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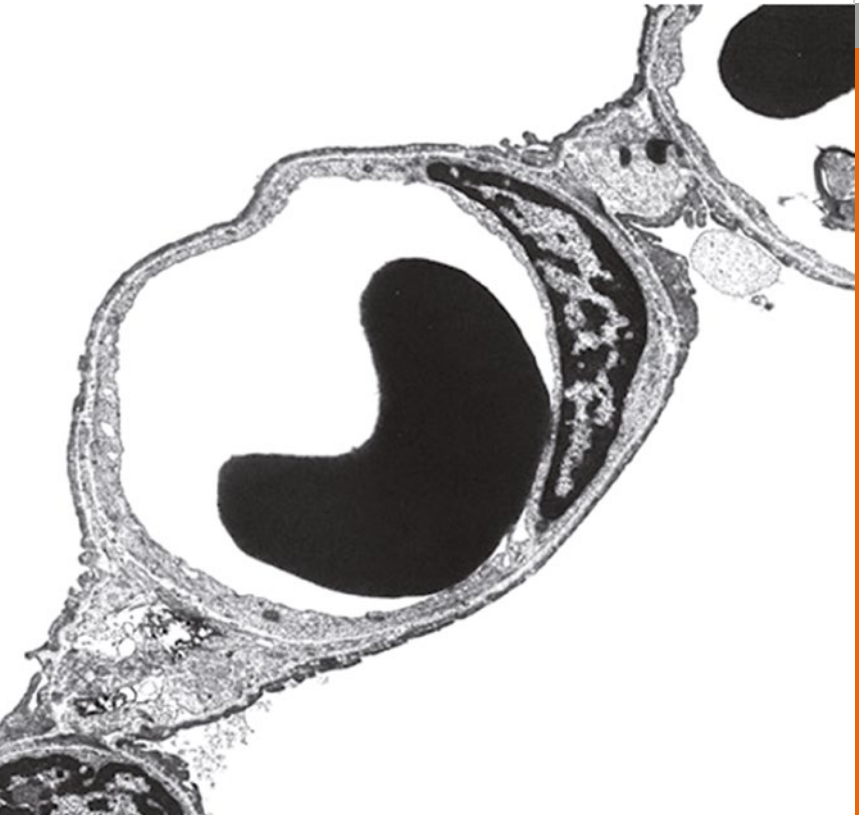
Refractory persistent pulmonary hypertension of the newborn responsive only to neuromuscular blockade



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INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is an abnormal early adaptation to the perinatal circulation transition. Failure of the normal postnatal decline in pulmonary vascular resistance (PVR) leads to right-to-left intra- or extra-cardiac shunting, (which impairs systemic oxygenation) and right ventricular failure. PPHN affects 2 to 6 per 1000 live births (1). Mortality rate is still high (up to 48%) and adverse neurological sequelae in survivors are common (up to 46%) (2).

In the pre inhaled nitric oxide (iNO) era (before 1993), a wide variation in treatment of this entity was noted and one of the possibilities was the use of neuromuscular blockers (3, 4). We present a patient with PPHN refractory to iNO for whom neuromuscular blockers were beneficial.

CASE REPORT

We report the case of a male infant who was delivered by emergency caesarean section at 27 weeks of gestation because of placental abruption. The patient was born in a regional hospital, but was nonetheless taken care of by a trained neonatologist. No antenatal corticosteroids had been administered, membranes were still intact and amniotic fluid was clear. Birth weight was 1090 g (P 50-90), length 36 cm (P 50-90) and head circumference 25.5 cm (P 50-90). Apgar scores were 5, 8, and 9 at 1, 5, and 10 minutes, respectively, and arterial and venous umbilical cord pH values were

7.37 and 7.45. Respiratory distress and oxygen requirement up to 60% were apparent after a few minutes and the baby was intubated at 5 minutes of life. An umbilical venous catheter was inserted, 10 ml/kg of crystalloids were administered because of hypotension (mean arterial pressure 24 mmHg) and a dose of surfactant was given (Curosurf® 120 mg/kg) prior to air transfer to our tertiary neonatal intensive care unit. Upon arrival in our unit, seven hours after birth, the baby was put on high frequency oscillatory ventilation (HFOV) as per protocol.

At 48 hours of life, he developed clinical evidence of severe pulmonary hypertension, with pre- and post-ductal oxygen saturation differences of up to 60%. Echocardiography revealed a large patent ductus arteriosus (PDA) with bidirectional shunt, tricuspid valve regurgitation and right-to-left shunting across the foramen ovale, confirming PPHN (Fig. 1). iNO was started and the newborn was adequately sedated with a continuous infusion of fentanyl. As sepsis was also suspected because of a metabolic acidosis (pH 7.31, pCO2 3.9 kPa, bicarbonate 14 mmol/l, BE -11 mmol/l, lactate 4 mmol/l) associated with leukopenia (total leukocyte count 1.9 G/l) and CRP concentrate of 45 mg/l, antibiotics (ampicillin and gentamycin) were started. Chest x-ray changes were non-specific with areas of impaired aeration (right > left), compatible with partially treated hyaline membrane disease following the administration of surfactant. (Fig. 2).

Despite intensive care therapy including HFOV (mean airway pressure 12 cm H2O, amplitude 55 cmH2O, frequency 15 Hz, after a recruitment manoeuvre), iNO 20 ppm, a better control of acid-base balance by reducing pCO2 (pH 7.31, pCO2 4 kPa), sedation and treatment of infection, PPHN worsened (post ductal saturation constantly between 30 and 70%) and oxygen requirement did not decrease (FiO2 0.5). At 55 hours of life, a bolus of 0.2 mg/kg of mivacurium was administered. Within 30 seconds after administration, the post-ductal saturation increased dramatically to 89% without any other hemodynamic or respiratory changes. After 10 minutes, the post-ductal saturation decreased again to 62%. To reproduce these encouraging results for a longer period, a single bolus of pancuronium 0.1 mg/kg was given. The post-ductal saturation rose again to 90% (Fig. 3). In the following 48 hours, iNO was weaned and the patient was successfully extubated on day 5 of life. Due to positive blood cultures for Staphylococcus aureus, amoxicillin and gentamycin were discontinued after 4 days and replaced by vancomycin; this treatment was continued for 2 weeks.

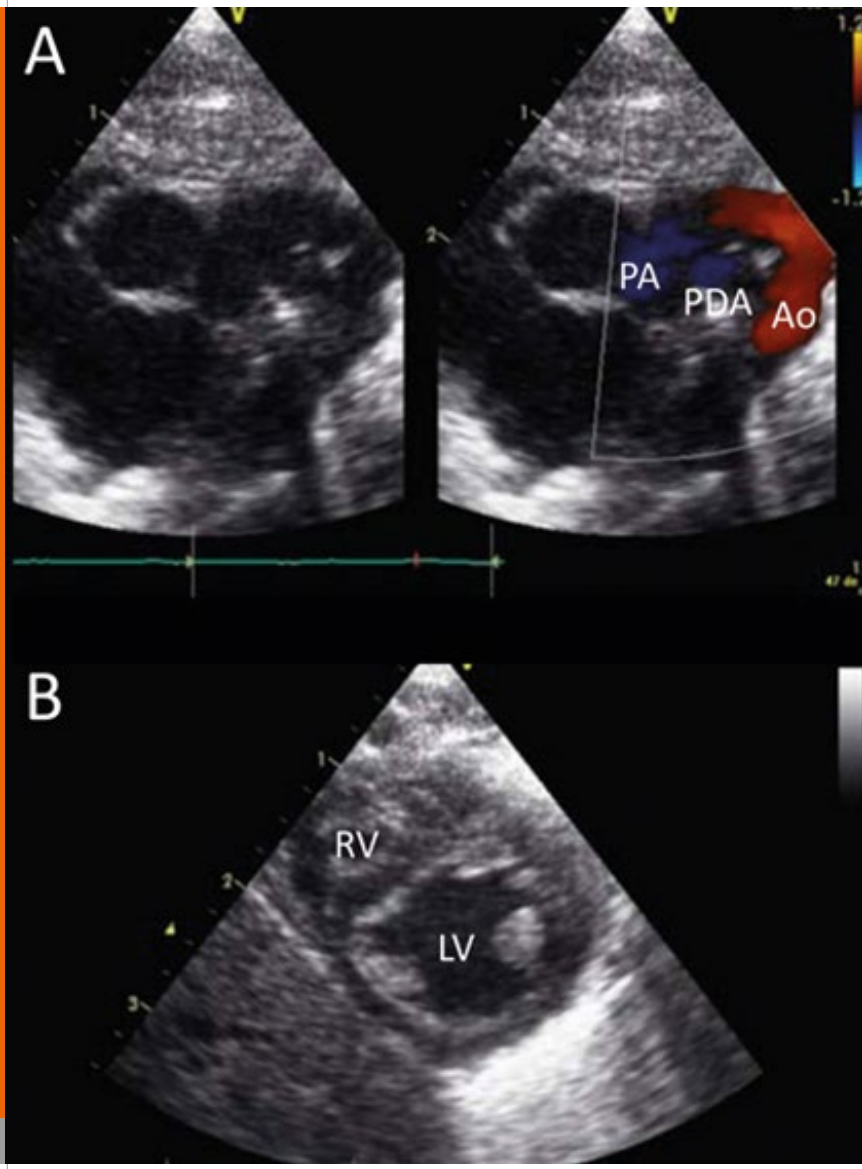

Fig. 1

Cardiac ultrasound: Panel A shows the large patent ductus arteriosus (PDA) between the pulmonary artery (PA) and the aorta (Ao); Panel B shows the relationship between the right (RV) and left ventricle (LV), with the interventricular septum protruding into the LV.

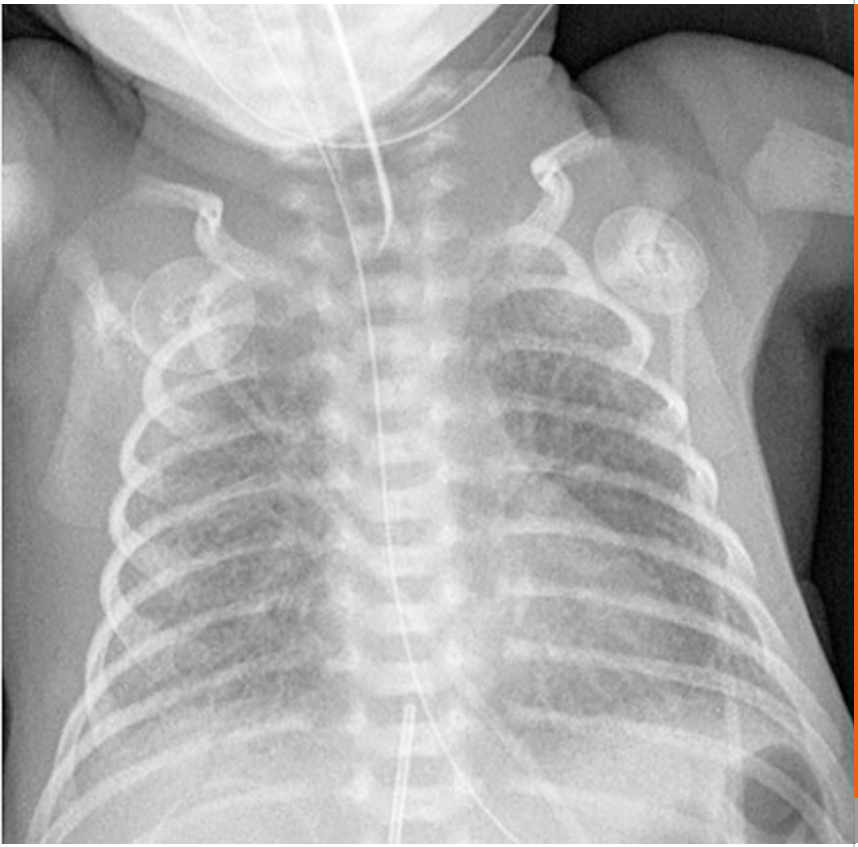

Fig. 2

Chest X-ray: non-specific with areas of impaired aeration (right > left), compatible with partially treated hyaline membrane disease following the administration of surfactant.

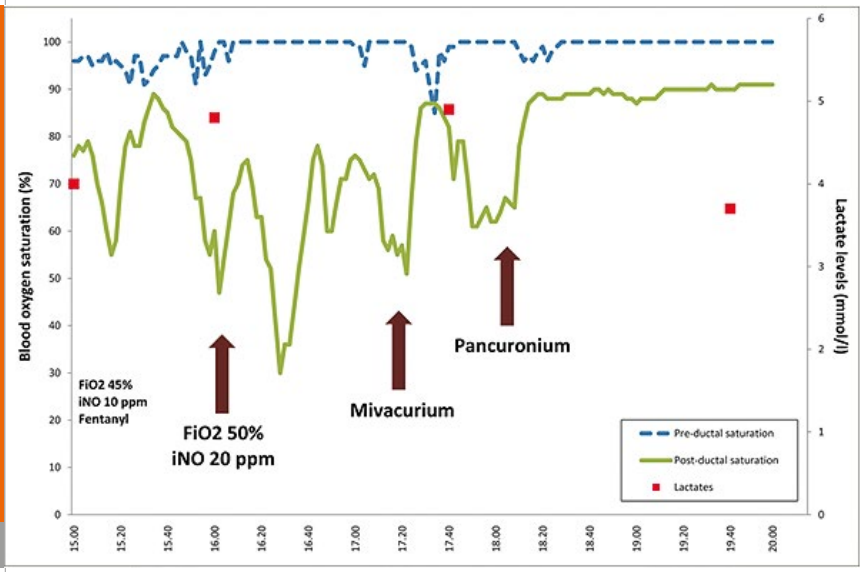

Fig. 3

Evolution of the pre- and post-ductal saturations (dashed blue and full green line, respectively) as well as lactate concentrations (squares, secondary scale on the right) in relation to different interventions (vertical arrows).

PPHN is characterized by sustained elevation of PVR, decreased lung perfusion and continuous right-to-left intra- (through the foramen ovale) or extra- (through a patent ductus arteriosus) cardiac shunting, leading to impaired systemic oxygenation and decreased right ventricular function. This may lead to dilatation of the right ventricle with compression the left ventricle resulting in decreased cardiac output.

PPHN generally presents as one of three pathophysiological mechanisms (5): 1) a structurally normal but abnormally constricted pulmonary vasculature (e.g., in meconium aspiration syndrome, sepsis, respiratory distress syndrome); 2) a structurally abnormal vasculature following antenatal remodelling (i.e., idiopathic PPHN); or 3) a hypoplastic vasculature (e.g., in congenital diaphragmatic hernia). As pulmonary vascular tone is mediated by competing vasodilatory and vasoconstrictive factors, the primary aim of therapies is to produce selective pulmonary vasodilatation.

Despite advances in the management of this condition, no single therapeutic approach has been shown to be universally effective in the treatment of PPHN. Therefore, practice variations are common (2). The majority of physicians choose therapies that promote optimal lung inflation with recruitment strategies and correction of stimuli known to increase PVR (acidosis, polycythemia, pain).

Second tier treatments, such as iNO specifically target pulmonary vascular tone. Although this therapy is now standard of care in PPHN, 30% of patients are non-responders, as in our case (6). For these patients, rescue therapies with sildenafil, milrinone, prostacyclin or bosentan have been reported (7).

The use of neuromuscular blocking agents in the treatment of PPHN with severe hypoxemia has scarcely been described, and solely prior to the iNO era. In 1976, Levin et al. (8) reported an increasing in pO2 after administration of curare; they attributed this finding to more effective ventilation and release of histamine. Henry et al. (3) described similar findings and suggested that curare induces respiratory paralysis, which would reduce right-to-left shunting, hence improving pO2 and finally decreasing mortality in infants with severe PPHN. One year later, Hutchison and Yu (4) examined the effect of curare in the treatment of PPHN. Curare decreased PVR in only one infant out of thirteen.

In the presented case of refractory PPHN, a clear and certain benefit following curare administration was noted, permitting decreases of FiO2 and ventilator settings. Some explanations may be proposed. Firstly, this could have been related to improved and more effective ventilation due to better chest wall compliance and fully synchronized ventilator breaths (i.e., decreased struggling) but our patient appeared com-

fortable on HFOV and continuous infusion of fentanyl. Secondly, the neuromuscular blocker could have triggered the release of histamine, which has been described to act as a pulmonary vasodilator in two studies in dogs and rats (9, 10); however, our patient did not present any signs of systemic vasodilatation. Thirdly, respiratory paralysis may have reduced oxygen consumption and peak transthoracic pressures, but our patient was ventilated on HFOV and was already apneic prior to curare. Finally, thoracic rigidity caused by fentanyl is possible but would not be expected to significantly impair ventilation on HFOV; however, by paralysing the diaphragm and the abdominal wall muscles, the intra-abdominal pressure might have decreased, possibly decreasing the intra-thoracic pressure, improving lung recruitment, decreasing PVR and hence right-to-left shunting.

In conclusion, since iNO has been introduced to treat PPHN, neuromuscular blocking agents are only rarely used. Nevertheless, they might still be useful in some selected newborns with PPHN refractory to classical treatments.

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