The management of neonatal pulmonary hypertension

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ABSTRACT

Most neonates with clinically significant pulmonary hypertension (PH) will have either persistent PH of the newborn (PPHN) or bronchopulmonary dysplasia. Cyanotic congenital heart disease must be actively ruled out as part of the differential diagnosis of PPHN. The maintenance of ductal patency with prostaglandins E1 or E2 in cases of doubt is safe and potentially beneficial given their pulmonary vasorelaxant properties. Specific tools in the treatment of PPHN include modern ventilatory strategies, inhaled nitric oxide, sildenafil, prostacyclin and extracorporeal membrane oxygenation. Rarely will a cardiac lesion be primarily responsible for neonatal PH although pulmonary vein stenosis and the persistence of an arterial duct must be considered, particularly in the older preterm baby with bronchopulmonary dysplasia.

INTRODUCTION

At the most recent world symposium on pulmonary hypertension (PH) held at Dana Point, California, USA in 2008, the pre-existing definition of PH was rationalised and to some extent simplified.[1] The difference between precapillary and postcapillary PH was highlighted to make clearer the role of left heart disease. Importantly Group 1, pulmonary arterial hypertension (which forms the largest group in the newborn presentation of PH), became a more homogeneous clinical and pathological entity (table 1).

Thus, PH can be diagnosed in children and adults if there is an elevated mean pulmonary artery pressure of ≥25 mm Hg.[2] In pre-capillary PH, such as may be found in parenchymal lung disease, the pulmonary capillary wedge pressure is ≤15 mm Hg. Conversely, in postcapillary PH the pulmonary capillary wedge pressure is >15 mm Hg and this situation can occur with left heart disease or pulmonary venous obstruction. Normal pulmonary artery pressure is virtually age-independent outside of the neonatal period with a mean of 14 ± 3 mm Hg.[3] However, this definition of PH is not valid in the newborn because even under normal circumstances, we are born relatively pulmonary hypertensive.

In utero, the lungs are filled with amniotic fluid and do not participate in gas exchange. The pulmonary vascular resistance (PVR) is high, about 10 times newborn levels. The systemic vascular resistance is low by virtue of the placental circulation. The oval foramen and arterial duct both serve to bypass the high resistance pulmonary vasculature (figure 1). The two major influences on the normal fall in PVR at birth are physiological changes in response to activation of stretch receptors following lung inflation with the onset of breathing and the potent effect of oxygen as a pulmonary vasodilator.[4] While there is a brisk fall in PVR at birth, it takes up to 6 weeks to fall to normal adult levels.[5] Pulmonary artery pressure is the product of pulmonary blood flow and vascular resistance (in the same way as electrical voltage is related to current and resistance, as described by Ohm's law). Hence, PH can be the result of elevated PVR, increased pulmonary blood flow (as seen with large left-to-right cardiac shunts) or a combination of the two.

In the newborn, PH usually results from a failure of the PVR to fall to normal levels at birth, hence persistent pulmonary hypertension of the newborn (PPHN). Secondly, clinically important PH is seen in neonatal practice in the context of bronchopulmonary dysplasia (BPD). Least commonly, it may be encountered with specific forms of congenital heart disease. These three broad groupings of neonatal PH will be considered in turn (table 2). In neonatal practice PH can be particularly acute. Acidosis and alveolar hypoxia are potent stimuli for pulmonary vasoconstriction and there can be severe exacerbations in the form of pulmonary hypertensive crises.[6 7]

Clinically there may be considerable overlap in Group A subgroups of neonatal PH. Histopathological abnormalities of the pulmonary vascular bed in established PH were well described in Heath and Edwards' classic paper of 1958, defining six stages in the progression of the disease process.[8] While the latter stages of this classification are less applicable to neonatal PH, it is well recognised that abnormal muscularisation (remodelling) of the pulmonary vascular bed is present in a proportion of these patients, with extension of medial hypertrophy into the smaller, normally non-muscular vessels.[9] Furthermore, fibrotic and inflammatory changes are prominent in babies with BPD, affecting not only the alveolar parenchyma but also the arteriolar bed.[10]

DIAGNOSING PH

ECG is useful in looking for right ventricular hypertrophy as a feature of established PH, but cannot be used to rule it out. The mainstay of PH diagnosis is echocardiography, which also serves to exclude cardiac structural abnormalities, particularly pulmonary vein stenosis. In those patients with tricuspid regurgitation (TR) measurable with continuous wave Doppler, the modified Bernoulli equation for right ventricular-atrial pressure difference provides an estimate of right ventricular systolic pressure and in the absence of right ventricular outflow tract obstruction, pulmonary artery systolic pressure (peak pressure difference = 4 × peak TR velocity^2, figure 2). The severity of PH as measured by peak TR velocity may be underestimated in the presence of a poorly functioning

Table 1 Clinical classification of pulmonary hypertension (Dana Point, 2008)

Group	Description
1	Pulmonary arterial hypertension *– includes persistent pulmonary hypertension of the newborn* 1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
2	Pulmonary hypertension secondary to left heart disease
3	Pulmonary hypertension secondary to lung diseases and/or hypoxia
4	Chronic thromboembolic pulmonary hypertension
5	Pulmonary hypertension with unclear multifactorial mechanisms

The full classification of Group 1 is much more detailed. Groups 4 and 5 rarely apply to neonatal practice.

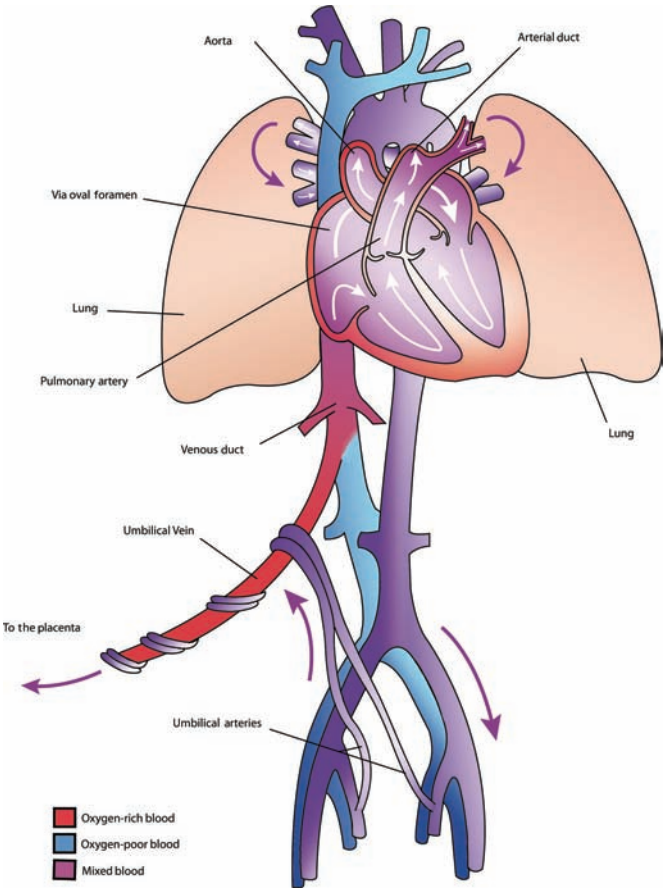

Figure 1 The fetal circulation.

Table 2 Main causes of neonatal pulmonary hypertension

Group	Description
A	Persistent pulmonary hypertension of the newborn (PPHN) (belongs to Group 1 in table 1) i. Pulmonary vasoconstriction—eg, meconium aspiration syndrome ii. Abnormal pulmonary vascular remodelling—idiopathic PPHN iii. Diminished pulmonary vascular bed—pulmonary hypoplasia
B	Pulmonary vein stenosis (Group 1′)
C	Pulmonary hypertension secondary to left heart disease (Group 2)
D	Pulmonary hypertension secondary to lung diseases and/or hypoxia (Group 3)

right ventricle, and this latter finding may in itself be a feature of severe PH. In the absence of TR, the geometry of the interventricular septum and other echocardiographic signs can help to give an estimate of right ventricular and pulmonary artery

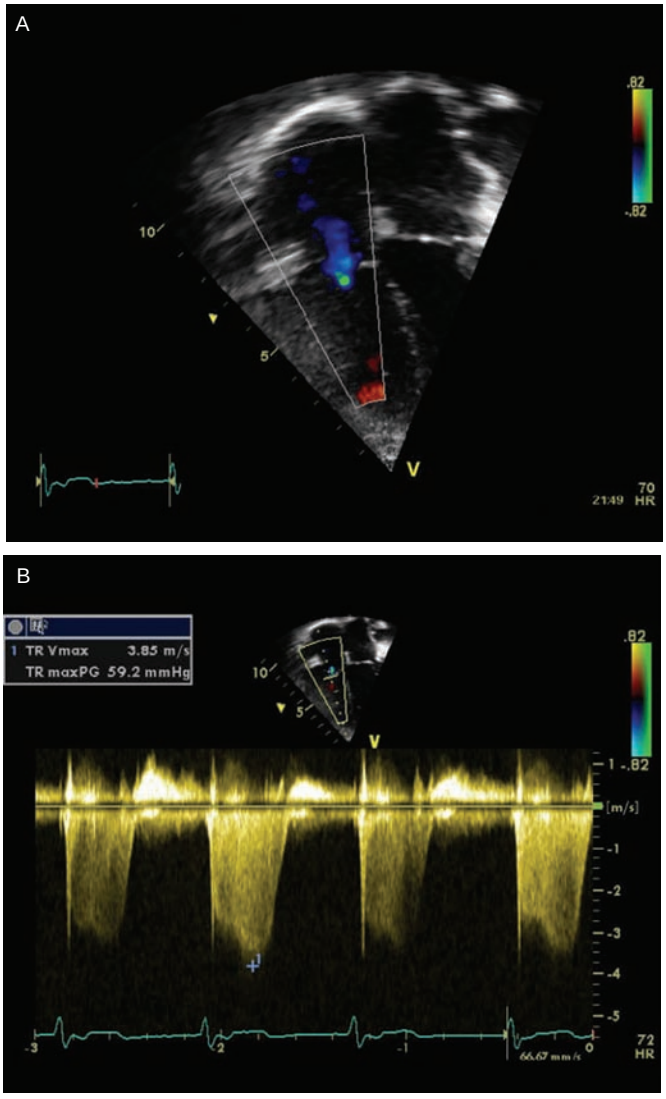

Figure 2 Use of continuous wave Doppler to measure right ventricular pressure. (A) Colour flow map of tricuspid regurgitation (TR) on echocardiography. (B) Spectral Doppler of TR indicating a pressure drop approaching 60 mm Hg, implying PH.

pressure. For example, the end-diastolic velocity of pulmonary regurgitation, when measurable, will give an estimate of pulmonary artery diastolic pressure.

Echocardiography and ECG are useful for diagnosing PH and for monitoring its progress. Cardiac catheterisation is only indicated in a few selected older patients (possibly beyond the neonatal period, but still on the neonatal unit) with severe PH, particularly if there are cardiac left-to-right shunts that might warrant device closure.

MANAGEMENT OF SPECIFIC TYPES OF PH

Persistent PH of the newborn

Failure of the PVR to fall after birth is the most common mechanism in the presentation of newborn PH. It affects principally infants at or close to term. There is a surprising paucity of epidemiological data concerning the incidence of PPHN, even in developed countries. Most series are vague about the denominator and therefore incidence is unclear. While most authors suggest that the incidence is 1–2 per 1000 live births, it may be as high as 7 per 1000 live births.[11] The incidence in babies with trisomy 21 is possibly even higher, up to 12 per 1000

live births.[12] The mortality in affected babies is high, around 10–20%. The pathophysiology is conventionally divided into three varieties (table 2).[4]

In the first of these the pulmonary vasculature is abnormally constricted due to lung parenchymal diseases and their associated hypercapnia, acidosis and alveolar hypoxia. Meconium aspiration syndrome is the most common cause and affects up to 2% of live births and up to 5% of term babies admitted for neonatal intensive care.[13] Other causes include pneumonia and respiratory distress syndrome. Clinical features are similar whatever the underlying cause and are characterised by acidosis, and hypoxaemia refractory to supplemental oxygen and ventilation.

In the second subgroup, the lung has normal parenchyma but there is abnormal remodelling of the pulmonary vasculature, also known as idiopathic PPHN. The chest radiograph will usually show reduced pulmonary vascular markings and little or no lung parenchymal changes. In these cases echocardiography is particularly useful in confirming the diagnosis and ruling out cyanotic congenital heart disease. Since the recognition from animal work that the maternal administration of non-steroidal anti-inflammatory drugs (NSAID) could contribute to neonatal PPHN through premature ductal closure,[14] a number of human neonatal cases have been reported, linked to last trimester maternal NSAID use. There have also been suggestions that PPHN may be linked to maternal use of selective serotonin reuptake inhibitors, although this remains controversial.[15]

Least commonly, but associated with the highest mortality, the pulmonary vasculature is hypoplastic in the presence of pulmonary hypoplasia, as seen in renal agenesis and congenital diaphragmatic hernia (CDH). In this situation, there is an abnormal, and reduced pulmonary vascular bed and an increased PVR.[16] Bilateral renal agenesis has an extremely poor prognosis with most babies surviving no more than a few hours. With lesser degrees of renal dysplasia and oligohydramnios, pulmonary hypoplasia may not be so severe as to be incompatible with survival. The outlook for CDH has steadily improved in recent years, with survival to discharge currently reported at 85%.[17] The management of PH in pulmonary hypoplasia of this context follows general principles, as described below, with surgical repair of CDH where applicable.

Management of PPHN

Classically, within a few hours of birth the baby with PPHN will be poorly perfused and cyanosed, often markedly so, with postductal saturations even lower than preductal, as a result of right-to-left shunting at ductal level. The differential diagnosis will include severe sepsis and cyanotic congenital heart disease. In the absence of radiological evidence of lung disease (eg, meconium aspiration, respiratory distress syndrome, pneumonia, CDH), echocardiography is particularly useful in ruling out cyanotic congenital heart disease and confirming PPHN pathophysiology. Supplemental oxygen is usually administered at an early stage and the cyanosis is likely to be refractory, leading to an escalation of therapy, initially involving positive pressure ventilation. Standard therapy includes correction of hypothermia, together with analgesia, sedation and commonly paralysis. Surfactants are also commonly used. Right ventricular afterload is increased and inotrope use is not unusual. Acidosis must be corrected, being a potent stimulus for pulmonary vasoconstriction. The use of alkalinisation although widely practiced, is more debatable. Aside from these general measures, there are a number of specific therapies.

High frequency oscillatory ventilation

Initial management of PPHN usually involves conventional positive pressure ventilation (CV) but contributes to lung injury and chronic lung disease. Theoretically, by maintaining oxygenation and ventilation at minimal tidal volumes, high frequency oscillatory ventilation (HFOV) minimises pulmonary volutrauma and thus reduces lung injury. Experimental animal studies have supported this benefit. However, two recently updated Cochrane systematic reviews have failed to find a clear benefit of HFOV over CV used as elective or rescue therapy in term or preterm neonates with acute respiratory failure.[18 19] Specifically, there was lack of evidence of reduction in mortality, failed therapy, intracranial injury or the development of BPD. In the preterm, there was a borderline reduction in BPD. More work is needed in this area to establish the potential efficacy of this therapy over CV.

Inhaled nitric oxide

Nitric oxide is an endogenous vasodilator which also inhibits smooth muscle growth and platelet aggregation.[20] It acts through the stimulation of soluble guanylate cyclase and the production of guanosine 3′,5′-cyclic monophosphate (cGMP). By inhalation, it has a selective effect on the pulmonary vasculature and has become well established as a therapy for PPHN.[21] It has also been shown to have bronchodilatory and anti-inflammatory effects. It has an added benefit over intravenous or oral pulmonary vasodilators in that it may improve rather than exacerbate the effects of ventilation-perfusion mismatch (figure 3). The Cochrane systematic review addressing the use of inhaled nitric oxide (iNO) in term neonates concluded that there was a clear benefit in terms of prompt improvement of oxygenation indices and sparing the need for extracorporeal membrane oxygenation (ECMO), although mortality was not

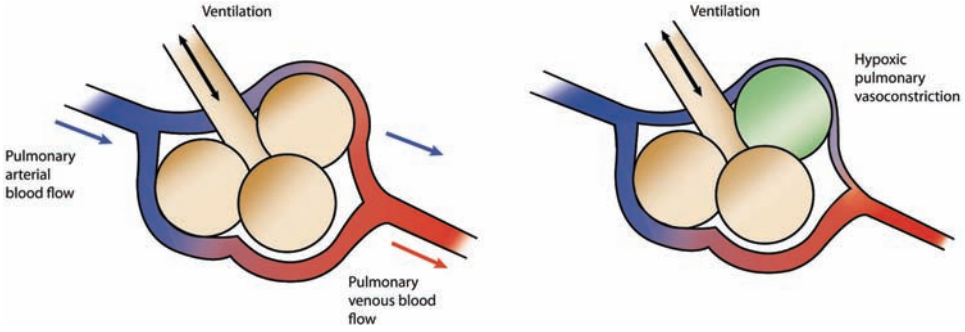

Figure 3 The protective effect of hypoxic pulmonary vasoconstriction. In the second frame, the pulmonary arteriole supplying the poorly ventilated alveolus (in green) constricts to reduce ventilation-perfusion mismatch.

affected.[22] However, the benefit did not extend to babies with CDH. In fact, there was a suggestion that outcome was slightly worse in this subgroup.

An initial inhalation dose of 20 ppm is commonly used, although once established, lower doses may be effective. The production of the potentially toxic by-products NO_2 and methaemoglobin, whose concentrations must be monitored, can thus be minimised. Rebound PH during withdrawal of iNO can be a significant problem and weaning should be effected slowly.

Prostaglandins

While to some extent supplanted by iNO on the neonatal unit, prostacyclin is a potent pulmonary vasodilator, whether administered intravenously or by inhalation. As the mechanism of action is reliant on increasing cAMP in vascular smooth muscle cells, it may have a role in the treatment of PPHN refractory to iNO. Combination therapy with iNO has also been reported.[23 24] In neonates, higher doses may be required than those conventionally used in older children (>20 ng/kg/min). Systemic vasodilation and hypotension may be problematic, but can be mitigated by the use of inotropes.

Cyanotic congenital heart disease forms part of the differential diagnosis of PPHN and while this can be rapidly resolved by echocardiography, this modality is not always immediately available. Where there is suspicion of ductal dependancy (of the pulmonary or systemic circulation, or in transposition physiology), prostaglandins E1 or E2 are routinely infused to maintain ductal patency. Aside from being safe and appropriate in this situation, both agents have been shown to have the benefit of producing pulmonary vasodilation, particularly prostaglandin E1.[25]

Phosphodiesterase inhibitors

The phosphodiesterases (PDE) are responsible for hydrolysing cGMP to GMP and the most active in smooth muscle is thought to be PDE5. Sildenafil and related compounds are selective inhibitors of PDE5, which is abundantly present in the lungs. By this mechanism, it increases intracellular concentrations of cGMP in pulmonary vascular smooth muscle and brings about pulmonary vasorelaxation. Interestingly, by preserving the increased cGMP generated by iNO, the two agents have been reported to work synergistically.[26] Sildenafil has been shown to attenuate pulmonary inflammation in a rat model of neonatal hyperoxic lung injury.[27] It appears to be safe, and aside from being a definitive therapy for PH in its own right, has become established as a means to effect a withdrawal of iNO therapy.[28] Because of the superior speed of action, targeted pulmonary effects, lack of reliance on gastric absorption and titratability of iNO, sildenafil is unlikely to become its replacement as initial therapy, except perhaps in developing countries where iNO is unavailable.

The optimum dose of oral sildenafil in neonates and children is still not entirely clear. The British National Formulary for Children advises starting doses of 0.25–0.5 mg/kg/dose up to a maximum of 2 mg/kg/dose.[29] Because of a relatively short half-life, sildenafil can be given up to 4 hourly although it is usually administered 6–8 hourly. It is also available though less readily, as an intravenous preparation.

Milrinone, a selective inhibitor of PDE3 in vascular smooth muscle and cardiac myocytes has been shown to improve oxygenation in term neonates with PPHN refractory to iNO.[30] This was a limited case series and does not reflect routine practice. Systemic hypotension did not occur, presumably related to the well-documented inotropy of this agent. Pulmonary vasorelaxation has been demonstrated in animal studies. It is usually administered intravenously but has also been successfully administered by inhalation.[31] The usual dose range by intravenous infusion is 0.3–0.7 mcg/kg/min. Neonatal PPHN series are small but there is likely to be more information emerging on this topic in the near future.

Extracorporeal membrane oxygenation

This therapy is adapted from cardiopulmonary bypass. Venous blood is siphoned from the great veins commonly by cannulating the superior caval vein via the internal jugular vein. It is then passed to a membrane oxygenator where gas exchange takes place. The blood is warmed to the correct temperature and returned to the patient's corporeal circulation. It should be considered in any term neonate with PPHN refractory to the above therapies. The most commonly used measure in assessing whether to refer for ECMO is the Oxygenation Index (OI).

$$OI = \frac{(F_iO_2 \times \text{Mean Airway Pressure})}{P_aO_2}$$

Where F_iO_2 is expressed as a percentage, mean airway pressure in cm H_2O and P_aO_2 in mm Hg. ECMO should be considered if the OI is >40. A number of exclusion criteria apply, the main requirement being that the underlying condition should be reversible or correctable, without significant intracranial injury or coagulopathy or a lethal chromosomal anomaly. Typical gestational age and birthweight cut-offs for initiation of this therapy are >35 weeks and >2 kg respectively. Four trials of ECMO in the treatment of newborn respiratory failure were subjected to Cochrane review and all showed a strong benefit in terms of survival, without evidence of increased risk of severe disability.[32] They recruited clinically similar groups with newborn respiratory failure due to PPHN and other causes, although two of the trials excluded infants with CDH. The benefit in the subgroup with CDH was unclear.

Magnesium sulphate

Magnesium sulphate (Mg) acts as a vascular smooth muscle relaxant. There have been a number of relatively small non-randomised animal and human series reporting the use of intravenous Mg infusion in the treatment of PH. However the Cochrane review on the topic updated at the end of 2009 failed to find any eligible studies.[33] Since then there has been one recently published randomised controlled trial of iNO versus Mg in the treatment of PPHN in babies receiving HFOV.[34] There was a better outcome with iNO.

PH associated with BPD

With improvements in neonatal care, there are more survivors of CV or HFOV who continue to require supplemental oxygen. When this requirement extends beyond 4 weeks or to the point of hospital discharge, these infants are regarded as having BPD (also called chronic lung disease of infancy). Other definitions of BPD are also commonly used and relate to the postnatal age at which a requirement for supplemental oxygen persists.[35] The best treatment of BPD is prevention. While a detailed examination of how this may be achieved is beyond the scope of this paper, there is no doubt that many developments have played a part in addressing this goal, including limitation of hyperoxic and ventilatory pulmonary injury,

surfactant instillation, iNO and therapeutic closure of the persistent arterial duct.

Careful attention to nutrition and growth is required. It has been shown that in the first 2 years of life, lung growth occurs by an increase in the number of alveoli and this process can be optimised to generate new healthy parenchyma.[36] Although data are limited and this therapy is not in general use, vitamin A supplementation has been shown to reduce the incidence of BPD in preterm neonates.[37] Intercurrent infections will increase oxygen requirements and may further damage the lung, and should be effectively treated. Specifically, neonatal infection with Ureaplasma urealyticum is associated with increased rates of BPD.[38] However, opinion remains divided as to whether the relationship is causal, and the most recent randomised controlled trial has failed to demonstrate conclusive benefit of azithromycin therapy in preventing BPD in the preterm.[39]

Pathologically, the condition is characterised by the appearance of alveolar simplification and abnormal capillary morphology, with variable interstitial cellular and fibroproliferation. A reduction in the number and size of intra-acinar pulmonary arteries has been shown in infants with BPD.[10] This contraction of the pulmonary vascular bed alone, or in combination with abnormal pulmonary arterial muscularisation can result in increased PVR and consequential PH. Although the role of pulmonary inflammation in BPD has been well recognised, the benefit of treatment with steroids has not been found to conclusively outweigh risks.[40]

Management of PH in BPD

By definition, BPD implies a persisting need for oxygen, but the threshold for defining this need varies between neonatal units. The role of hypoxic pulmonary vasoconstriction (figure 3) must be recognised and balanced against the risk of oxygen free radical toxicity and the inconvenience of oxygen supplementation, particularly in an outpatient setting. While there is a lack of evidence base for the choice of oxygen saturation in the convalescent baby with BPD, there are genuine concerns that relative hypoxaemia may exacerbate PH. In practice, many units advocate maintenance of oxygen saturations in the low 90s or even high 80s. Where BPD and PH are documented to be severe, more 'normal' saturations (≥95%) may be indicated.

In animal models of BPD, sildenafil has been shown to benefit alveolar growth, pulmonary angiogenesis and survival, and reduce pulmonary inflammation in addition to the well-documented effects on PVR. A recently published retrospective series of 25 patients with BPD aged <2 years showed haemodynamic improvement in 88%, with adverse events in two patients.[41] The experience with endothelin receptor antagonists in this population is limited. As a cautionary note, the protective mechanism of hypoxic pulmonary vasoconstriction can be over-ridden by the use of oral pulmonary vasodilators (figure 3). Whereas iNO has the potential to better match lung perfusion to ventilation, oral pulmonary vasodilators have a less specific effect and do not preferentially vasodilate the better ventilated areas of lung. In this way, ventilation-perfusion mismatch may be exacerbated, resulting in deteriorating oxygen saturations.

PH associated with congenital heart disease

The UK incidence of congenital heart disease is around eight per 1000 live births. In the majority of these cases the lesions are relatively simple such as small to moderate sized septation defects or mild valvar stenoses. Arterial ducts are normally present in the newborn, but typically close within the first few days of life in well, term babies. Because of the relatively high PVR in the newborn period many of these lesions will not be diagnosed until later life. Specific cardiac lesions in the following categories form part of the differential diagnosis of PPHN and need to be identified:

a) Duct dependent pulmonary circulation, eg, pulmonary atresia
b) Duct dependent systemic circulation, eg, hypoplastic left heart syndrome
c) Transposition of the great arteries
d) Total anomalous pulmonary venous drainage
e) Ebsteins malformation of the tricuspid valve (severe cases).

Those in categories (d) and (e) are not usually duct-dependent, unless associated with other major lesions. Newborn babies with common arterial trunk will usually have a degree of cyanosis at birth but have been known to pass a pulse oximetry test. Left heart disease contributing to significant PH in the newborn is rare, but could be seen in the context of severe ventricular impairment (eg, cardiomyopathy) or in the presence of severe mitral valve stenosis with intact atrial septum, which sometimes falls into the spectrum of (b) above.

Congenital pulmonary vein stenosis, while rare, is associated with prematurity.[42 43] When bilateral and extensive, it is a cause of severe PH and carries a poor prognosis. It has been known to clinically mimic BPD.[44] Recognition is important for appropriate cardiac intervention and so that inappropriate pulmonary vasodilator therapy is not used.

Electrocardiography, chest radiography and pulse oximetry are simple investigations which may shed light on a cardiac diagnosis. However the mainstay of definitive cardiac diagnosis is echocardiography. In most of the categories of major cardiac lesions described above, transfer to a paediatric cardiac facility will be necessary for further specific therapy, usually involving cardiac surgical or interventional management.

In summary, most cases of neonatal PH will involve a diagnosis of PPHN or BPD. Cyanotic congenital heart disease is part of the differential diagnosis of PPHN and must be actively ruled out, particularly in cases refractory to initial treatment regimes. Rarely will a cardiac lesion be primarily responsible for neonatal PH although pulmonary vein stenosis and the persistence of an arterial duct must be considered, particularly in the older preterm baby with BPD.

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