REGULAR REVIEW

Treatment of persistent pulmonary hypertension of the newborn: update

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Persistent pulmonary hypertension of the newborn is primarily characterised by persistence of, or return to, the suprasystemic pulmonary vascular resistance and pressure normally found in the fetus. The increased pulmonary pressure causes right to left shunting through the ductus arteriosus or the foramen ovale, or both. The resulting hypoxaemia and acidosis may produce further pulmonary vasoconstriction and lead to a vicious cycle of shunting, hypoxia, and acidosis.

Aetiology

About half the pulmonary arteries in a newborn infant contain muscle. Abnormal formation of muscle in the small pulmonary arteries can occur before or after birth and is characteristic of all forms of pulmonary hypertension in childhood. Smooth muscle precursors (the pericytes and the intermediate cells) can develop into mature smooth muscle cells within days if 'switched on' by an effector—for example, hypoxia, increased pulmonary pressure or blood flow, mediators, or endothelial cell damage.[1] [2] These changes in turn reduce the total pulmonary cross sectional area either directly or by enhancing thrombosis.[3] Persistent pulmonary hypertension of the newborn was initially described in asphyxiated infants who were cyanosed with relatively normal lungs, and right to left shunting in infants without congenital cyanotic heart disease. Infants with persistent pulmonary hypertension of the newborn are usually full term or post term infants, and often have had perinatal asphyxia (13%), meconium aspiration (66%), or diaphragmatic hernia, pneumonia, or sepsis (21%).[4-7]

Incidence

Accurate estimates of the incidence of persistent pulmonary hypertension of the newborn are not available, but estimates of about 1/1500 live births with a range from 1/1454 to 60/2602 have been reported, which accounts for about 1% of admissions to neonatal intensive care units.[7] [8]

Risk factors for death

The average mortality is about 40% (range 34%–60%) despite aggressive management with hyperventilation, fluids, vasopressors, and vasodilators.[4-7] Infants with alveolar–arterial oxygen gradients (A–aDO$_2$) of 82·46 kPa all die, and among those with A-aDO$_2$ of 79·8 kPa or more for 12 hours the mortality was 94%.[5]

Clinical presentation

Persistent pulmonary hypertension of the newborn may present with severe hypoxia, severe acidosis, tachypnoea, tricuspid or mitral regurgitation, patent ductus arteriosus, hypovascularity on the chest radiograph, relatively clear lung fields and no anatomical cardiac lesions. The patient may develop right ventricular heave, electrocardiographic changes of myocardial ischaemia, and right ventricular overload. The disease may present immediately after birth—for example, in asphyxiated infants or those with diaphragmatic hernia with severe lung hypoplasia. It may present after 4–12 hours (subacute)—for example, in infants with meconium aspiration syndrome, or it may present after 12–24 hours (late)—for example, infants with sepsis and those with progressive airways obstruction.[4-7] [9]

Treatment

The aetiological diversity of the disease means that no single treatment will be uniformly effective. No controlled comparisons of treatments have been carried out. Once it has been diagnosed, therapeutic efforts should be simultaneously directed towards the specific treatment of the particular cause suspected and towards the reduction of pulmonary vascular resistance. All infants should be given a broad spectrum antibiotic. Adequate blood pressure should be maintained with vasoconstricting drugs and fluid infusions. Alkalis should be given to achieve a normal arterial pH if there is metabolic acidosis. Mechanical hyperventilation has been used to decrease pulmonary pressure and achieve normal oxygenation.[4] A very low carbon dioxide tension has a potentially deleterious effect on cerebral and renal blood flow. Complications include chronic lung disease (31%) and pneumothorax (45%).[9] Muscle relaxants and sedatives are used to prevent agitation and fluctuations in oxygen tension. Extracorporeal membrane oxygenation has been used to treat persistent pulmonary hypertension of the newborn with varying degrees of success, and survival has been reported as ranging from 58 to 100%.[5] [10] Several serious complications have been reported, however, and this type of treat-

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ment is not available at most neonatal centres. A conservative approach has sometimes been used,[11] but I know of no controlled trials that test the efficacy of this treatment.

Pulmonary circulation vasodilators

There are no drugs that specifically dilate the pulmonary vasculature and reduce pulmonary hypertension. Consequently our experience has been limited to trials of vasodilators that have been developed to control systemic hypertension with variable success.

ARACHIDONIC ACID AND ITS METABOLITES

Archidonic acid metabolites play an important part in the normal regulation of pulmonary vascular tone and in the pulmonary vascular responses to various pathological stimuli.[12] There are two pathways of arachidonic acid metabolism, which synthesise most of the biologically important eicosanoids: the cyclo-oxygenase pathway that generates prostaglandins (E_2, D_2, and I_2) and thromboxanes, and the lipoxygenase pathway that catalyses the formation of leukotrienes and hydroxy acids.[13] Inhibitors of these enzymes modify the calcium dependent responses in isolated smooth muscle and white cells. There is evidence that high concentrations of lipoxygenase inhibitors reduce smooth muscle reactivity through an effect on calcium entry.[13] Lack of oxygen diverts endogenous arachidonic acid from the cyclo-oxygenase to the lipoxygenase pathway and the metabolites that are formed accelerate the entry of calcium.[14-15] The excessive increase of cytoplasmic calcium leads to tissue hypoxia, loss of cellular function, and eventually structural damage.[16] Raj and Chen showed that alveolar hypoxia leads to pulmonary arterial and venous constriction in isolated lamb lungs perfused with blood,[17] and that leukotrienes mediate arterial and venous constriction with thromboxane A_2 being necessary for venous constriction.[18] They concluded that the interaction between 5-lipoxygenase and cyclo-oxygenase products of arachidonic acid results in the characteristic pulmonary hypoxic vasoconstrictor response.

Phospholipase A_2 in the vessel and platelet walls releases arachidonic acid, and thereby prostaglandins and thromboxanes, when activated. Prostacyclin (PGI_2) and prostaglandins D_2 and E_1 prevent platelet aggregation, whereas thromboxane A_2 (which is mainly released by platelets) promotes platelet aggregation. It is possible that a vasoactive, platelet aggregating substance such as thromboxane, released as a result of hypoxia or vascular endothelial injury, might in turn mediate both the platelet aggregation and the pulmonary hypertension.[19] An association between persistent pulmonary hypertension of the newborn, thrombocytopenia, and platelet trapping with pulmonary microthrombi has been reported.[3] Thromboxane seems to be crucial in mediating septic pulmonary hypertension, but not hypoxic pulmonary hypertension, which implies that different types of pulmonary hypertension may be mediated by

different biochemical agents.[20] Prostaglandin E_1,[12] PGI_2,[21] and prostaglandin D_2[22] have been used to try and reduce pulmonary hypertension, but with inconsistent results and many complications.

VASCONSTRICTIVE EFFECT OF CALCIUM

Contraction of the smooth muscle cells in the walls of blood vessels and the consequent reduction of tissue perfusion is initiated when the cytoplasmic free calcium concentration rises above $0 \cdot 1$ mmol/l.[16][23] This increase could be the result of mobilisation of calcium from intracellular calcium pools or to increased permeability of the cell membrane to extracellular calcium because of the increase in endogenous vasoconstrictors, together with hypoxia or ischaemia.[16][23-24]

CALCIUM CHANNEL BLOCKERS

Pulmonary vasoconstriction is dependent on the availability of calcium to the affected cells,[25] and so calcium channel blockers have been given in an attempt to induce pulmonary vasodilation. These agents can influence cardiovascular haemodynamics by a complex interplay of systemic arterial vasodilation, a negative inotropic effect, and reflex phenomena.

Calcium antagonists inhibit the activation of platelets by arachidonic acid,[26] block the synthesis of thromboxane by platelets,[27] and block thromboxane induced cerebral arterial constriction.[28] Blockade of prostaglandin and thromboxane synthesis by indomethacin prevents pulmonary hypertension being caused by infection.[29] Reeves *et al* showed that the calcium antagonists hydralazine and diazoxide had roughly equal effects in reducing acute pulmonary hypertension, but captopril had little effect.[30] Verapamil and nifedipine both seem to reduce the pulmonary and systemic vascular pressures, but do not change the right to left shunt ratio in animals.[31-32] In patients with primary pulmonary hypertension nifedipine decreased pulmonary and systemic vascular resistance, increased cardiac output, and improved the oxygenation of the blood but the ventilation:perfusion ratio deteriorated because there was an increased perfusion of units with low ventilation: perfusion ratios.[32] Nitroprusside has been used with variable results and an overall 47% survival rate.[33] Isoproterenol and noradrenaline,[34] phenoxybenzamine, and chlorpromazine[35] have also been used as vasodilators in pulmonary hypertension with varying success. Tolazoline is the most widely used vasodilator, which has complex pharmacological effects including α-adrenergic antagonism and agonism, cholinergic antagonism and agonism, and histaminergic agonism.[36] Response to tolazoline is variable and predictors of success are unclear. About 70% of infants with persistent pulmonary hypertension of the newborn treated with tolazoline had a wide range of complications; only 59% of the infants improved and 54% survived.[36]

Magnesium in pulmonary hypertension

Magnesium is an essential activator of about 300

enzymes and is a necessary cofactor for ATPase. Thus magnesium is a vital cofactor in the maintenance of several energy demanding processes at the cellular level such as oxidative phosphorylation, neuromuscular excitability, and muscle contraction.

Lipman *et al* have shown that a continuous intravenous infusion of magnesium sulphate can control sympathetic crises and suppress the release of catecholamines.[37] Magnesium sulphate also activates adenyl cyclase, which plays a part in the synthesis of cyclic AMP.[38] increases in the amounts of cyclic AMP in smooth muscle promote relaxation by inhibiting the activity of myosin light chain kinase caused by accumulation of calcium by the sarcoplasmic reticulum, and resulting in a fall in intracellular free calcium to concentrations at which the myosin light chain kinase is not active.[39] The effect of magnesium on cyclic AMP is of particular interest because there are data that suggest that increased cyclic AMP concentrations promote vasodilation.[40] Magnesium sulphate causes peripheral arteries to dilate by various mechanisms. An indirect curare like action retards the release of acetylcholine and interferes with transmission at the neuromuscular junction and sympathetic ganglia. A direct action of the cation reduces the responsiveness of smooth muscle to sympathomimetic amines as well as to non-sympathomimetic vasopressors.[37 41-42] After an episode of ischaemic anoxia, concentrations of arachidonic acid rise rapidly in anoxic neurons.[43] The influx of calcium ions to anoxic arterioles results in vascular spasm.[44] In animal studies, magnesium antagonises calcium ion entry thereby promoting vasodilatation and alleviating the effect of severe hypoxia on the brain, liver, and kidneys.[45-48]

Thrombosis and consumption of platelets occur in small blood vessels in pulmonary hypertension.[3 19] Magnesium has an antithrombotic effect which—at least theoretically—has a role in the treatment of pulmonary hypertension.[49]

In patients with severe hypertension of pregnancy, Cotton *et al* found that both systemic vascular resistance and pulmonary vascular resistance fell after magnesium sulphate was given, and by 30 minutes had returned to baseline values.[50] McMurtry *et al* showed in isolated rat lungs that calcium antagonists inhibited hypoxic pulmonary vasoconstriction and that the hypoxic mechanism was critically dependent on the transmembrane influx of extracellular calcium.[51] Similarly, inhibiting hypoxic vasoconstriction in dogs by increased plasma concentrations of magnesium chloride[52] was possibly related to calcium antagonism by magnesium.[46-47] Cropp showed in dogs that there was a pronounced rise in pulmonary vascular resistance during hypoxia with normal concentrations of magnesium in the blood. As the magnesium concentrations were increased, the rise in pulmonary vascular resistance during hypoxia decreased. Hypoxic pulmonary vasoconstriction usually did not occur if magnesium rose above 5 mmol/l. Magnesium concentrations of less than 6·5 mmol/l did not cause hypotension or hypoventilation. He concluded that a controlled increase in the blood magnesium concentration to 5–6 mmol/l will block hypoxic pulmonary vasoconstriction without causing deleterious changes in haemodynamics or pulmonary ventilation. Attempts to use magnesium to decrease the pulmonary hypertension that was induced by hypoxia were not investigated in these studies.[52]

Paidas *et al* showed that continuous infusion of ATP and magnesium chloride produced a significant decrease in mean pulmonary artery pressure after induced hypoxia with little or no systemic side effects. They also reported that magnesium chloride had no effect when infused alone.[53] The doses of magnesium chloride given were small and the concentrations in serum were not measured. It is well known that a slight or moderate rise in blood magnesium does not affect the circulation. This study did, however, show the effect that magnesium preparations had in reducing pulmonary arterial pressure and resistance, and their likely useful therapeutic effect in pulmonary hypertension syndromes, but it failed to show the effect of magnesium alone because of the study design. Oral treatment with magnesium aspartate hydrochloride has been shown by Mathew *et al* to attenuate monocrotaline induced pulmonary hypertension, right ventricular hypertrophy, and pathological changes in the pulmonary vasculature in Wistar and Spraque-Dawley rats.[54] Abu-Osba *et al* showed in a placebo controlled study of anaesthetised and ventilated sheep that during induced hypoxia (by breathing 10% oxygen) a sharp increase in the mean (SD) pulmonary artery pressure occurred from 16 (2·8) to 26 (5·3) mm Hg.[55] During hypoxia there was no change in pulmonary arterial pressure (27 (5·7) mm Hg) after a placebo had been given. In contrast there was a sharp decrease after magnesium sulphate infusion (dose 200 mg/kg, serum concentration 2·88 mmol/l) in the right atrium; mean pulmonary arterial pressure was 25 (5·7) and 17 (5·6) mm Hg before and after treatment, respectively, p<0·001. There was no change in the cardiac output and a transient decrease in the heart rate.

In severely sick infants born at full term with persistent pulmonary hypertension of the newborn and who did not respond to conventional treatment for 46–72 hours, magnesium sulphate was used as a vasodilator, a muscle relaxant, and a sedative (YK Abu-Osba *et al*, abstract presented at Paediatric Research Society Meeting, Leeds, March 1989).[56] No other drugs were given or changes in the respirator settings or fractional inspiratory oxygen (F_IO_2) were made after the magnesium sulphate had been given unless oxygen tension rose; F_IO_2 and respirator settings were then reduced. Four infants had $A-aDO_2$ gradients of over 84·5, and one had an $A-aDO_2$ of 81·9 kPa, with predicted mortalities of 100% and 94%, respectively. After treatment with magnesium sulphate, mean (SD) oxygen tensions and haemoglobin oxygen saturation increased significantly within six hours from 4·3 (1·9) to 11·8 (7·6) kPa, p<0·04, and 58 (30) to 95 (5)%, respectively (p<0·03). One infant died with a persistent $A-aDO_2$ of over 84·5 kPa. None had intraventricular haemorrhage, bronchopulmonary dysplasia, or bradycardia requiring intervention.

These studies show that magnesium is beneficial in reducing hypoxia induced pulmonary hypertension in both animals and in full term infants with persistent pulmonary hypertension of the newborn. Its efficacy in preterm infants and for other non-hypoxic causes of pulmonary hypertension should be investigated. Some reports have described a beneficial vasodilating effect together with reduction of complications after ischaemic hypoxia in the central nervous system, heart, kidneys, and liver.[45 46-48] These conditions frequently coexist with pulmonary hypertension and severe hypoxaemia in neonates. Though a controlled multi-

centre large study is required before recommending magnesium as a first line of treatment, these studies suggest its possible benefits in persistent pulmonary hypertension of the newborn when conventional treatment has failed, is contraindicated, or is unavailable. Close monitoring of blood pressure, kidney function, glucose calcium concentrations should be undertaken. Long term follow up is needed.

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