Persistent pulmonary hypertension in an extremely low birth weight infant

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Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome with estimated incidence of 1:1500 live births. It is characterized by severe hypoxemia attributed to failure of pulmonary vascular resistance to decrease below that of systemic pressure after birth, resulting in right to left shunt of the blood at the intra- as well as extra-pulmonary level through the ductus arteriosus and/or foramen ovale. While more common in term infants, PPHN is observed rarely in extremely low birth weight infants. The use of inhaled nitric oxide (iNO) in premature infants in the treatment of PPHN has remained controversial.[1,2] We report a case of a newborn of 23-weeks gestation that experienced typical PPHN and responded successfully to iNO.

Case Report

The 664-gram, male was born by a spontaneous vaginal delivery at 23-weeks gestation confirmed by antenatal ultrasound and a last menstrual period to a 25-year-old primigravida mother. The pregnancy was uneventful apart from one episode of urinary tract infection, which was treated successfully. The mother completed one course of dexamethasone prior to delivery. The baby required intubation in the delivery room for inadequate breathing and bradycardia. His Apgar scores were 2, 5, and 6 at the first, fifth, and tenth minutes, respectively. Surfactant (Survanta) was given in the delivery room. The chest x-ray was compatible with respiratory disease. Two more doses of surfactant were given. Despite maximum ventilatory and hemodynamic support, systemic oxygenation was compromised and differential cyanosis was noted with a more than 10% difference between pre- and post-ductal oxygen saturation. Echocardiography confirmed the diagnosis of PPHN with pulmonary pressure exceeding systemic levels, and right to left shunting of the blood through the patent foramen ovale (Figure 1). High frequency oscillatory ventilation (HFOV) was started but there was no improvement. His oxygenation index (OI) and the alveolar arterial gradient (a/A) during HFOV were 40.4 and 0.0534, respectively. Inhaled nitric oxide was decreased gradually to discontinuation over five days. No acute toxicity during iNO therapy was observed. Ultrasound of the head showed grade 2 intraventricular hemorrhages that resolved with time. Apart from episodes of feeding intolerance and mild chronic lung disease during his early hospital course, the baby did well and was discharged home in good health at 36 weeks corrected age. There were no neurological deficits observed during his outpatient visits.

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Discussion

There is an assumption that preterm infants lack sufficient arteriolar musculature to maintain a prolonged elevated pulmonary vascular resistance after birth. This report shows that extremely low birth weight infants are at risk of developing PPHN. The baby's response to iNO confirms that midgestation pulmonary vasculature is responsive to iNO. Reports available in the literature described larger premature infants with evidence of perinatal asphyxia.[3,4] In this report, the infant had no evidence of perinatal asphyxia, but his PPHN was attributed to lung disease. The infant received an early dose of surfactant as prophylaxis in the delivery room, which was repeated twice. Despite the surfactant therapy, the infant developed PPHN, which was not controlled by HFOV. He showed a dramatic response to iNO with clear reverse of the shunt as evidenced by the echocardiogram.

These extremely premature infants are at the ultimate edge of embryological viability and, by definition of pulmonary hypertension, their lungs have major structural and functional defects. In the human fetus, the preacinar arteries and those at the terminal bronchiolar level are muscular, and continue to increase in thickness throughout the fetal life, while the intraacinar arteries (those accompanying respiratory bronchioles) are partially muscular (surrounded by spiral muscles) or non-muscular. At 23-weeks gestation, the main respiratory unit is the respiratory bronchioles accompanied by a partial yet developing muscular layer.[5,6] The surfactant-producing unit is virtually immature, which may explain the poor and partial response to surfactant therapy in the 23-25 weeks premature infants.[6] Kinsella et al[7] demonstrated in some experimental models of hyaline membrane disease that pulmonary vascular resistance fails to decrease in response to mechanical ventilation alone and surfactant therapy does not change the direction or the magnitude of the systemic to pulmonary shunting across the patent ductus arteriosus. It was shown that endogenous nitric oxide production could alter the basal pulmonary vascular tone very early in the ovine fetus and contribute to increases in pulmonary blood flow in extremely premature infants. They also observed deterioration of gas exchange despite a

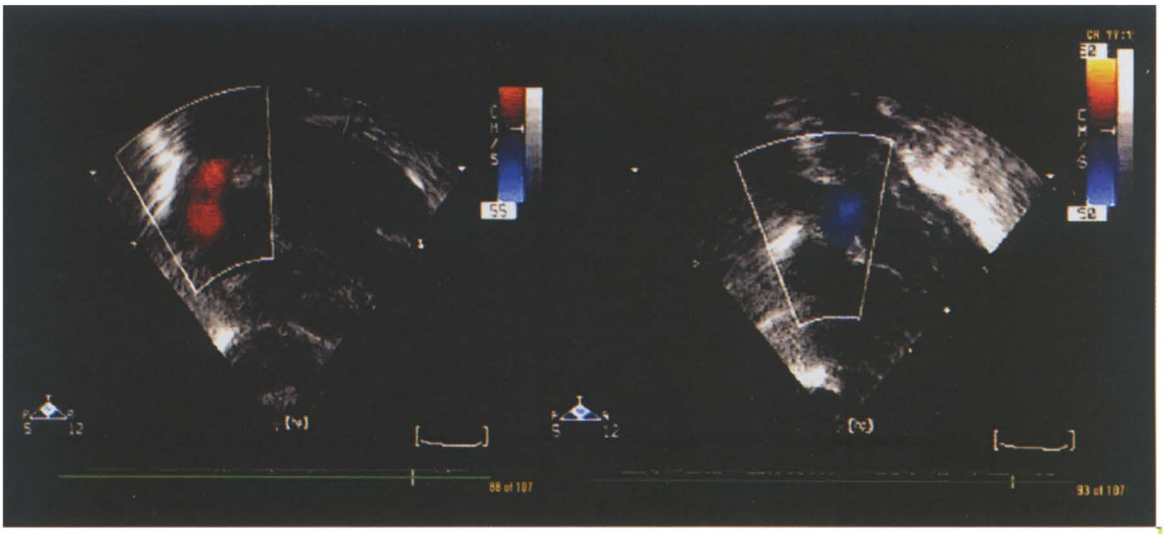

Figure 1. Echocardiogram showing right to left shunt at the ductus arteriosus (right) and reversal of the shunt (left) shortly after iNO administration.

good initial response to exogenous surfactant while there was a satisfactory response to exogenous iNO. Skimming et al[8] described similar observations. Preliminary studies in human premature infants, with severe hypoxemic respiratory failure, support the role of low does of iNO as adjuvant therapy, which has led to significant improvement in oxygenation.[7,8]

Ochikubo et al[9] assessed the echocardiographic findings of 25 newborn infants older than 32 weeks gestation who developed PPHN and who were receiving iNO therapy, and demonstrated a decreased pulmonary vascular resistance and improved oxygenation with a reversed shunt. The long-term effect of iNO is not clear and the risk of intracranial hemorrhage is not yet resolved.[7,8] We conclude that extreme premature infants are at risk of developing PPHN and early use of iNO may be justified when other treatment modalities have been tried.

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