Persistent Pulmonary Hypertension (PPHN)

Definition:
Classically, PPHN is defined as a failure of the normal postnatal fall in pulmonary vascular resistance which leads to persisting right to left shunts across the fetal channels and resultant hypoxia.\(^1\) This is a simplified view of what is a complex condition and in many babies the major shunt is occurring at an intrapulmonary level.\(^2\) It is important to think of PPHN as primary or secondary.\(^3\)

- **Primary PPHN** is the form of PPHN which most closely fits the classical definition, typically presenting soon after birth with hypoxaemia in a baby with clinically and radiologically normal lungs.\(^3\) This condition is probably due to a primary dysfunction in the pulmonary endothelial vasodilating mechanisms.\(^2\)
- **Secondary PPHN** is PPHN which is secondary to a disease in the parenchyma of the lungs. This is over-diagnosed and while most babies with lung disease will have pulmonary artery pressures above normal. Only the sickest (oxygenation index >25 in term babies\(^2\) or >15 in preterm babies\(^4\)) will consistently have pulmonary pressures close to or above systemic pressures. In these babies the pulmonary vasoconstriction is probably secondary to hypoxia, acidosis and high ventilatory pressures.

Incidence:
This is not a common condition and the true incidence is confounded by problems of definition and classification. In the two years 1995/96 there were 24 babies admitted to John Spence Nurseries with clinical and echocardiographic evidence of primary or secondary pulmonary hypertension ie one baby a month.

Risk Factors:
- **Primary PPHN** is usually idiopathic in origin. Although it is associated with a variety of complications of pregnancy\(^5\) including maternal diabetes, maternal hypertension, prolonged gestation and maternal indomethacin. It has also been described in association with polycythaemia, fetal anaemia,\(^2\) premature ductal closure.
• **Secondary PPHN** is related to a range of respiratory disorders, particularly meconium aspiration, pneumonia, severe hyaline membrane disease and diaphragmatic hernia and other forms of pulmonary hypoplasia.

---

### Clinical Diagnosis:

- **Primary PPHN** presents in the early postnatal period as cyanosis often with a degree of respiratory distress and can closely mimic the presentation of cyanotic congenital heart disease. There may be differential cyanosis between upper and lower body, clinically and on blood gases. The lung fields are clear or minimally opacified on X-ray. The degree of hypoxia is variable and the pCO₂ is normal or sometimes low.

- **Secondary PPHN** presents primarily as respiratory distress with PPHN becoming apparent as the lung disease deteriorates with the need for higher oxygen requirements and ventilatory pressures. Parenchymal lung opacity abnormality is apparent on the x-ray.

- **In both groups** PPHN may be suggested by a prominent precordial impulse, the low parasternal murmur of tricuspid incompetence and a large cardiac shadow on chest x-ray.

### Echocardiographic diagnosis:\(^5\)

This allows accurate diagnosis of PPHN and should be done as soon as practical in the clinical course. With echocardiography one can:

- Exclude congenital heart disease.
- Define the pulmonary artery pressure using tricuspid incompetence or ductal shunt velocities.
- Define the presence, degree and direction of shunt through the duct and foramen ovale. These shunts are often less that is assumed, firstly because pulmonary pressures are subsystemic and secondly because both fetal channels but particularly the ductus close early in the course of the disease.\(^2\)
- Define the ventricular outputs. These are commonly very low in the early course.\(^2\)

---

### Interventions.

The aim of treatment is to maintain normal arterial oxygen levels and normal oxygen delivery to the organs of the body. The two most potent natural pulmonary vasodilators are oxygen and lung inflation.

1. **Oxygen**

   This will help to maintain arterial oxygen levels and will act as a pulmonary vasodilator. However animal data would suggest that optimal pulmonary vasodilation occurs with a pO₂ around 120mmHg. No benefit is likely from higher levels of inspired oxygen which may also contribute to secondary lung injury. Therefore, aim to maintain pO₂ between 100-120 mmHg.
2. Conventional ventilation

This is the mainstay of respiratory support, the principles will be much as described for ventilation of preterm babies but with the following differences.

- Sedate and paralyse the term and near term babies to ensure optimal ventilator efficiency.
- Use the Ventrak respiratory function monitor to measure ventilation flows and volumes.
- To maintain normal blood gases it is often necessary to ventilate with high minute volumes (>300 mls/kg). Oxygenation is often very sensitive to small reductions in minute volume such as can occur with retained secretions.
- Aim to maintain normal to low normal pCO$_2$ in the range 35 to 40 mmHg, pCO$_2$ lower than this may cause cerebral vasoconstriction. However if the pCO$_2$ does not come down easily despite good minute ventilation on the Ventrak it is often unhelpful to continue to drive up the ventilatory pressures.

3. High Frequency Oscillatory Ventilation (HFOV):

Randomised studies comparing HFOV with conventional ventilation in babies with severe hypoxic respiratory failure have shown that HFOV gives better oxygenation in a proportion of babies.\textsuperscript{6,7} The best effect is seen in babies with secondary PPHN and HFOV probably works in this situation by allowing better lung inflation and "alveolar recruitment".\textsuperscript{6} HFOV should not be started without senior consultation and supervision. (HFOV is not currently routinely available on JSN but is likely to be in the near future. When available, an HFOV guideline will be drawn up).

4. Inotropes:

The role of inotropes in PPHN is poorly substantiated. Low ventricular outputs are common in these babies however it is not clear that this is due to primary pump failure. Observational studies here and elsewhere have suggested that low output may reflect the right ventricle struggling with a high afterload to get blood through the lungs, which in turn causes a low left ventricular output.\textsuperscript{2,8} In an ongoing study, we have recorded significant increases in ventricular outputs with Nitric oxide in term babies and this may be a more rational approach to circulatory support than inotropes. In animal studies, dopamine has similar vasoconstrictor activity on the pulmonary as on the systemic vasculature, so at an empirical level, dobutamine is the preferred inotrope starting at 10 µg/kg/min.

5. Vasodilators:

A. Nitric oxide (NO)

- NO is the vasodilator of choice term in babies with PPHN.\textsuperscript{9} However the evidence to support its use in preterm babies is not yet available. Randomised trials in term babies with primary and secondary PPHN have shown that:
  - NO significantly improves oxygenation.\textsuperscript{10,11}
  - NO significantly reduces the need for rescue with ECMO.\textsuperscript{11}
  - Response to NO depends on the underlying pathophysiology. Marked improvement is seen with NO alone in babies with primary PPHN. In babies with secondary PPHN, the effects of NO are augmented by HFOV.\textsuperscript{6}

- Indications for Nitric oxide: should be considered in:
  - any baby with severe hypoxic respiratory failure who is unable to maintain a pO$_2$ above 80mmHg despite maximal respiratory support.
any ventilated baby with a significant (>50%) oxygen requirement and echocardiographic evidence of pulmonary artery pressures close to or above systemic pressure especially if there is evidence of poor cardiac output (<150mls/kg/min).

- **Dosing, setting up NO circuit and monitoring:** see nitric oxide guideline.

**B. Tolazoline and Prostacycline**

- These have been widely used in PPHN although there are no randomised trials to support their use. Both drugs have similar vasodilator effects on the systemic and the pulmonary circulation and so may cause systemic hypotension. In babies with primary PPHN and predominantly extrapulmonary right to left shunting, they can produce dramatic increases in oxygenation. But in the more common haemodynamic scenario where most of the shunt is occurring in the lungs, their general vasodilating properties may increase intrapulmonary right to left shunt. Nitric oxide is more specific and has more evidence to support its use and has largely superseded these drugs.

- **In critical situations where there is no time to set up the NO circuit, a slow intravenous bolus of tolazoline (0.5-1mg/kg) can be life saving.**

**6. Extracorporeal membrane oxygenation (ECMO).**

Since the introduction of NO and HFOV, the need for ECMO has declined. However the UK collaborative trial showed a significant reduction in mortality with ECMO treatment in babies with an oxygenation index >40. So in babies with an OI >40 despite NO and HFOV (if available), transfer to Sydney Children’s Hospital for ECMO should be considered.

---

**Key Points**

<table>
<thead>
<tr>
<th>Key Points</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPHN should be classified as primary or secondary to lung disease.</td>
<td>2</td>
</tr>
<tr>
<td>Echocardiography will accurately define the haemodynamics.</td>
<td>5</td>
</tr>
<tr>
<td>The major right to left shunt is often intrapulmonary.</td>
<td>2</td>
</tr>
<tr>
<td>Adequate oxygenation and ventilation (conventional) are the mainstay of therapy.</td>
<td></td>
</tr>
<tr>
<td>Nitric oxide (NO) is the vasodilator of choice in term babies. Best response to NO is seen in primary PPHN.</td>
<td>6</td>
</tr>
<tr>
<td>HFOV ± NO is the best rescue treatment in babies with secondary PPHN.</td>
<td>6</td>
</tr>
<tr>
<td>ECMO should be considered in babies who fail to respond to HFOV and NO.</td>
<td>12</td>
</tr>
</tbody>
</table>
References


2. Evans N, Kluckow M, Currie A. Range of echocardiographic findings in term and near term babies with high oxygen requirements. *Arch Dis Child* 1998; in press


