Persistent pulmonary hypertension of the newborn

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ABSTRACT

This article attempts to define a complicated, yet not rare disease of the neonate, which presents with extreme hypoxemia due to increased pulmonary vascular resistance, resulting in diversion of the pulmonary venous blood through persistent fetal channels, namely ductus arteriosus and foramen ovale. Pathophysiology, diagnostic approach and the various modalities of management are analyzed. Persistent pulmonary hypertension of the newborn is multi-factorial, which is reflected in the management as well. These babies are extremely labile to hypoxia and should be stabilized with minimum handling. One hundred percent oxygen and ventilation are the mainstay of treatment. The role of hyperventilation, alkalinization, various non-specific vasodilators such as tolazoline, magnesium sulphate, selective vasodilators such as inhaled nitric oxide, adenosine and the role of high frequency oscillatory ventilation and extra corporeal membrane oxygenation are discussed. With the newer modalities of management, the outlook has improved with mortality of less than 20% and fewer long-term deficits.

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First described in 1969, persistent pulmonary hypertension (PPHN) of the newborn, still remains a challenging condition with high morbidity and mortality. It occurs usually in term or post-term babies soon after birth, often within 12 hours of birth. The approximate incidence is one in 700 births.[1] The synonyms for PPHN include persistent fetal circulation (PFC), persistent transitional circulation, persistent pulmonary vascular obstruction or pulmonary vasospasm.[2] It may occur as idiopathic or complicate a variety of neonatal disorders, including meconium aspiration, birth asphyxia, pneumonia, hyaline membrane disease (RDS), and pulmonary hypoplasia associated with congenital diaphragmatic hernia or oligohydramnios. Persistent pulmonary hypertension of the newborn, by definition, is a cardiopulmonary disorder characterized by systemic arterial hypoxemia secondary to elevated pulmonary vascular resistance with resultant shunting of pulmonary venous blood to the systemic circulation through fetal channels, namely, the ductus arteriosus and foramen ovale, thus bypassing the lungs and resulting in severe systemic arterial hypoxemia. Depending on the likely etiology, 3 types are described 1) PPHN associated with pulmonary parenchymal disease - this is called secondary PPHN and is seen associated with perinatal asphyxia, meconium aspiration syndrome or severe hyaline membrane disease or with severe pneumonia especially group B *Streptococcal pneumonia*. The low alveolar oxygen tension appears to be the major determinant of pulmonary arterial vasoconstriction. 2) PPHN with radiologically normal lungs and no evidence of parenchymal disease. This is called primary PPHN or persistent fetal circulation (PFC). 3) PPHN associated with hypoplastic lungs, most often seen with diaphragmatic hernia or oligohydramnios. There is an anatomic reduction in the pulmonary capillary numbers.

Changes occurring at birth in pulmonary circulation. In the fetus, due to its high pulmonary vascular resistance, blood is diverted away from the

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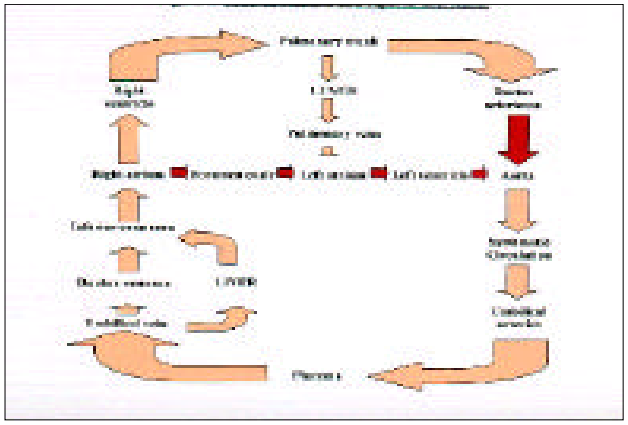

Figure 1 - Fetal circulation and the right to left shunts.

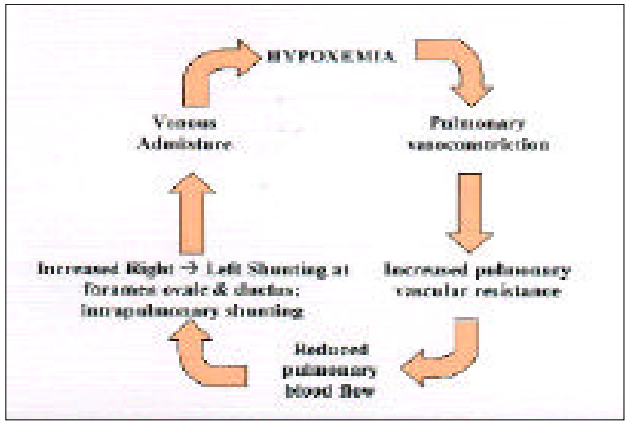

Figure 2 - The hypoxic vicious cycle of persistent pulmonary hypertension.

lungs through the foramen ovale and patent ductus arteriosus into the low resistance systemic and placental circuit (**Figure 1**). Fetal PaO_2 averages between 20-25 mm Hg only and hypoxemia is a potent vasoconstrictor, resulting in persistent pulmonary vasoconstriction. Ductus arteriosus is oxygen sensitive and remains patent when hypoxemia persists. The transition from fetal to postnatal circulation takes place in 4 phases namely, the in-utero phase, the immediate phase, the fast phase and the final phase.[3] 1) The in-utero phase is characterized by pulmonary vascular resistance exceeding systemic vascular resistance, resulting in right atrial pressure exceeding left atrial pressure keeping foramen ovale patent and shunting blood from right to left. Only 10% of the output from the right ventricle perfuses the lungs; most is shunted across the ductus arteriosus to the aorta. 2) Immediate phase is the second phase of transition takes place within the first minute of birth. The fluid filled lungs are distended with air, resulting in a distension of the pulmonary vascular bed and a consequent rapid decrease in pulmonary vascular resistance, allowing more oxygenated blood to perfuse the lungs. Improved oxygenation reverses the vasoconstrictive effect of hypoxemia. 3) Fast phase occurs in the 12-24 hours after birth. It accounts for the greatest reduction in pulmonary vascular resistance. The drop in pulmonary vascular resistance is associated with the production of the vasodilators prostacyclin and nitric oxide (NO). Prostacyclin is produced in the neonatal lungs in response to the rhythmic distension of the lungs. Persistent pulmonary hypertension of the newborn has been observed in infants of mothers receiving aspirin or non-steroidal anti-inflammatory agents that inhibit prostacyclin production.[3] Nitric oxide is synthesized in the vascular endothelial cells of the lungs. Multiple factors at birth such as the initial stretching of the pulmonary vasculature, ventilation, increased oxygenation and clearance of lung fluid stimulate the release of NO and ultimately result in the normal transition to the adult circulation.[4] Studies indicate severe hypoxemia or increased pulmonary vascular resistance may directly impede the release of NO, possibly contributing to PPHN.[4] 4) Final phase involves remodeling of the pulmonary vascular musculature. In the fetal and term lung, fully muscularize arteries extend to the level of the terminal bronchioles. Within days of delivery, the thickness of these vessels decreases. Hypoxia at birth prevents the remodeling and regression of smooth muscle in the pre-acinar bronchiolar arteries. In-utero or after birth chronic hypoxia stimulates cells of the alveolar arteries to differentiate into smooth muscle and connective tissue, resulting in abnormally thickened and reactive arteriolar musculature.[3,4] When pulmonary arterial pressure remains persistently higher than the systemic pressure, blood flow takes the least resistant pathway of foramen ovale and ductus arteriosus. Thus, the baby enters a profound hypoxic vicious cycle of PPHN (**Figure 2**).

Pathogenesis. **Table 1** shows that both physiological and structural factors contribute to the development of PPHN. Physiologic abnormalities include pulmonary vasoconstriction and polycythemia hyperviscosity. Structural abnormalities include pulmonary arterial smooth muscle hypertrophy and reduced cross-sectional area of the pulmonary vascular bed. Repeated intrauterine hypoxia stimulates hypertrophy of medial smooth muscles, which surround pulmonary arterioles. Endothelial cell dysfunction has been postulated as a contributing factor as it leads to an alteration in the balance of the 3 endothelial derived mediators called NO, endothelin and the prostaglandin analogues.[4,5] Arginine deficiency has been documented in infants with PPHN (NO is synthesized from L-arginine) and L-arginine infusion (500mg/kg over 30 minutes) was reported to improve oxygenation in these infants.[6]

Endogenous NO production modulates vascular tones in fetal and postnatal lung. Endothelin-1 is a potent endothelium derived vasoconstrictor peptide, found elevated in PPHN. Thromboxane (a prostaglandin mediator) metabolites are elevated in infants with PPHN.[7] Other mediators such as leukotrienes and platelet activating factor may also cause active pulmonary vasoconstriction and resultant hypoxemia (**Table 2**).

Diagnosis. Usually it is a term or post-term baby with acute perinatal asphyxia and meconium aspiration syndrome. There is respiratory distress with tachypnea and chest recessions and cyanosis. The second heart sound is often loud and single. There may be a prominent precordial impulse, and the low parasternal murmur of tricuspid incompetence. Systemic hypotension may occur later due to heart failure and persistent hypoxemia. Chest radiograph may be normal as in primary PPHN (PFC) or demonstrate various abnormalities of aspiration, pneumonia, hyaline membrane disease or diaphragmatic hernia. The majority of cases stabilize within a week but sustained improvement occurs by second week only.

Echocardiography. This allows accurate diagnosis of PPHN and should be carried out as soon as practical in the clinical course. With echocardiography one can a) exclude congenital heart disease, b) define the pulmonary artery pressure using tricuspid incompetence or ductal shunt velocities, define the presence degree and direction of shunt through the ductus and foramen ovale and define the ventricular outputs. Other investigations include preductal and post ductal pulse oximetry and blood gases, to demonstrate the hypoxemic gradient. Preductal (obtained from right radial artery) and post ductal (umbilical artery, left radial or posterior tibial artery) differences in PaO_2 of >15 mm Hg in the blood gas estimation or SaO_2 difference of >5% (higher in the preductal) are indicative of a significant right to left shunt. Hyperoxia test with 80-100% oxygen results in an improvement in PaO_2 in most infants with parenchymal disease but no response is seen in those with PPHN or cyanotic heart disease. In hyperoxia hyperventilation test, infant manually ventilated at 100-150 breaths per minute for 10 minutes and is considered positive if $PaCO_2$ is reduced to 25 mm Hg and an increase in PaO_2 by 30 mm Hg. This test helps to differentiate PPHN from congenital cyanotic heart disease. Little or no response is seen in congenital cyanotic heart disease. Thrombocytopenia is a poor prognostic factor and the following conditions must be satisfied before labeling as PPHN:[2] 1) Profound hypoxemia with or without acidosis, while breathing 100% oxygen. 2) Normal cardiac anatomy on echocardiographic examination. 3) Evidence of right to left shunting of blood through either the ductus arteriosus or the foramen ovale. 4) Sustained systemic or supra-systemic pulmonary artery pressure.

Management. Basic treatment goals include 1) Stabilized the infant; maintain systemic arterial blood pressure and perfusion. 2) Improve alveolar oxygenation. 3) Minimize "inappropriate" pulmonary vasoconstriction. 4) Induce an alkalotic

Table 1 - Conditions associated with persistent pulmonary hypertension of the newborn.

Pulmonary vasoconstriction
Perinatal asphyxia
Meconium aspiration syndrome
Respiratory distress syndrome
Bacterial pneumonia
Pulmonary microthrombi syndrome
Severe hypoxemia or acidosis from any cause
Hypothermia
Hypoglycemia
Polycythemia-hyperviscosity syndrome
Pulmonary arterial smooth muscle hypertrophy
Chronic intrauterine hypoxia
Placental insufficiency
Postmaturity
Ductus arteriosus constriction
(maternal salicylate ingestion; maternal indomethacin therapy)
Decreased cross-sectional area of pulmonary vascular bed
Primary pulmonary hypoplasia
Diaphragmatic hernia
Lung cysts; congenital cystadenomatous malformation
Peripheral pulmonary artery stenosis
Congenital alveolar capillary dysplasia
Surfactant protein B deficiency

Table 2 - Mediators of pulmonary vascular tone in the newborn.

Vasoconstrictors (Maintain high fetal PVR)	**Vasodilators (Decrease PVR during transition)**
Norepinephrine	Prostaglandin I_2,
α-adrenergic stimulation	Nitric oxide
Hypoxia	Cyclic – Guanylate monophosphate
Endothelin	Oxygen
Thromboxanes	Adenosine
Leukotrienes	Adenosine triphosphate
Platelet activator	

PVR - pulmonary vascular resistance

state. 5) Trial of vasodilatation. 6) Newer modalities (high frequency ventilation [HFV]; extracorporeal membrane oxygenation [ECMO] support: Liquid ventilation)

General stabilization. Correct factors, which increase pulmonary vascular resistance such as hypothermia, acidosis, polycythemia, and hypoglycemia. Sedation and paralysis may be required in an agitated infant. Minimal handling ("hands-off" in PPHN) is ideal, as these babies are extremely labile and become hypoxemic and crash. Fentanyl, Morphine, Midazolam or Phenobarbitone may be used. Paralysis with Pancuronium or Atracurium is not routinely used now as it leads to massive tissue edema and atelectasis of dependent lung regions and ventilation-perfusion mismatch. With the newer patient-triggered ventilators, paralysis is seldom necessary. Maintenance of systemic arterial blood pressure and thereby pulmonary perfusion is beneficial. Increasing systemic arterial pressure may decrease R-L shunt flow across PDA, thereby increasing pulmonary blood flow and thus oxygenation. Volume expanders, Dopamine and Dobutamine have been frequently utilized to improve cardiac output and systemic blood pressure.

Improve alveolar ventilation with a supplemental oxygen and conventional mechanical ventilation. Improvement in alveolar oxygenation with 100% oxygen will often result in a normal relaxation of the pulmonary arteries and increase pulmonary blood flow.

Conventional ventilation. This is the mainstay of respiratory support. Gentle conventional ventilation is preferred with a low positive end expiratory pressure (PEEP) and prolonged expiration to prevent air trapping. To maintain normal blood gases it is often necessary to ventilate with high minute volumes. Oxygenation is often very sensitive to small reductions in a minute volume such as can occur with retained secretions. The aim must be to maintain normal to low normal pCO_2 in the range of 35-40 mm Hg; mild hypocapnic alkalosis is recommended but pCO_2 lower than this may cause cerebral vasoconstriction. Weaning from ventilator should be very slow and cautious with step wise reduction in fractional inspired oxygen (FiO_2) and peak inspiratory pressure (PIP) reductions by only1-2cms H_2O, due to its exquisite sensitivity of pulmonary vessels in PPHN to alveolar PO_2 and acidosis. Parenteral nutrition may be required to provide optimal nutritional support.

Hyperventilation. By over-ventilating and producing hypocapnia, hypoxic vasoconstriction can be blunted, allowing pulmonary blood flow to increase. But studies[8] have shown that hypocapnic alkalosis by mechanical ventilation can result in pulmonary trauma and cerebral vasoconstriction and may be related to neuro-developmental deficits and sensorineural hearing loss noted on follow-up. Wung et al[9] has shown that gentle conventional ventilation can give better results as well as a low incidence of chronic lung disease.

High frequency ventilation. Close to 50% of infants with severe respiratory failure who reach the criteria for ECMO can be successfully managed with high frequency oscillatory ventilation (HFOV).[10] High frequency oscillatory ventilation employs the delivery of near or less than dead space tidal volumes at frequencies (HZ) greater than 150 breaths per minute. Gas exchange during HFOV may depend on convectional or bulk flow, pendelluft gas movement, asymmetric velocity profiles, Taylor dispersion and molecular diffusion.[10] Response can be rapid and extreme care must be taken to avoid over distension. One advantage of oscillatory ventilation is its ability to provide ventilation and oxygenation while avoiding acute or chronic lung injury. Pulmonary interstitial emphysema on conventional ventilation is an indication to initiate HFOV.

Surfactant. This is another lung recruitment strategy, especially in PPHN associated with RDS. Exogenous surfactant helps to reverse atelectasis and alveolar hypoxia. Surfactant is also indicated in severe parenchymal disease such as meconium aspiration syndrome or pneumonia. It decreases pulmonary vascular resistance and increases pulmonary blood flow.

Alkalinization using sodium bicarbonate. Since vasoconstriction is related to intracellular pH rather than PCO_2, initial bolus of 2 mEq/kg body weight and if unable to maintain alkalotic state, 0.25-0.50 mEq/kg/hour continuous infusion can be given.[11] However, if CO_2 clearance is a problem, or there is hypernatremia, 1-2 mmol/kg tromethamine (THAM) maybe a useful alternative. Tromethamine is contraindicated if baby is anuric or uremic. Alkalinization has positive benefit in some, but not all infants.

Vasodilators. Disadvantage of most of the vasodilators is that they are non-specific and frequently result in vasodilatation of both pulmonary and systemic vascular beds.

Non-selective vasodilators. Tolazoline (Priscoline). Tolazoline being an alpha sympathetic blocker was introduced as an effective pulmonary vasodilator in 1961. An intravenous (IV) loading dose of 1-2 mg/kg followed by an IV infusion of 1-2 mg/kg/hour. It should be infused via right hand or scalp vein. Response rate is only 60% and complication rate is high (70%). Complications include systemic hypotension, oliguria, gastrointestinal hemorrhage, duodenal perforation, seizures and thrombocytopenia.[12] Endotracheally administered Tolazoline has been reported to be useful.[13] However, Tolazoline use in PPHN has

been mostly abandoned due to problems with profound systemic vasodilatation after an initial positive response. Tolazoline is not currently used in our center.

Prostaglandins. Prostaglandin I_2 dilates pulmonary and systemic vasculature (non-specific). Prostaglandin I_2 (Prostacyclin) is a major endogenous vasodilator in lung and normally produced when lung vessels are in a constricted state, thereby producing relaxation. Sodium nitroprusside is a non-specific vasodilator (pulmonary and systemic). It may also serve as a NO donor in the lung. Dosage was 0.2-6 ug/kg/minute.

Magnesium sulphate ($MgSO_4$) has been used for many decades to treat toxemia of pregnancy. A natural calcium antagonist, it acts on the metabolism of prostaglandin, suppresses the release of catechol amines, reduce the responsiveness of smooth muscles to vasopressors.[14] At high concentrations, it is a potent vasodilator and can prevent and reduce hypoxia induced PPHN, sedative, muscle relaxant and has an anti-thrombotic effect on the brain and kidney.[15] Many studies have shown good results with $MgSO_4$.[16-19] A loading dose of 200 mg/kg of $MgSO_4$ given over 30 minutes, followed by a continuous infusion of 20-150mg/kg/hour thus, as to obtain a magnesium blood concentration between 3.5-5.5 mmol/L. Side effects of high dose include hypotension, generalized skin rash, respiratory depression, hyporeflexia and gut dysmotility. In our experience, we had to discontinue the loading dose in a few cases due to hypotension and severe skin rashes.

Selective pulmonary vasodilators. Inhaled nitric oxide (iNO) is a physiological vasodilator synthesized in vascular endothelial cells. Nitric oxide diffuses from the endothelium into adjacent vascular smooth muscle cells, where it activates guanylyl cyclase, catalyzing the formation of cyclic guanylyl monophosphate (cGMP). The intracellular accumulation of cGMP facilitates phosphorylation of several proteins by the cGMP-dependent protein kinase, which leads indirectly to dephosphorylation of myosin light chains, and thereby relaxation of smooth muscle cells.[20] Vascular endothelial growth factor is also a potent vasodilator that mediates the release of NO.[21] Increased release of endogenous NO is necessary for the smooth transition of pulmonary circulation at birth. Nitric oxide is the vasodilator of choice in term babies with PPHN. Inhaled nitric oxide diffuses into vascular smooth muscle, dilates pulmonary arteries associated with the ventilated lung unit, enhances ventilation perfusion matching. Randomized trials in term babies with primary and secondary PPHN have shown that[22] a) iNO significantly improves oxygenation, by reducing pulmonary vascular resistance, and increasing pulmonary blood flow. b) Nitric oxide significantly reduces the need for rescue with ECMO. c) 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.[23,24] Nitric oxide should be considered in any baby with severe hypoxic respiratory failure who is unable to maintain PaO_2 above 50 mm Hg despite maximal respiratory support. Its selective action on the pulmonary circulation without causing systemic hypotension is due to rapid binding of NO by hemoglobin forming methemoglobin and excreted as urinary nitrites and nitrate. In one recent study[25] the survival rate was 62.5%. Nitric oxide significantly decreased oxygenation index (OI) and improved the arterial/alveolar (a/A) oxygen ratio within the first 2 hours of NO therapy. The administration system must permit continuous and accurate measurement of NO and NO_2 concentration in the inspired gas, minimize contact between oxygen and NO and remove NO and NO_2 from exhaled gases. Clinical studies have shown that inhaled NO therapy, at doses 10-80 parts per million (ppm) by volume for 30 minutes, improved oxygenation in term infants with severe PPHN who met the criteria for ECMO without causing systemic hypotension. Even at low doses 20 ppm for 4 hours and then 6 ppm for 24 hours showed sustained improvement in oxygenation.[26] Multicentric studies have shown that iNO has reduced the need for ECMO by 50%.[25,26] In PPHN with severe parenchymal disease, HFOV plus iNO is more useful to recruit lung volume.[23,24,26] However, nearly 20-30% of cases do not respond to NO,[27] especially those with severe parenchymal lung disease (as in meconium aspiration syndrome) or pulmonary hypoplasia (as in congenital diaphragmatic hernia).

Adenosine. A purine nucleotide with half life <10 seconds has been shown to be an effective pulmonary vasodilator in animals and in recent human trials.[28,29] Adenosine has been shown to cause endothelium-dependent vasodilation in fetal lambs.[30] The proposed mechanism of action is vascular endothelial A_2 adenosine receptor stimulation, leading to an increase in cyclic AMP levels followed by release of endogenous NO.[30] Endothelium derived NO thus partly mediates the vasodilator effect of adenosine. Adenosine has also been shown to cause stimulation of K+ATP channels, leading to hyperpolarization of smooth muscle and to decrease the entry of calcium into vascular smooth muscle leading to vasodilation.[31] Simplicity of use, rapid onset of action, extremely short half-life and probable safety suggests adenosine may be a therapeutic option in management of PPHN. In our experience, adenosine infusion in doses of 25-50 microg/kg/minute showed significant improvement

in oxygenation, defined as an increase in postductal PaO_2 of ≥20 mm Hg from pre-infusion baseline, without causing hypotension or bradycardia.

Extracorporeal membrane oxygenation. Infants with severe PPHN considered to have <15% probability of survival, had 90% survival rate when treated with ECMO. It is a complex technique for providing life support in severe but potentially reversible respiratory failure. The technique oxygenates blood outside the body, obviating the need for gas exchange in the lungs and, if necessary, provides cardiovascular support. It is most commonly used to support mature newborn infants, as preterm infants are not suitable both due to its size of the cannulae required, and of their additional risk of intra-ventricular hemorrhage associated with the use of heparin. The concept arose as an off-shoot of cardiopulmonary bypass technology. In previous study they reported the first mature newborn treated successfully with ECMO.[32] It subsequently became clear that mature infants with PPHN were particularly suited to ECMO since the better oxygenation and physiological stability produced by ECMO improved pulmonary blood flow without the risk of further barotrauma. Extracorporeal membrane oxygenation is an extremely invasive and technically involved procedure and should be reserved for the sickest babies not responding to other forms of treatment. Traditional ECMO uses 2 large gauge catheters, one placed in a central vein and the other in a central artery (venoarterial). It is essential to achieve adequate flow rates (approximately 100-120 mLs/kg/minute) and as a result cannulae are normally 12-14 French gauge. Blood is drained passively via the venous catheter, which is inserted into the internal jugular vein and positioned in the right atrium. Blood then passes on to a pump, which maintains flow in the circuit and then on to an oxygenator where a sweep gas passes in counter current to the blood. The concentration of oxygen in the sweep gas can be adjusted depending on the needs of the patient. Before re-entering the body warming occurs in a heat exchange column. Blood is returned via the common carotid artery at systemic pressure. This type of ECMO is able to support both pulmonary and cardiac function, acting as an artificial heart and lung for the baby, while baby's lungs heal and recover.[33] More recently veno-venous (V-V) ECMO, which provides just pulmonary support, has become popular with the use of double lumen venous catheters. The particular advantage of V-V ECMO is that the cerebral arterial blood supply is not disrupted. While on ECMO additional gas exchange by the lungs is not essential and therefore ventilation is normally reduced to 'rest' settings. This is typically 5-10 cm H_2O positive end expiratory pressure and 10-20 breaths per minute. This strategy prevents any further lung damage secondary to barotrauma but arrests the atelectasis, which might follow acute withdrawal of respiratory support and enhances clearance of secretions. Baseline criteria for ECMO are as follows 1) More than 34 weeks' gestation. 2) Weight greater than 2000 gm. 3) No major intracranial hemorrhage (cranial sonogram showing less than grade II hemorrhage). 4) Reversible lung disease; on mechanical ventilatory support for not more than 10-14 days. 5) No lethal congenital anomalies or inoperable cardiac disease.

The indication for ECMO was oxygenation index (OI) of >40

$$OI = \frac{(Fi0_2) \times (\text{mean airway pressure cm } H_20) \times 100}{PaO_2 \text{ in mm Hg.}}$$

Disadvantage of ECMO is that it is very invasive, labor intensive and expensive, with high complication rate. Complications include cerebral infarct, hemorrhage and seizures. Its use has declined with the availability of iNO and HFOV.[33-35] Newer directions was L-Arginine, which is precursor for NO formation. Arginine deficiency has been reported in infants with PPHN. Anecdotal use for PPHN shows improved oxygenation without systemic hypotension.[36] Viagra known generically as sildenafil treats impotence by relaxing smooth muscle and increasing blood flow to erectile tissue. Researchers found that intravenous Viagra was "at least as effective" as inhaled NO in relaxing and dilating pulmonary blood vessels.[37,38] Sildenafil (Viagra) cause an increase in intracellular cGMP levels by inhibiting an enzyme (phosphodiesterase V) which breaks down cGMP. Oral sildenafil has been shown to be a potent selective pulmonary vasodilator in animal studies, in adult humans and in a small number of babies with PPHN. It can augment the effects of iNO, and can be used to help wean patients off iNO.[38] Liquid ventilation using perfluorocarbons is another method of recruiting lung volume. They have a low surface tension and high oxygen solubility and serve as the liquid medium for gas exchange. The role of cyclic GMP in muscle relaxation, the elevated levels of endothelin-1 and also platelet activating factor (an endogenous phospholipid mediator) and absence of endogenous nitric oxide synthetase (NOS) mRNA in infants with PPHN, the role of pentoxifylline, and the phosphodiesterase inhibitor (dipyridamole) in treatment are areas of current research.

Pulmonary hypertension of the newborn outcome and complications. The development of PPHN is multi-factorial and hence no single treatment modality is curative. Acute complications from persistent hypoxemia include shock, intra-cranial hemorrhage, cardiac and renal failure and multiple organ damage. Long term effects of hypoxia on survivors include broncho-pulmonary dysplasia, hyperactive airway disease, seizures, developmental delay and neurological deficits. Sensory-neural hearing loss has been reported in

survivors of hyperventilation and HFOV.[39] In ECMO, complications are high. Nitric oxide and NO_2 are toxic and requires good monitoring. Fifteen years ago, mortality in PPHN was >50% but now with newer modalities of management, mortality is <20% and only less than one fifth of surviving infants experience long-term physical or developmental complications.

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