

Favorable response of Eisenmenger syndrome to inhaled nitric oxide during pregnancy

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OBJECTIVE: Our goal was to evaluate the effectiveness of therapy with a specific pulmonary vasodilator, nitric oxide, in a woman with Eisenmenger syndrome during pregnancy.

STUDY DESIGN: Eisenmenger syndrome consists of a congenital communication between the systemic and pulmonary circulation with secondary pulmonary hypertension causing reversal of flow through the shunt. Maternal morbidity is approximately 50% with the greatest risk of death being in the peripartum period. Pharmacologic therapy to relieve worsening pulmonary hypertension is confounded by the undesired effects of vasodilators on the systemic circulation. Therapy with a specific pulmonary vasodilator, nitric oxide, was attempted.

RESULTS: A 27-year-old woman with Eisenmenger syndrome at 36 weeks' gestation was treated with inhaled nitric oxide during the second stage of labor and the postpartum period when she experienced progressive refractory hypoxemia. Administration of nitric oxide was followed by improved oxygenation and lowering of pulmonary artery pressures. A brief episode of methemoglobinemia responded to lowering of the nitric oxide concentration and administration of intravenous methylene blue. Nitric oxide was discontinued after 48 hours. The patient died 2 days later despite continued vasodilator therapy including intra-pulmonary artery prostacyclin.

CONCLUSION: Inhaled nitric oxide can be used to correct the hypoxemia of Eisenmenger syndrome. Nitric oxide inhalation is easily performed, and pulmonary vasodilatory effects commence within minutes after administration. (*Am J Obstet Gynecol* 1999;180:64-7.)

Key words: Eisenmenger syndrome, pulmonary hypertension, nitric oxide

Eisenmenger syndrome includes patients with a congenital cardiac lesion and severe pulmonary hypertension in whom reversal of a left-to-right shunt has occurred. The condition carries a high maternal mortality rate in pregnancy with most of the reported deaths occurring at delivery or in the days immediately afterward.¹⁻³ The cause of the excess deaths in the peripartum period is not known. In cases described in sufficient detail, 2 patterns of decline have been observed—refractory hypoxemia worsening over hours to days and, less commonly, sudden death. In the former setting, attempts to reverse worsening pulmonary hypertension by means of vasodilators is confounded by the effect on the systemic circulation resulting in decreased peripheral resistance and worsening of the right-to-left shunt.

Inhaled nitric oxide acts as a selective pulmonary vasodilator. We describe the use of inhaled nitric oxide in the treatment of worsening hypoxemia related to Eisenmenger syndrome in the peripartum period.

Case report

A 27-year-old Hispanic woman, gravida 2, para 1, was transferred at 36 weeks' gestation for evaluation of possible pulmonary hypertension. The prenatal course had been uncomplicated except for 2 weeks of increasing shortness of breath and occasional chest pain before admission. She had had 1 uncomplicated vaginal delivery in Mexico 4 years previously; her medical history was otherwise normal.

On physical assessment the pulse rate was 83/min, respiratory rate 23/min, and blood pressure 124/71 mm Hg. There was marked peripheral cyanosis and clubbing. A right ventricular heave was noted, and there was a fixed split second heart sound. No murmur was noted.

The hematocrit value was 43%, and the platelet count was 131,000/ μ L. An arterial blood gas measurement (on room air) showed a P_{O_2} value of 54 mm Hg, a P_{CO_2} value of 24 mm Hg, and pH of 7.47. The peripheral oxygen saturation was 83%. The chest x-ray film revealed right atrial and right ventricular enlargement, prominent pulmonary vessels, and an enlarged cardiac silhouette. The electrocardiogram showed right bundle branch

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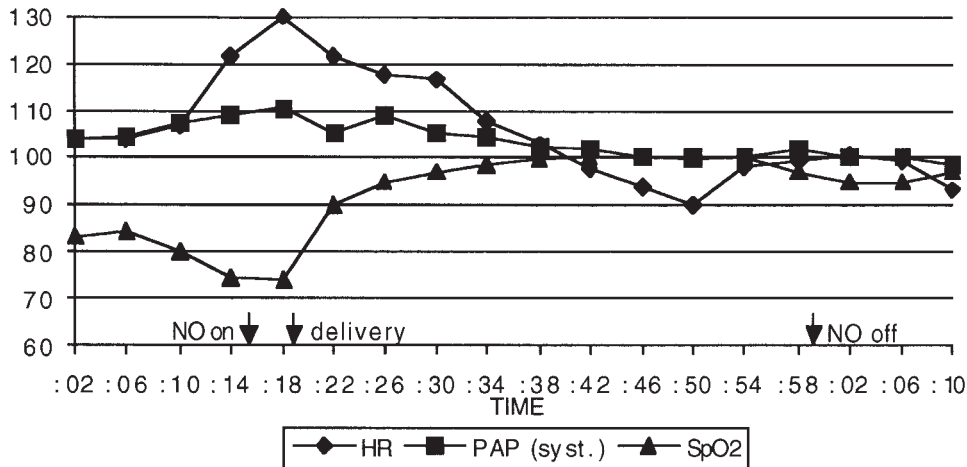


Fig 1. Effect of nitric oxide on oxygen saturation and hemodynamic parameters around delivery.

block and right ventricular hypertrophy. Echocardiography showed right ventricular and right atrial dilatation, mild mitral regurgitation, moderate tricuspid regurgitation, and bidirectional shunting through an atrial septal defect. The pulmonary artery pressure was estimated at 90 mm Hg.

A pulmonary artery catheter was placed, and the following values were determined while the patient was receiving 50% F_{iO_2} by face mask: pulmonary pressure 90/30 mm Hg and pulmonary capillary wedge pressure 12 mm Hg. The systemic blood pressure at the same time was 133/71 mm Hg.

Ultrasonographic evaluation of the fetus showed marked oligohydramnios, which was believed to require prompt delivery. Approval for the use of inhaled nitric oxide in case of maternal decompensation was given by our institutional review board and the Food and Drug Administration. Oxytocin induction of labor was started. A narcotic epidural was placed when the contractions became painful at 2 cm of cervical dilatation. Ampicillin and gentamicin were given for endocarditis prophylaxis.

Despite administration of 100% oxygen via nonre-breather mask, oxygen saturation declined gradually during the active phase of labor. Maternal pushing during the second stage of labor resulted in a more rapid decrease in the oxygen saturation coincident with an elevation in the pulmonary artery pressure (Fig 1). Nitric oxide (20 ppm) was entrained through the mask through a T connector. Five minutes later a 2640 gm male infant with Apgar scores of 8 and 9 was delivered by low forceps. The nitric oxide was continued for a total of 45 minutes, by which time the oxygen saturation and pulmonary artery pressures had returned to their initial baseline values and the hypoxemia had corrected (Fig 1).

Nitric oxide was discontinued, and the patient was transferred to the cardiac care unit. Intravenous heparin was started. During the first 2 postpartum days, the patient remained stable but there was some increase in the pulmonary artery pressure. Attempts to lower the pul-

monary pressure with nifedipine and hydralazine were unsuccessful because of lowering of the systemic pressure.

On postpartum day 3 hypoxemia worsened more rapidly despite maximal oxygen therapy. When the oxygen saturation could not be maintained above 60%, the patient was intubated. Saturation remained low until nitric oxide was entrained through the endotracheal tube. The nitric oxide was rapidly titrated up to 80 ppm with steady improvement in hemodynamic parameters and oxygen saturation (Fig 2). Several attempts were made to lower the concentration of nitric oxide but prompt desaturation was noted. Twelve hours after the nitric oxide was started, the methemoglobin had risen from 0.7 g/dL to 6.4 g/dL (acceptable limit 5 g/dL). Intravenous methylene blue, 2 mg/kg, was administered, and the nitric oxide concentration was decreased to 40 ppm despite worsening oxygen saturation. The methemoglobin level fell to 1.2 g/dL within 4 hours, and the patient was maintained thereafter on 60 ppm for the next 14 hours. Peripheral oxygen saturation during this time averaged 86%.

Limited supplies of nitric oxide necessitated discontinuation on postpartum day 5 after almost 48 hours of treatment. Immediately on discontinuation, marked oxygen desaturation was noted. Prostacyclin (10 ng/kg per minute) was administered peripherally and later through the pulmonary artery catheter. After a transient improvement, the hypoxemia worsened steadily and the patient died on postpartum day 6. Autopsy findings were consistent with Eisenmenger syndrome resulting from an atrial septal defect. A single 1-cm thrombus in the left pulmonary artery was noted.

Comment

This case adds to the emerging information regarding therapeutic implications of nitric oxide. The proximate goal of therapy in this case was to attempt to get through the period of maximum stimulus to the worsening of pulmonary hypertension that is characteristic of the peripar-

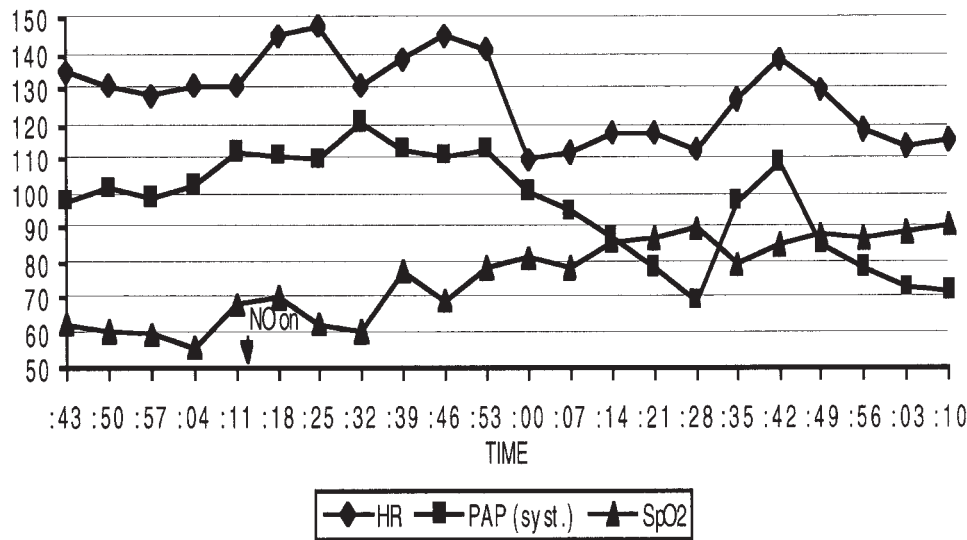


Fig 2. Effect of nitric oxide on oxygen saturation and hemodynamic parameters post partum.

tum period. Although deaths have been reported as late as 2 weeks after delivery, the majority occur within days.

Chronic pulmonary hypertension has 2 components, fixed and reactive. The fixed component is caused by vascular remodeling of the pulmonary vasculature in response to chronic elevations of pulmonary flow or pressures. Pulmonary arterial vasoconstriction, usually resulting from hypoxia, contributes to the reactive component. Although the fixed component, which is less responsive to pharmacologic manipulation, predominates in Eisenmenger syndrome, there was a clear response to inhaled nitric oxide in this patient with reduction in pulmonary artery pressures and improvement in arterial oxygenation. Unfortunately, because the arrangements for the nitric oxide had been made under urgent circumstances, it was not possible to maintain a supply sufficient for indefinite usage.

The general properties of inhaled nitric oxide have been reviewed.^{4,5} There are no studies on the use of nitric oxide in secondary pulmonary hypertension such as in our patient. The effect of nitric oxide on chronically constricted pulmonary vessels may be greatly attenuated, especially if the vascular muscle is too distant from the alveolus to allow diffusion in sufficient concentrations, because the downstream venous muscle is protected by the intravascular hemoglobin. Morphologic changes in the endothelium itself may be expected to contribute to a diminished response to nitric oxide. Despite these factors, a clinically significant response, without effect on the systemic circulation, was seen in our patient.

At inhalation doses below 100 ppm, methemoglobin formation is reportedly minor in adults and children.⁶ Nevertheless, our patient had an episode of methemoglobinemia prompting reduction in the nitric oxide dose

and administration of methylene blue. Neither tolerance to nitric oxide nor loss of pulmonary selectivity has been reported during inhalation exposure. Rebound reactions such as intensified pulmonary vasoconstriction and hypoxemia after sudden withdrawal of inhaled nitric oxide therapy have been described and may precipitate cardiopulmonary collapse.

The safety of long-term use of nitric oxide is not well established. The longest duration of continuous inhalation has been reported to be 68 days in a patient with primary pulmonary hypertension awaiting heart-lung transplantation. No significant adverse experiences were noted during that time period with an inhaled concentration of 50.4 ± 23 ppm.⁷

Among patients with Eisenmenger syndrome, the majority of deaths have occurred in the early postpartum period and were preceded by refractory hypoxemia. The cause of desaturation is not clear.

Hemodynamic changes immediately before and after delivery could exacerbate hypoxemia, setting off a cascade of catastrophic changes. However, the deterioration preceding death often has little temporal association with these hemodynamic changes, as was the case with our patient. Small and large pulmonary emboli are believed by some to be a contributing factor. The fact that these patients experience deterioration despite adequate anticoagulation suggests that other mechanisms may be involved. Significant changes in estrogen levels during the first 2 weeks after delivery may be responsible for altered vascular reactivity, especially in the pulmonary circulation.⁸

Sudden death has been postulated to be the result of thromboembolism, systemic hypotension with shunt reversal leading to hypoxemia-induced arrhythmias, or abrupt right ventricular failure. Transient hypotension

may be seen with normal delivery but also with general or conduction anesthesia. Unfortunately, sudden deaths in Eisenmenger patients have not been consistently reported to follow a hypotensive episode, and thromboembolism sufficient to cause sudden death has rarely been reported.¹ The more common scenario of gradual deterioration has been attributed to multiple small pulmonary emboli or a cycle of hypoxemia triggering pulmonary vasoconstriction.

Although the trigger for deterioration is unknown, the favorable response to nitric oxide in the case described suggests its possible role in helping patients with Eisenmenger syndrome and primary pulmonary hypertension through the peripartum period.

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