Persistent Pulmonary Hypertension of the Newborn: Case Study and Pathophysiology Review

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ABSTRACT

Pulmonary hypertension, though quite normal in the fetus while the burden of oxygenation is on the maternal placenta, can be rapidly fatal if severe resistance to pulmonary blood flow continues as the infant attempts to make the transition to extrauterine life. This article reviews the pathophysiology of and current management priorities for persistent pulmonary hypertension of the newborn.

BABY GIRL E, HENCEFORTH REFERRED TO AS BGE, WAS born at 42 weeks gestation via normal vaginal delivery to a 41-year-old healthy primiparous mother. At delivery, a tight nuchal cord was found and released. Apgars were 6 and 8 at one and five minutes, respectively. BGE was alert and active, with a vigorous cry, and was admitted to the special care nursery for close observation, with 40 percent oxygen by head box. Within the first few hours after birth, BGE's respiratory status began to deteriorate. Bilateral pneumothoraces were diagnosed and treated with needle aspiration, followed by chest tube placement, with minimal improvement in respiratory effort or blood gases.

Soon after chest tube placement, BGE was orally intubated, and ventilatory support was initiated. She required immediate maximum ventilatory support, as well as sedation and neuromuscular blockade to optimize her respiratory status. She developed hypotension which was treated with hetastarch (Hespan) boluses and dopamine/dobutamine infusions. Even with maximum support it was difficult to maintain adequate oxygenation. With oxygen saturations in the 80s, metabolic acidosis occurred and required multiple sodium bicarbonate boluses to correct. At this time, the differential diagnosis included sepsis, PPHN, and cyanotic heart disease. A prostaglandin infusion was started prior to confirmation of normal cardiac anatomy by echocardiogram. Broad spectrum antibiotics had been started in the early treatment of her respiratory symptoms, and plans for transport to a tertiary center for probable extracorporeal membrane oxygenation (ECMO) were initiated.

BGE's critical status was complicated by the parents' beliefs and refusal of blood product administration and ECMO support. The parents did, however, consent to their child's transport for further evaluation and treatment, although frequent episodes of desaturation, bradycardia, and hypotension almost ruled out transport.

Upon admission to the intensive care nursery, stabilization and work up included securing the airway with a larger endotracheal tube and continuing maximum ventilatory support, obtaining an echocardiogram that confirmed normal cardiac anatomy and right-to-left shunting (PGE_1 was discontinued). A head ultrasound showed no intracranial hemorrhage. Fluid resuscitation continued, and after establishing protective custody for the infant, blood products were administered to improve systemic pressure and optimize the oxygen-carrying capacity. Additional bicarbonate boluses to treat acidosis and attempt alkalinization were given. A trial with nitric oxide therapy was initiated; with no indication of improvement in oxygenation, the infant was placed on full ECMO support. Despite optimum therapies, a sustained improvement in oxygenation continued to be impossible to establish. Three hours after admission, BGE had a cardiorespiratory arrest, from which she could not be resuscitated.

This case illustrates the importance of prompt assessment, diagnosis and treatment when a term or postterm infant pre-

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FIGURE 1 ■ Fetal circulation showing right-to-left shunt through PDA.

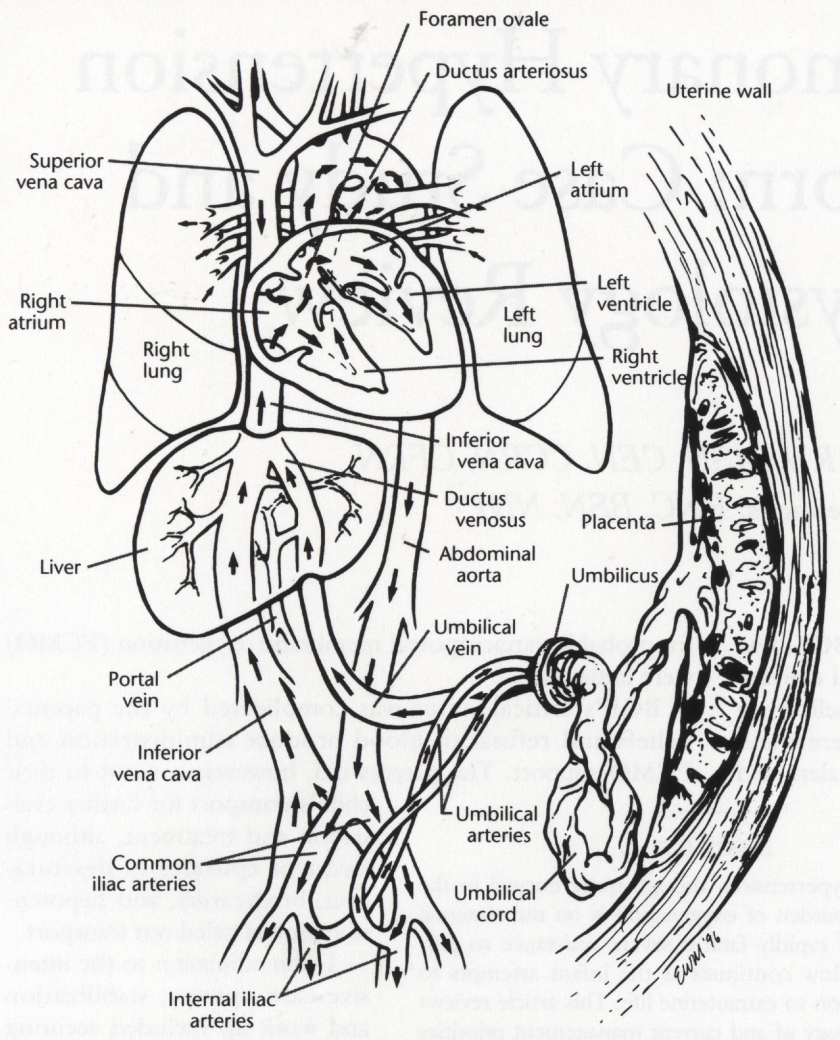
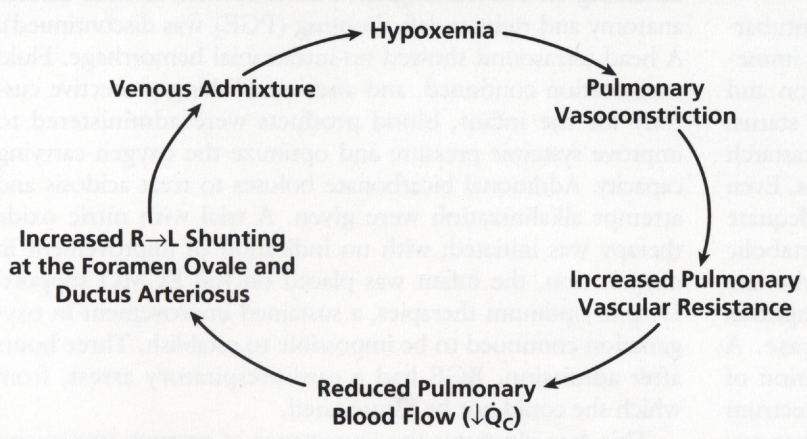


FIGURE 2 ■ Final common pathway of both hypoventilation and hypoperfusion.



sents with respiratory distress or cyanosis with a persistent oxygen requirement. Sepsis, cyanotic heart disease, and PPHN must be considered early in the workup of infants with such clinical findings. History, assessment, and response to interventions can provide direction for diagnosis. As the diagnostic workup is in progress, it is imperative that therapy to optimize oxygenation be initiated. It is not clear what caused BGE's initial oxygen requirement; however, her increasing respiratory compromise secondary to pneumothoraces and hypoxia were unresponsive to interventions. The possibility of PPHN complicating her course became very real.

BGE's chest x-ray showed minimal lung disease and no pneumonia, her blood cultures ultimately proved negative, and echocardiogram demonstrated normal cardiac anatomy with a right-to-left shunt at the level of the foramen ovale and the ductus arteriosus. In light of her clinical course, and these findings it was determined that the most likely diagnosis was PPHN. Whether it was the cause of her initial oxygen need or a syndrome that occurred in response to a persistent hypoxemia is not clear.

FETAL-TO-NEWBORN CIRCULATION

"When one considers the complexity of the pulmonary and hemodynamic changes occurring after delivery, it is surprising that the vast majority of infants make the transition to extrauterine life so smoothly and uneventfully."[1] A basic understanding of the fetal and newborn cardiorespiratory systems is necessary to a discussion of the specifics of PPHN.

Before birth, the fetus depends solely on the mother for nutrition and oxygen delivery. The lungs are fluid filled and receive only 10–15 percent of the cardiac output. Fetal circulation is designed to deliver highly oxygenated blood from the placenta to the fetal brain and other major organs and to allow blood to be diverted away from the pulmonary circulation. Oxygenated blood from the placenta enters the heart via the ductus venosus and the inferior vena cava and then travels preferentially from the right atrium through the foramen ovale to the left atrium. Some blood, mainly from the superior vena cava, continues from the right atrium to the right ventricle and on to the lungs, but most of the blood flows into the aorta via the patent ductus arteriosus (Figure 1). Because pulmonary

vascular resistance is high and systemic vascular resistance is low, most blood entering the main pulmonary artery flows through the ductus arteriosus into the descending aorta, effectively bypassing the lungs. Because the placenta is responsible for oxygenation, most of the blood can be safely "detoured" to the body.

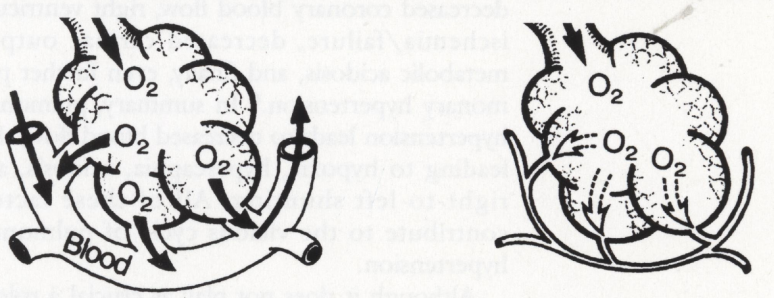
At birth, the infant must make the change from fetal to postnatal, or "normal adult," circulation. Blood must be oxygenated in the lungs, and the left heart must become a high-pressure system. Most crucial in this transition is that pulmonary hypertension, which was appropriate and physiologically needed *in utero,* must now decrease quickly for effective lung oxygenation to occur. The entrance of oxygen into the pulmonary vasculature is the most important initiator of vasodilation; without oxygenation, continued hypoxia and acidosis will result in continued vasoconstriction. As the lungs are filled with air for the first time, most of the fluid within the alveoli is displaced into the pulmonary interstitium, where it is assimilated into the pulmonary capillaries and removed by the lymphatic system.[1] The lung fluid is subsequently reabsorbed, and alveolar hypoxia is eliminated, producing pulmonary vasodilation. The medial muscle layer of the pulmonary arteries begins to thin immediately after birth and continues to regress during the first days of life. These changes contribute to a rapid fall in pulmonary vascular resistance.

The ductus arteriosus usually functionally closes 10–24 hours after birth, primarily as a result of the rise in the neonate's arterial oxygen tension, but also involving the levels of prostaglandin, adenosine, and other vasoconstrictive substances. The foramen ovale functionally closes with the fall in pulmonary vascular resistance (which lowers right heart pressures) and the removal of the placenta (which increases systemic vascular resistance).[2]

PATHOPHYSIOLOGY OF PPHN

The high vascular resistance in the fetal lung is primarily the result of pulmonary arterial vasoconstriction.[1] PPHN is a situation characterized in its simplest form by persistent increased pulmonary vascular resistance during the newborn period. Infants with PPHN fail to experience the pulmonic vasodilation necessary for proper oxygenation for a variety of reasons, including hypoxia, acidosis, abnormal muscle formation,

FIGURE 3 ■ Pulmonary perfusion.



Normal pulmonary perfusion

Decreased pulmonary perfusion

From: Bloom R, and Cropley C. 1994. *Textbook of Neonatal Resuscitation.* Dallas, Texas: American Heart Association, 1–9. Reprinted by permission.

circulating substances, and other, as yet unknown, causes. Alveolar hypoxia is the most potent and consistent stimulus resulting in pulmonary vasoconstriction.[2] Fetal PO_2 of 20–25 mmHg is normal *in utero* and contributes greatly to the active vasoconstriction of the pulmonary vessels. This in turn results in only a very small amount of pulmonary blood flow.[3,4]

In the infant with PPHN, continued high pulmonary vascular resistance impedes pulmonary blood flow, leading to hypoxemia, acidemia, and eventually lactic acidosis (Figure 2). As hypoxemia continues, further pulmonary vasoconstriction ensues. This results in an additional decrease in blood flow and initiates a "vicious cycle."[5]

As previously stated, hypoxia is the most potent initiator of pulmonary vasoconstriction. In infants with PPHN, ventilation is not usually difficult, but maintenance of adequate pulmonary perfusion is a completely different matter. Oxygen can be delivered relatively easily to the alveoli. The problem is permitting blood to reach the alveoli to receive oxygen and release wastes (CO_2). The exact mechanism by which hypoxia induces pulmonary vasoconstriction remains controversial, but the effects of hypoxia on the pulmonary vasculature are well documented and contribute to further vasoconstriction (Figure 3).[3]

The ability of fetal/newborn circulation to shunt blood easily depends on the pressure differences between the left and right circulations. With pulmonary hypertension, the heart shunts blood from right-to-left secondary to increased pulmonary pressures. This can result in right heart failure, as evidenced by increased right

ventricular pressures and end-diastolic volumes, decreased coronary blood flow, right ventricular ischemia/failure, decreased cardiac output, metabolic acidosis, and finally, even further pulmonary hypertension.[6] In summary, pulmonary hypertension leads to decreased blood flow, thus leading to hypoxia, hypercapnia, acidosis, and right-to-left shunting. All of these factors contribute to the vicious cycle of pulmonary hypertension.

Although it does not play as crucial a role in pulmonary hypertension as hypoxia, abnormal pulmonary vascular musculature can contribute to hypertension. After birth, expected pulmonary vasodilation may not occur in some infants because of an unexplained abnormality in the growth of the musculature in the pulmonary blood vessels. In some infants, the medial smooth muscle layer, normally found only in the arteries surrounding airways larger than the terminal bronchioles, is also found in the arteries surrounding the alveolar air sacs. This muscle layer narrows the internal lumen of the pulmonary vessels, thus decreasing pulmonary blood flow. Blood flow can be diminished further because this muscle has an increased responsiveness to stimuli that cause vasoconstriction, increasing pulmonary vascular resistance.[7] When pulmonary vascular resistance becomes higher than systemic resistance, right-to-left shunting of blood from the pulmonary circulation to the systemic circulation occurs.

Another mechanism affecting pulmonary blood flow and contributing to the incidence of PPHN is underdevelopment of the pulmonary vascular bed. This occurs in infants with pulmonary hypoplasia or space-occupying lesions such as congenital diaphragmatic hernia. If there are too few vessels to accommodate the flow of blood, pulmonary vascular resistance increases and right-to-left shunting of blood may occur.

A variety of factors may challenge the ability of the infant to make the cardiorespiratory changes necessary to establish adequate oxygenation. These may include intrauterine and peripartum hypoxia, meconium aspiration, air leak syndrome, pulmonary hypoplasia, congenital diaphragmatic hernia, sepsis and pneumonia, hypothermia, and prematurity. In any of these situations the possibility for developing PPHN exists.

The effects of pharmacologic mediators on the maturation of the newborn pulmonary vascular bed are well documented.[8–10] The release of mediators, particularly the prostaglandins with their vasodilatory effects, influence the pulmonary vasculature. In the normal newborn, as ventilation is initiated, alveolar fluid is replaced with air, resulting in a marked increase in the oxygen concentration of the blood in the pulmonary vascular bed. Both the displacement of alveolar fluid and the resolution of local hypoxia contribute to dilation of the pulmonary vascular smooth muscle. Also, these changes can cause the release of vasodilating substances, such as bradykinin and prostacyclin (PGI_2). Bradykinin, a potent pulmonary vasodilator, is released with exposure to oxygen. This release then prompts endothelial cell production of endothelium-derived relaxing factor, otherwise known as nitric oxide, which is also a powerful vasodilator. PGI_2, produced like bradykinin by pulmonary vascular endothelial cells, is derived from the metabolism of arachidonic acid. Possessing pulmonary vasodilatory effects, PGI_2 is released when the lung is exposed to mechanical ventilation or to vasoactive substances, such as bradykinin or angiotensin II. However, with PPHN and continued cellular hypoxia, other vasoactive substances such as leukotrienes may be released. These actively constrict the pulmonary circulation and diminish flow through the lungs.[9]

TREATMENT APPROACHES TO PPHN

The treatment of PPHN focuses on preventing the cyclic pattern or on stopping its progression. Interventions are aimed at increasing pulmonary blood flow by decreasing pulmonary vascular resistance or increasing systemic vascular resistance. Both approaches impede right-to-left shunting.

Attempts to decrease pulmonary vascular resistance in the pulmonary realm involve intubation, ventilatory support, and hyperventilation to induce hypocarbia and alkalosis. Although the exact mechanism remains unknown, alkalosis (respiratory or metabolic) produces a direct vasodilatory effect on the pulmonary vasculature, decreasing pulmonary vascular resistance and improving oxygenation.[11] Concurrently, with vigorous infants or increased ventilatory pressure requirements, sedation and/or neuromuscular blockade are utilized to decrease the possibility of air leaks and to facilitate maximum oxygenation. If ventilatory support does not produce adequate alkalinization, intravenous

bicarbonate or tromethamine (THAM) may be administered as a bolus or a continuous infusion to aid in achieving the desired pH. In addition to mechanical ventilation and alkalinization, infusion of vasodilators has been considered to decrease pulmonary vascular resistance.[10,12] In the presence of systemic hypotension, volume expanders such as isotonic crystalloids (lactated ringers or 0.9 normal saline), albumin, plasma, or packed red blood cells should be administered.[13,14] Infusion of vasopressors (such as dopamine, dobutamine, or isoproterenol) and/or afterload reducers (nitroprusside) has also been advocated.[14–17] Vasopressors increase the systemic vascular resistance, thereby decreasing the amount of right-to-left shunting, which increases cardiac output.[18]

Some centers are also examining new modalities for treating PPHN and minimizing the barotrauma associated with high peak inspiratory pressures. These approaches include high-frequency or oscillatory jet ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO).[10,13,19–24] As more studies and trials are conducted on infants with PPHN, the benefits and/or hazards of these therapies will become better known and documented.

NURSING INTERVENTIONS

An understanding of the pathophysiology of PPHN provides the foundation for the nursing assessments and interventions that are essential in the care of newborns with this problem. Because PPHN occurs in response to acidosis and hypoxia, the goal of care must be to optimize oxygenation and minimize hypoxia and acidosis.[25–27]

Newborn care begins with the collection of information available about the maternal history and the labor and delivery course. Identification of risk factors—such as perinatal asphyxia, meconium aspiration, low Apgar scores, and neonatal sepsis—alerts caregivers to anticipate infant needs beyond stabilization. Newborn resuscitation requires the presence of trained staff, and necessary equipment that is ready to use when the need is established.[28] Hypoxia in the first minutes of life can initiate the downward spiral that results in PPHN and its multisystem sequelae. Collaborative management of infants at risk for PPHN is imperative.[25–27]

The case of Baby Girl E can provide lessons in the nursing management of infants with PPHN. An infant at term or postterm with a persistent oxygen requirement must be evaluated for the possibility of PPHN or cyanotic heart disease and treated accordingly. Because term and postterm infants are at minimal risk for developing retinopathy of prematurity, it is common to be generous in the delivery of oxygen when the risk of hypoxia resulting in constriction of the vascular bed is high.[26] Once the PPHN cycle has begun, it is increasingly difficult to break it and to improve oxygenation.[25,26]

Nursing assessment and procedures assist in the diagnosis and management of these infants. Arterial blood sampling, preferably with an indwelling umbilical catheter, will help establish the diagnosis. An oxygen tension differential of >15 torr between preductal (right radial arterial sample) and postductal (umbilical arterial sample) is indicative of PPHN.[26] A similar differential may be seen in oxygen saturations when dual oximeters are strategically placed to read pre- and postductal saturations. An improvement in oxygen saturations or oxygen tension (>100) when the infant is placed in 100 percent oxygen rather than room air (or 40 percent hood) makes a diagnosis of cyanotic heart disease less likely.[25] If the infant is intubated and hyperventilated, causing a rise in the arterial pH, oxygenation is likely to improve as a result of the pulmonary vascular bed dilatation in response to alkalosis; the infant should then continue to improve in response to oxygenation. Again, what may be considered toxic levels of PaO_2 in the preterm infant are less so in the term or postterm infant; therefore, liberal use of oxygen is encouraged.

Pulmonary vascular resistance remains labile in the first hours after birth. This is particularly true in infants who did not tolerate labor well or who are having a difficult transition to extrauterine life. A goal of care is to enhance the infant's ability to oxygenate and to limit the infant's work of breathing. Providing a warm environment for thermoregulation, delaying the bath, clustering care, preventing fatigue, and providing exogenous glucose are all measures that help decrease oxygen requirements. These interventions decrease the potential for hypoxia, a major reason the pulmonary vascular resistance fails to fall.[25,27] If the infant seems to be fighting care, unable to relax, or experiencing severe respiratory distress, then intubation, mechanical ventilation, sedation, and muscle paralysis may be

required to prevent or treat PPHN.[26,27,29] Again, the readiness of expertise, equipment, and staff are important in providing essential care.

After the airway has been secured, continuous monitoring of oxygen saturations, vital signs, and response to any treatment or handling permits ongoing evaluation of the infant's status. Nursing care specific to an infant experiencing the effects of drug induced muscle paralysis includes assessment of the need for redosing because the drug's effects are baby-specific, eye care to prevent corneal abrasions, judicious suctioning to clear the hypopharynx of pooled secretions, position changes and skin care, bladder credé or catheterization, and parent teaching to explain the temporary but necessary effects of the drug.[27,29,30] Concurrent use of sedation and pain-relief drugs is recommended because muscular paralytics do not alter the infant's pain threshold.[29,30]

In PPHN, the pulmonary vascular bed responds to acidosis with constriction, so treatment is aimed at reversing that effect. Both respiratory alkalosis, achieved with hyperventilation, and metabolic alkalosis, achieved with bicarbonate infusions, often relax the pulmonary vascular bed, allowing increased pulmonary blood flow and improved oxygenation.[10,26] There is often a critical pH that will allow this improvement. Accurate documentation of infant status, ventilatory settings, oxygen saturation changes, and blood gas results, coupled with a team approach in the judicious weaning of support, often influences outcomes. The maximum ventilatory support required puts these infants at high risk for pulmonary air leaks; early detection and treatment rely on continuous, thorough nursing assessments.

Along with factors that promote or hinder the fall in the pulmonary vascular resistance, changes occur that increase the systemic vascular resistance. This pressure gradient is crucial for the change from a right-to-left blood flow across the ductus arteriosus and foramen ovale to a left-to-right flow of blood into the pulmonary vascular bed. It is important to maintain the systemic blood pressure.[15,17] Clinical assessments include description of peripheral pulses, capillary refill time, and observance for tachycardia and diminished renal blood flow (urinary output). Serial blood pressure checks are important, but keep in mind that, with decreased perfusion and peripheral vascular constriction, a cuff blood pressure reading may be misleading. Adequate perfusion is undoubtedly better documented by clinical assessment and invasive blood pressure monitoring.

Interventions may include intravenous fluid resuscitation and, after ensuring that the vascular volume is adequate, the use of vasopressor agents such as dopamine and dobutamine. Presumably, vasopressor drugs work to improve cardiac contractility, increase cardiac output, and raise systemic pressure. Nursing concerns include an understanding of the dosing, calculation, and administration of these drugs.[15,17] The infiltrates of these drugs can be caustic, so deep or central venous lines are recommended for administration, with meticulous attention paid to the assessment of these lines. Documentation of infant response to all therapies should be clear and concise.

When the conventional therapies fail, other treatment modalities may become necessary. These include magnesium sulfate, nitroprusside, or L-arginine infusions; ECMO; nitric oxide inhalation; and high-frequency ventilation. For nursing care specific to these modalities, the reader is referred to other resources.[10,13,16,19–24,31,32]

Even with a collaborative-care approach that individualizes care according to the infant's response, PPHN continues to present a challenge to the care team and carries with it a high morbidity and mortality probability for the infant.

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