g/d; 3 days later, she was successfully extubated. Her treatment was changed to oral prednisolone, 40 mg/d, and she was discharged on the eighth hospital day.

On follow-up visits, the patient remained asymptomatic, and the prednisolone was tapered to 15 mg/d by 6 months and was stopped by 9 months, with chest radiography showing residual bilateral pleural thickening, and significant improvement on pulmonary function testing (Table 1). On follow-up, there was no relapse 4 months after discontinuation of steroid therapy.

**DISCUSSION**

Our patient satisfied the criteria for the diagnosis of CEP. Pulmonary involvement may occur in 40% of patients with idiopathic hypereosinophilic syndrome (HES) and may therefore closely resemble CEP. However, because of the absence of multiorgan involvement with signs of end-organ damage, one of the triad of HES and the characteristic radiologic findings of CEP in our patient, the diagnosis of HES was excluded. Bronchiolitis obliterans with organizing pneumonia may also mimic CEP, but the radiologic and BAL findings were incompatible with the diagnosis of bronchiolitis obliterans with organizing pneumonia.

The onset of CEP is usually insidious, and symptoms are present for at least a few months before diagnosis, as in our patient. If the diagnosis is delayed, progression to respiratory failure may occur. Bronchial asthma is present in about half of the cases. Peripheral eosinophilia occurs in most patients with CEP and may be associated with elevated IgE levels. The latter may parallel the disease activity. In 25% of patients with CEP, chest radiography shows the characteristic, extensive bilateral peripheral infiltrates, described as a photographic negative image of pulmonary edema. This was not present in our patient.

Pleural effusion is uncommon in CEP. In a review of 19 cases of CEP, only 2 patients had pleural effusion, and in a multicenter study, 2 of 62 patients had bilateral small-size pleural effusions. The mechanism of pleural effusion in CEP is unknown. However, it might be because of tissue damage induced by infiltration with eosinophils, antibody-mediated cellular toxicity, or the release of intracytoplasmic leukotriene that increases microvascular permeability.

Our patient had severe restrictive lung disease, as reported in the majority of patients with CEP. Durieu et al. found that 9 of 19 patients with CEP had restrictive abnormalities and 4 patients had obstructive abnormalities, and on long-term follow-up, 8 of the 19 patients showed complete recovery. The high diffusion capacity of the lung for carbon monoxide/alveolar volume ratio in our patient could be explained, initially, by the large pleural effusion, collapse and entrapment of the lungs, and, lately, by pleural thickening.

Open lung biopsy is performed when the diagnosis is in doubt, and this usually shows interstitial alveolar infiltration with eosinophils, microabscesses, Charcot-Leyden crystals, and bronchiolitis obliterans. The prompt response to corticosteroids, as seen in our patient, is characteristic in CEP. The prognosis of CEP is excellent, but there may be relapse of disease. Therefore, decreasing doses of corticosteroids are recommended for at least 6 to 12 months.

**CONCLUSION**

Although not reported before, rapidly accumulating pleural effusions could be a presenting feature of CEP. Early recognition of this is important in view of the good response to treatment with corticosteroids.

**REFERENCES**


**One-Year Continuous Inhaled Nitric Oxide for Primary Pulmonary Hypertension**

Gregorio Pérez-Peñaate, MD; Gabriel Julià-Serdà, MD; Juan María Pulido-Duque, MD; Elías Górriz-Gómez, MD; and Pedro Cabrera-Navarro, MD

We describe a case of long-term administration of nitric oxide (NO) in a 32-year-old man who was admitted with exertional dyspnea and anasarca. A
diagnosis of primary pulmonary hypertension was made. An acute vasodilator trial with inhaled NO showed a 5% reduction of the mean pulmonary artery pressure. Long-term NO inhalation therapy was initiated. Twenty days later, the dyspnea improved, the anasarca resolved, and the PaO₂ level increased. After 12 months of NO therapy, the patient remained stable and no signs of toxicity or tachyphylaxis were observed. To our knowledge, this is the first report of 1 year of continuously inhaled NO in an adult patient with primary pulmonary hypertension. These findings suggest that prolonged NO therapy might be an effective alternative, at a lower cost, to the continuous IV infusion of epoprostenol. (CHEST 2001; 119:970–973)

Key words: nitric oxide; primary pulmonary hypertension; pulmonary vasodilator

Abbreviation: NO = nitric oxide

Nitric oxide (NO) is a potent pulmonary vasodilator produced in vivo by the endothelium via the metabolism of L-arginine in the presence of NO synthetase. Systemic hypotension is avoided when NO reaches the bloodstream, and it is rapidly inactivated by hemoglobin, forming nitrates. NO also inhibits the proliferation of vascular smooth muscle and alters the gene expression of growth factors, vasoconstrictors, and endothelial cell adhesion molecules. Inhaled NO has been used in the treatment of persistent pulmonary hypertension in the newborn, primary pulmonary hypertension, and postoperative graft dysfunction after lung and heart transplantation. At the later stages of primary or secondary pulmonary hypertension, inhaled NO might offer a promising alternative treatment. We used NO, 80 ppm, for as long as 12 months to treat a patient with severe primary pulmonary hypertension.

CASE REPORT

A 32-year-old man, who was an ex-addict of inhaled heroin, was admitted to the hospital with a 2-year history of dyspnea and anasarca (New York Heart Association functional class IV). Physical examination showed a systolic murmur in the pulmonary area and generalized edema. The results of laboratory tests were normal except for a creatinine clearance of 59 mL/min/1.73 m². The results of an arterial blood gas test carried out while breathing room air (PaO₂ 70 mm Hg) showed a 5% reduction of mean pulmonary artery pressure and a 23% reduction in calculated pulmonary vascular resistance accompanied by a 21% increase in cardiac output was noted after the completion of the short-term trial. Informed consent was obtained from the patient and from the ethics committee of the hospital to initiate continuous NO inhalation therapy. A tank of NO mixed with N₂ in a concentration of 800 ppm was connected to an oxygen-demand valve (Demand-flow-62; Air Products and Chemicals; Allentown, Pa.) and administered to the patient through a nasal cannula at the beginning of the inspiratory cycle. The system is activated on demand at −1.5 cm H₂O inspiratory pressure. To produce an inspired NO concentration of 80 ppm for the patient’s baseline minute volume of 8 L, the NO-N₂ air mixture flow was 0.9 L/min. Twenty days later, there was an improvement in dyspnea, renal function (creatinine clearance: 92 mL/min/1.73 m²), edema, and gas exchange while breathing room air (PaO₂ 65 mm Hg; PaCO₂ 34 mm Hg). The patient continued inhaled NO therapy at home using a tank 7.5 m³ in size. A portable aluminum tank of 1 m³ was supplied for ambulation. No complications or adverse effects were noted, and the concentrations of NO and NO₂ measured at the patient’s home were negligible. After 12 months of NO therapy, the patient was in New York Heart Association functional class II, with no edema, and his baseline PaO₂ level was 70 mm Hg. A 9% reduction of mean pulmonary artery pressure was demonstrated. Results of the first and second right heart catheterization are shown in Table 2.

DISCUSSION

Primary pulmonary hypertension is a disease that involves the small pulmonary arteries, which exhibit intimal proliferation and fibrosis, medial hypertrophy, and thrombosis. Treatment of the disease is based on therapy with anticoagulation and vasodilator agents, such as calcium-channel blockers and epoprostenol. Long-term infusion of epoprostenol improves clinical symptoms, hemodynamic characteristics, and survival of pulmonary hypertensive patients. Tolerance of epoprostenol with long-term treatment can only be overcome by continuing to increase the dosage over time. In addition, major adverse effects of long-term therapy are attributable to the complexity and

### Table 1—Pulmonary Function at Baseline and After 1 Year of Continuous Inhaled NO Therapy

<table>
<thead>
<tr>
<th>Data</th>
<th>Baseline (% Predicted)</th>
<th>1-Year NO (% Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC, L</td>
<td>4.36 (102)</td>
<td>4.27 (100)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>3.60 (99)</td>
<td>3.33 (92)</td>
</tr>
<tr>
<td>Total lung capacity, L</td>
<td>5.67 (97)</td>
<td>5.75 (95)</td>
</tr>
<tr>
<td>Residual volume, L</td>
<td>1.44 (88)</td>
<td>1.41 (86)</td>
</tr>
<tr>
<td>DlCO₂ mmol/min/kPa</td>
<td>6.05 (60)</td>
<td>6.7 (66)</td>
</tr>
<tr>
<td>DlCO₂VA ratio</td>
<td>1.47 (71)</td>
<td>1.67 (77)</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>55</td>
<td>70</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>pH</td>
<td>7.48</td>
<td>7.46</td>
</tr>
</tbody>
</table>

*DLCO = diffusing capacity of the lung for carbon monoxide; VA = alveolar volume.
The safety of continuous long-term NO inhalation has not been established definitely. A possible problem is the remarkable increase in pulmonary resistance after the interruption of NO inhalation, which has been reported in pulmonary hypertension of the newborn and in patients with ARDS. Inhaling NO at high levels may cause marked methemoglobinemia, but the inhalation of NO at low levels seems to be safe. Although high levels of NO may cause pulmonary edema and death, the lack of lung parenchymal abnormalities shown by electron microscopy in patients who have undergone lung transplants suggests that there is no significant tissue toxicity. No signs of NO toxicity or tachyphylaxis were detected in our patients with the dosage used. In addition, the oxygen-demand valve in the ambulatory NO inhalation system allowed the use of nasal cannulas with minimal contamination of the environment and negligible concentrations of NO and NO₂ measured at home. The use of a tank of NO mixed with NO₂ in a concentration of 800 ppm was equally as safe as the 80 ppm NO reported previously by others, and it lasted longer. In patients with ARDS, full pulmonary vasodilation requires a higher concentration of NO (as much as 100 ppm) when compared with the concentration (< 10 ppm) required to simply achieve an improvement in ventilation-perfusion matching. Adatia et al. have suggested a dose of 80 ppm NO as a starting point to control severe pulmonary hypertension.

In summary, as far as we are aware, this is the first report of inhaled NO therapy over 12 months in an adult patient with severe primary pulmonary hypertension. This mode of therapy may be an effective alternative to the continuous IV infusion of epoprostenol, at a lower cost and with a lower rate of complication.

ACKNOWLEDGMENT: The authors thank Carburos Metálicos, S.A., Barcelona (an Air Products company) for their technical support and Marta Pulido, MD, for editing the manuscript and editorial assistance.

REFERENCES


Table 2—Hemodynamic Data at Baseline, During Acute Vasodilator Trial and After 1 Year of Continuous Inhaled NO Therapy

<table>
<thead>
<tr>
<th>Data</th>
<th>Baseline</th>
<th>15 min</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systemic artery pressure, mm Hg</td>
<td>101</td>
<td>105</td>
<td>104</td>
</tr>
<tr>
<td>Mean right atrial pressure, mm Hg</td>
<td>22</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>78</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Pulmonary-capillary wedge pressure, mm Hg</td>
<td>15</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes/cm²</td>
<td>1,145</td>
<td>886</td>
<td>890</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.4</td>
<td>5.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes/cm²</td>
<td>1,436</td>
<td>1,228</td>
<td>1,208</td>
</tr>
</tbody>
</table>
Pregnancy and Primary Pulmonary Hypertension*

Successful Outcome With Epoprostenol Therapy

Rosalyn Stewart, MD; Divina Tuazon, MD; Gayle Olson, MD; and Alexander G. Duarte, MD

Primary pulmonary hypertension (PPH) associated with pregnancy carries a high maternal mortality rate. Short-term epoprostenol infusion has been demonstrated to improve the hemodynamic profile in patients with PPH. We report a successful maternal-fetal outcome with epoprostenol therapy during pregnancy, cesarean section, and postpartum in a patient with PPH. Epoprostenol therapy did not produce any physical or developmental abnormalities in the fetus. A favorable maternal-fetal outcome may occur with a multidisciplinary approach.

(CHEST 2001; 119:973–975)

Key words: cesarean section; epoprostenol; pulmonary hypertension; pregnancy

Abbreviations: PAC = pulmonary artery catheter; PPH = primary pulmonary hypertension

Primary pulmonary hypertension (PPH) is a rare, progressive condition aggravated by the physiologic changes occurring during pregnancy and surgery. The maternal mortality rate associated with pregnancy and pulmonary hypertension ranges from 30 to 50%. Administration of IV epoprostenol has been well-demonstrated to improve hemodynamics in nonpregnant patients with PPH. We report a successful maternal-fetal outcome in a pregnant woman in whom PPH was diagnosed who was treated with IV epoprostenol before, during, and after undergoing cesarean section.

Case Report

A 35-year-old, gravida (G2,P0) patient with a history of hypothyroidism presented at 26 weeks’ gestation with progressive exertional dyspnea and fatigue of several weeks duration. She also reported several recent syncopal episodes. Her first pregnancy was uncomplicated, and she denied prior cardiopulmonary disease, illicit drug use, or ingestion of anorexigens. On physical examination, her vital signs were as follows: BP, 90/60 mm Hg; heart rate, 105 beats/min; respiratory rate, 20 breaths/min; and oxygen saturation as measured by pulse oximetry, 92%. Jugular venous distension was present. Cardiac auscultation revealed a loud S2 and a grade 3/6 systolic murmur over the left lower sternal border that was accentuated on inspiration. Lung fields were clear to auscultation bilaterally. Extremities were without clubbing, and 1+ edema was present. An ECG was interpreted as representing normal sinus rhythm. A chest radiograph was unremarkable for parenchymal infiltrates, and a ventilation-perfusion scan was interpreted as revealing a low probability for a pulmonary embolism. Arterial blood gas measurements revealed the following: pH, 7.45; PCO2, 29 mm Hg; PO2, 79 mm Hg; and bicarbonate level, 20 mEq/L. An echocardiogram displayed a dilated right ventricle, paradoxical septal wall motion, and normal left ventricular wall motion.

The patient was admitted to labor and delivery and was prescribed bed rest, oxygen, diuretics, and heparin. Fetal heart tones were noted at 150 beats/min, and IM corticosteroids were administered to accelerate fetal lung development. Despite this therapy, the patient continued to report progressive dyspnea, and at 32 weeks’ gestation the placement of a pulmonary artery catheter (PAC) demonstrated moderate pulmonary hypertension (Table 1). IV epoprostenol therapy was initiated at 4 ng/kg/min, producing an improvement in the hemodynamic profile (Table 1). At 36 weeks’ gestation, while receiving IV epoprostenol, the premature rupture of membranes occurred followed by active labor. However, the progression of labor was inadequate, and a cesarean section was scheduled. Preoperatively, a PAC was placed and epidural anesthesia was administered. Subsequently, the cardiac output declined from 7.4 to 4.1 L/min and the epoprostenol infusion was increased to 10 ng/kg/min. The patient remained hemodynamically stable throughout the cesarean section and delivered a healthy male infant weighing 7 lbs with Apgar scores of 5 and 9, respectively, at 1 and 5 min. A bilateral tubal ligation was performed with patient consent. Following extubation, the PAC was maintained for 48 h to assist with IV fluid administration, and the hemodynamic profile remained stable with the patient receiving 10 ng/kg/min epoprostenol. On postoperative day 2, heparin therapy was resumed.

Three weeks later, the patient underwent a vasodilator trial with calcium-channel blockers but did not have a favorable response, hence, she was continued on epoprostenol therapy. Presently, she has resumed an active lifestyle as a housewife and mother. Furthermore, her 2-year-old son is in good health without any developmental delays.

Discussion

An early case series reported a 50% mortality rate associated with pregnancy and PPH. A more recent account noted a 30% mortality rate and partly attributed the decline in the mortality rate to earlier recognition, better understanding of the pathophysiology of pulmonary hypertension, along with improvements in medical therapy and critical-care obstetrics. Recognition of the elevated maternal-fetal mortality rate has led physicians to recommend effective contraception and, in the event of a pregnancy, early fetal termination. The maternal mortality rate is related principally to the increased demands on the cardiopulmonary system during pregnancy. Under normal circumstances, increases in cardiac output in the range of 30 to 50%, blood volume in the range of 40 to 50%, and oxygen consumption of 20% are observed during pregnancy. Other physiologic changes include an increase in cardiac output during labor in patients receiving local...