



CLINICAL PRACTICE GUIDELINE

Guideline coverage includes NICU KEMH, NICU PMH and NETS WA

Persistent Pulmonary Hypertension of the Newborn (PPHN)

This document should be read in conjunction with the [Disclaimer](#)

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a rather clumsy but well established term describing a condition with inappropriate resistance to blood flow through the pulmonary bed, presenting with Hypoxic Respiratory Failure (HRF).

In the past clinicians have considered HRF in terms of an oxygenation index but an oxygen requirement of > 60% to maintain saturations above 90% is a very practical and simple alternative (see [Appendix 1](#)). Not all HRF is PPHN and other causes should be excluded and where possible treated.

These include:

- Underventilation and atelectasis.
- Collapse / consolidation.
- Pneumothorax, pneumomediastinum.
- Pulmonary effusion.
- Mechanical problems (airway leak, disconnects etc.).
- Congenital heart disease.

Exclusion of the above suggests PPHN as an underlying component of HRF.

Diminished pulmonary blood flow is a common endpoint of many underlying pathophysiologies.

Anatomical

- Congenital heart disease:
 - RV outflow obstruction.
 - TGA.
 - Anomalies of pulmonary veins.
- Pulmonary anomalies:
 - Pulmonary hypoplasia (PPROM, diaphragmatic hernia).
 - Alveolar Capillary Dysplasia.
 - Severe cystic CCAM / Sequestration.

Low Cardiac Output

- Low preload:
 - Hypovolaemia.
 - Systemic venous obstruction.
- Poor contractility:
 - Prematurity.

- HIE.
- Sepsis.
- 1° cardiomyopathy.

Pulmonary Vascular Reactive Constriction

- 1° [Respiratory Distress Syndrome \(RDS\)](#).
- [Meconium Aspiration Syndrome \(MAS\)](#).
- [Pneumonia](#) (particularly GBS).
- 2° to metabolic triggers (acidosis, hypoxia etc.).
- Mechanical - obstruction by high MAP.

Management

Once other causes of HRF have been excluded management should be based on optimising all other physiological parameters without causing long term damage. The primary aim is not normal blood oxygen levels but long term intact survival. Manage for discharge not the end of a shift.

PPHN is best managed as an iterative physiological exercise. A thorough understanding of the physiology of vascular smooth muscle should underpin management (see [Appendix 2](#)).

Infants with PPHN are often unstable, care should be taken to minimise the impacts of handling and procedures.

Exclude Other Causes of HRF

- See list above.
- CXR, etc.

Optimise Ventilation

Ensure adequate chest movement and expansion.

Primary aim should be to improve efficiency of ventilation while minimising long term harm to the lungs. Gentle ventilation. HFJV may be the most appropriate modality to achieve this.

- **CO₂:**
 - Aim to reduce respiratory acidosis by keeping CO₂ 35 to 45 mmHg.
- **pH:**
 - Aim to keep pH as near to 7.4 as possible.
 - Adequate ventilation (see above).
 - Optimal perfusion (see below). Remember bicarb is not an efficient buffer above pH >7.0 and should be used sparingly. Beware of pH above 7.40 this is associated with reduced cerebral blood flow and particularly hearing loss.
- **FiO₂:**
 - Aim to keep FiO₂ as low as possible. Oxygen is toxic to the lung causing tissue damage, denaturing surfactant and impairing ciliary function. Reactive oxygen species (ROS) are potent activators of the RhoKinase inhibition of myosin kinase and hence induce vasoconstriction.
 - Remember there is diminishing return from increasing FiO₂ and that levels > 0.8 will induce atelectasis.
- **Lung Volume:**

- Aim for well expanded lungs but beware of over-distention, 9 posterior ribs on an X-ray is current standard.

iNO

The use of iNO (particularly in prems) is controversial with AAP statements suggesting it is experimental and unproven. We have enough evidence to consider iNO the mainstay of treatment in PPHN. It should be considered whenever $FiO_2 > 60\%$ and other causes of HRF have been actively excluded or managed. Ideally a cardiac echo should be performed before starting (see below) but don't delay use if this is not immediately available. The starting dose is also controversial, we have generally gone straight to 20ppm. A clear response to iNO is indicative of a significant reversible underlying pulmonary vasoconstriction.

Volume Expansion

Optimal preload is crucial in maintaining cardiac output in the newborn (particularly prems). This can only really be assessed on cardiac echo looking at venous and atrial distension. Where there is any doubt volume expansion with saline (or blood if indicated) should be given. Ideally preload should be re-assessed after a fluid bolus.

Optimise Metabolic Status

Electrolyte parameters should be measured and corrected. Na, K, Ca and Mg. Mg in particular is a potential vasodilator and levels should be in the upper normal ranges (1.00 mmol/L). Glucose should be maintained in the normal range. Haemoglobin should not be allowed to fall below 100 gm/dL.

Sedation

Infants may be unsettled, this can be managed by reducing respiratory acidosis (not always possible). Morphine infusion is useful in settling and preventing clinical instability. Be mindful of the potential hypotensive effects of morphine, these may be beneficial or harmful. Sedation with Benzodiazepines (Midazolam) is potentially harmful to the developing brain and should be avoided.

Inotropes

The use of inotropes in the management of PPHN is always a double edged sword. In the past a very simplistic model of increasing pulmonary perfusion by increasing systemic blood pressure was adopted. We now know that this model is not always correct and that inotropes may in fact lead to increased pulmonary vascular resistance decreased cardiac output and diminishing pulmonary blood flow (particularly in the preterm). The increased strain on an already compromised myocardium may hasten cardiac failure. Optimal use of inotropes can be aided by echocardiographic monitoring of the circulation. In situations of high output failure (usually low systemic resistance and increased CO from septic shock) vasopressors may be particularly helpful in maintaining the circulation. The choice of inotrope should be determined by the clinical situation.

Inodilators, PDH3 inhibitors (milrinone), were heralded as a potential benefit in this condition. Premature infants however rarely respond (?immaturity of receptors) and the response seen in term infants is not as great as in older children.

Prostin

Prostin to maintain patency of the Ductus Arteriosus (DA) has been considered advantageous in the management of CDH and should be considered in other forms of PPHN where there is a right to left DA shunt. Allowing right to left shunting across the DA depressurises a potentially failing right ventricle. Prostin is also a vasodilator and may have direct beneficial effects on PVR.

Sildenafil

Sildenafil is a PDH5 inhibitor that raises cGMP in the smooth muscle cell promoting vasodilation. The drug has been shown to be of benefit in third world settings where iNO is not readily available, it has also been shown to be a useful adjunct to iNO therapy and to enhance weaning. Currently sildenafil is only available as an oral preparation, hopefully an IV form will be available soon.

Prostacyclins

The synthetic PGI₂ agonist Iloprost has found favour in adult pulmonary hypertension where an imbalance in the TXA/PGI₂ may be a more significant etiological factor. Use in neonates has been with limited success. Iloprost is available as an inhaled or injectable form (Available as a special access scheme (SAS) medication).

Endothelin Receptor Antagonists (ERAs)

This family of drugs block the vasoconstrictive actions of Endothelin1 by competitively binding with the receptors ET_A and ET_B. Bosentan is the most widely studied and has been used with limited success in neonates. It is only available in tablet form.

Muscle Relaxation

Short term muscle relaxation with vecuronium may be beneficial in infants who will not settle with a morphine infusion. An initial single dose is preferable to an infusion. Long term muscle relaxation will lead to significant fluid shifts and peripheral oedema. Trial data has suggested an increased mortality from muscle relaxants, despite this they are worth consideration when all else is failing.

Surfactant

The role of repeated doses of surfactant in PPHN is unclear. Where the condition is thought to arise 2^o to RDS surfactant replacement should be beneficial. In other situations the potential for clinical deterioration with the giving of surfactant should be weighed against the potential for therapeutic benefit.

Steroids

There is no clear trail data supporting or refuting the use of steroids in managing PPHN. Supporting the circulation with hydrocortisone is likely to be potentially less harmful than administering universal vasoconstrictors such as dopamine or noradrenalin.

ECMO

The role of ECMO has diminished as we have collectively improved management of PPHN. ECMO may still however be considered where the infant is big enough (> 2000 grams), has a reversible underlying condition (often only assessable in retrospect), an ECMO team is available and the parents consent. These decisions are never easy and are best made by at least two senior neonatologists in conjunction with the ECMO team from PMH.

Role of Echocardiography

An understanding of the underlying cardiopulmonary interactions in PPHN gleaned from repeated functional echocardiographic studies has underpinned our progress in management. Repeated ascertainment of the relative systemic and pulmonary pressures, the contractility of the right and left myocardium and the adequacy of preload all inform clinical decisions.

At some stage normal cardiac anatomy needs to be confirmed including confirmation of pulmonary venous drainage.

Having said this care must be taken to avoid handling during examination and scans may need to be significantly limited. Only experienced scanners should assess these infants.

It can be very difficult to assess mild degrees of PPHN when the pulmonary pressures remain below systemic. A “normal” echocardiogram is not a reason to withhold iNO in an infant with HRF ($FiO_2 > 0.6$).

Appendix 1

Oxygenation Index (OI)

The OI reflects the efficiency of oxygen uptake by the cardiorespiratory system.

Note that you will need an arterial blood gas sample to measure PaO₂.

$$OI = \frac{FiO_2 \times MAP \times 100}{PaO_2}$$

A lower OI is better.

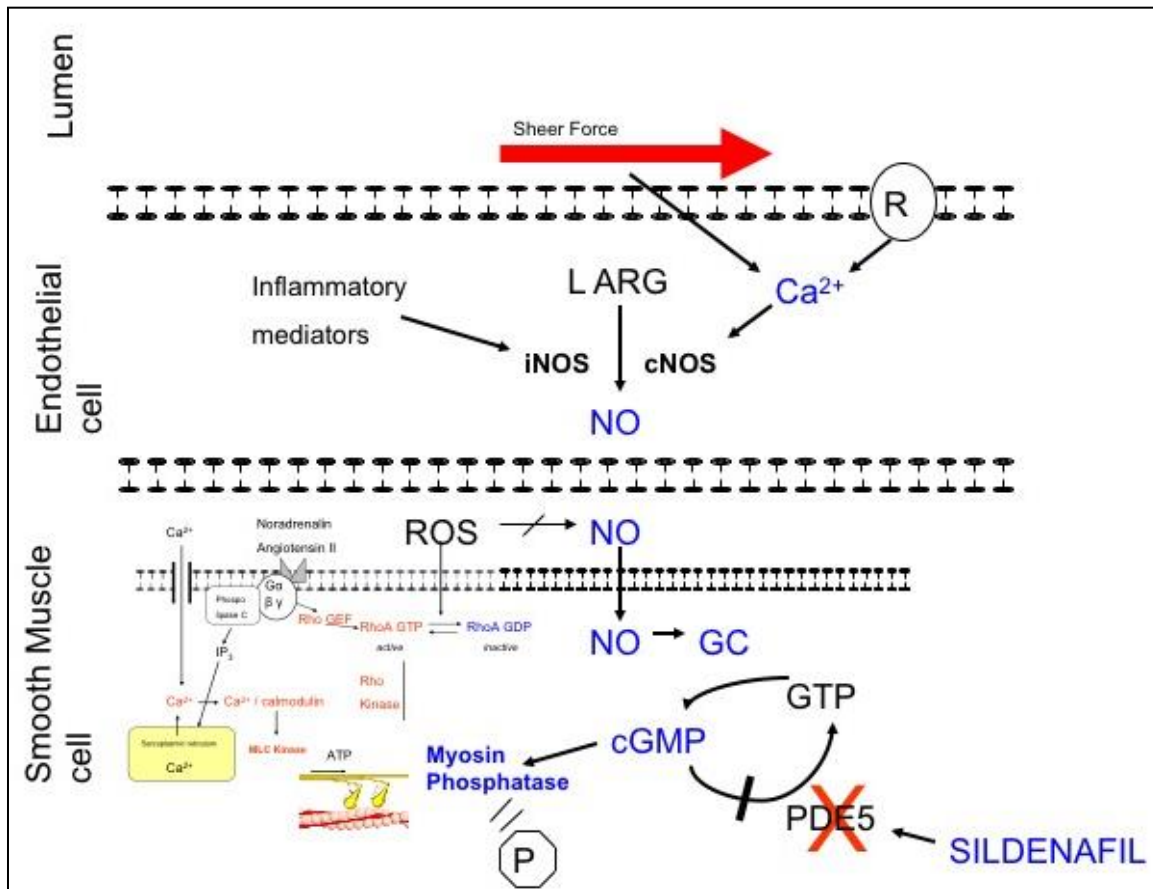
Support	FiO ₂	MAP cmH ₂ O	PaO ₂ mmHg	OI
CPAP	0.21	5	85	1
SIPPV	0.30	7	85	2
HFOV	0.60	14	85	10
HFJV	1.00	14	85	16
HFJV	1.00	16	55	30

The OI has been used in the past as a research tool, for assessing eligibility for surfactant (years ago when first introduced) and as a criteria for ECMO.

In the clinical setting it can be more practical to consider a FiO₂ > 0.6 (60%) as indication of significant hypoxic respiratory failure.

Appendix 2

Physiology of Vascular Smooth Muscle Contraction



Smooth muscle tone is a balance of myosin light chain kinase (MLCK), which induces contraction by activating myosin bound ATPase, and myosin phosphatase which dephosphorylates the myosin. Under normal conditions these actions are balanced.

Contraction is induced by the Ca²⁺ Calmodulin complex. There are many stimuli for raising intracellular Ca²⁺ through transmembrane channels including voltage gates and K⁺ dependent channels. Adrenalin and dopaminergic receptors activate inositol triphosphate (IP₃) mediated release of Ca²⁺ from the sarcoplasmic reticulum. An alternate, Ca²⁺ independent, activation pathway is via Rho/RhoKinase. This pathway is now thought to lead to more sustained contraction and has many activators including ROS. This pathway has been implicated in DA closure.

The relaxation pathway dependent on NO activation of guanylate cyclase (GC) upregulation of intracellular cGMP which in turn maintains activity myosin phosphatase. cGMP also promotes reuptake of Ca²⁺ into the sarcoplasmic reticulum. NO is produced in the endothelium by constitutional (cNOS) and inducible (iNOS) pathways. Sildenafil also acts to raise cGMP by blocking degradation by phosphodiesterase (PDE5). Milrinone has similar actions in blocking PDE3 which deactivates both cGMP and cAMP.

The prostinoid/thromboxane pathways are even more complicated and illustrated below.

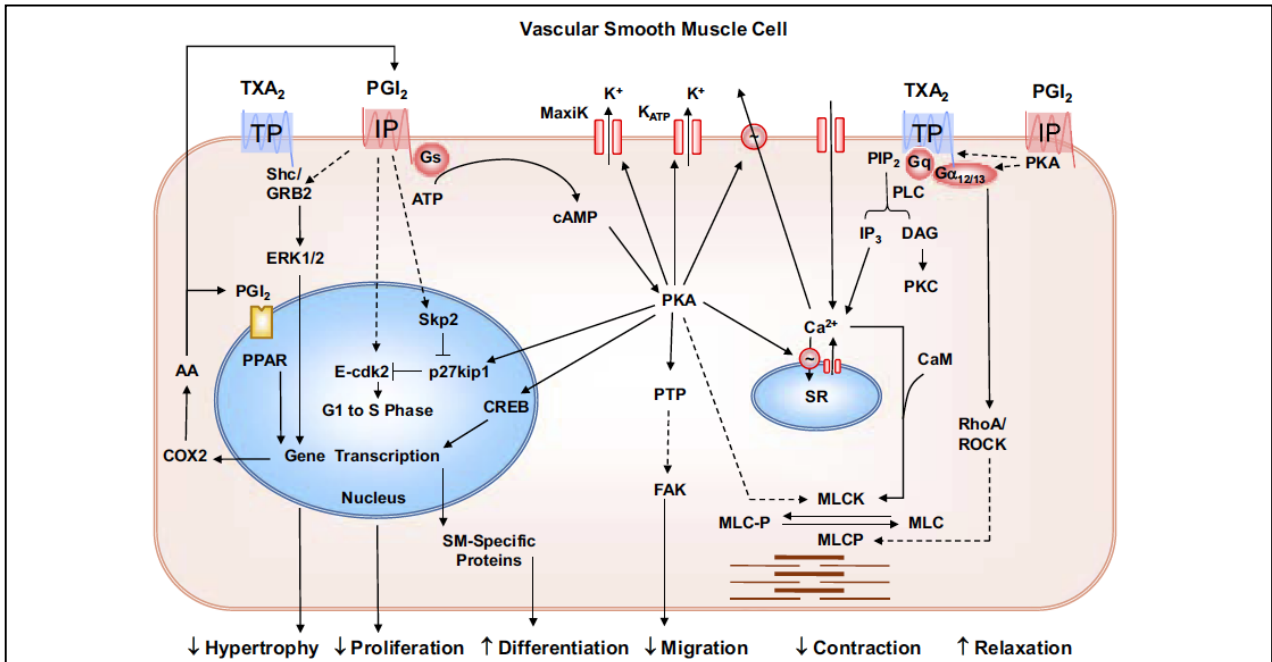



FIG. 5. PGI₂ signaling pathways in VSMCs. PGI₂/IP cell surface interaction is coupled primarily to G_s to activate cAMP/PKA leading to Ca²⁺ extrusion via cell surface and sarcoplasmic reticulum (SR) Ca²⁺ pumps, and activation of different K⁺ channels (including ATP-sensitive K⁺ channels and MaxiK channels), which in turn cause VSMC hyperpolarization and relaxation. In contrast, TXA₂/TP interaction causes stimulation of G_q, activation of phospholipase C (PLC), and increased production of inositol-1,4,5-trisphosphate (IP₃), which stimulates Ca²⁺ release from SR, and DAG, which activates PKC. Increased [Ca²⁺]_i causes activation of Ca²⁺/calmodulin/myosin light chain kinase (MLCK) pathway and stimulation of VSMC contraction. TP-mediated stimulation of G_{α_{12/13}} activates Rho signaling and the RhoA/Rho-associated protein kinase (ROCK) pathway, which inhibits myosin-light chain phosphatase (MLCP) and causes Ca²⁺ sensitization and enhancement of VSMC contraction. PGI₂/IP signaling via cAMP/PKA can inhibit TXA₂-induced VSMC contraction by PKA-mediated TPα phosphorylation and thereby inhibition of both G_q/PLCβ/Ca²⁺-dependent and G_{12/13}/RhoA Ca²⁺-independent signaling pathways. PGI₂ also activate genomic pathways and cellular processes including, as shown from left to right, PGI₂-induced PGI₂ release, PPAR, VSMC hypertrophy, proliferation, differentiation, and migration. PGI₂/IP signaling can induce COX2 expression in VSMCs to metabolize AA and produce PGI₂, which in turn may act in an intracrine fashion on the same VSMC or paracrine on nearby VSMCs (feedback loop). PGI₂ intracrine signaling may involve direct binding to PPAR nuclear receptors and gene transcription. PGI₂/IP signaling can inhibit Shc/GRB2 complex formation and subsequent ERK1/2 activation by TXA₂/TP signaling, thus inhibiting VSMC hypertrophy. PGI₂ also inhibits VSMC proliferation by inhibiting G₁-to-S phase progression through inhibition of cyclin E-cyclin-dependent kinase (cdk2) as well as activation of p27^{kip1}, which keeps cyclin E-cdk2 in an inactive state, either directly or via inhibition of the gene for S-phase kinase-associated protein (Skp2), which causes p27^{kip1} degradation. PGI₂ can also act through IP/cAMP/PKA-mediated activation of CREB or other SM-specific transcription factors to increase the expression of SM-specific differentiation markers and cause VSM differentiation. PGI₂ via cAMP-dependent activation of protein tyrosine phosphatase (PTP) causes inhibition of focal adhesion kinase (FAK) and disruption of focal adhesion formation, leading to inhibition of cell migration.

Mirza, H., et al., *Pulmonary hypertension in preterm infants: prevalence and association with bronchopulmonary dysplasia*. J Pediatr, 2014. **165**(5): p. 909-14 e1.

Related WNHS policies, procedures and guidelines

Neonatology Clinical Guidelines - [Respiratory Distress Syndrome \(RDS\)](#)
 Neonatology Clinical Guidelines - [Meconium Aspiration Syndrome \(MAS\)](#)
 Neonatology Clinical Guidelines - [Pneumonia](#)
 Neonatology Clinical Guidelines - [Nitric Oxide Therapy \(iNO\)](#)
[Neonatal Medication Protocols](#)

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