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Pulmonary Hypertension

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Pulmonary Hypertension

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Author Disclosure
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Objectives

After completing this article, readers should be able to:

1. Describe the presentation of and treatment for persistent pulmonary hypertension (PH) of the newborn.
2. Identify causes for PH in the pediatric age group.
3. Discuss how congenital heart disease causes PH.
4. Explain how PH is potentially reversible.
5. Recognize that changes associated with sleep may cause PH and cor pulmonale.

Introduction

PH occurs when a disease elevates pulmonary arterial pressure above normal. Pulmonary artery pressure=left atrial pressure+(pulmonary flow×pulmonary vascular resistance). Any single factor or combination of factors that increases left atrial pressure, pulmonary flow, or resistance can cause PH.

PH often is progressive, and if untreated, the right ventricle eventually becomes unable to support the circulation, resulting in significant morbidity and mortality. Pulmonary arterial pressure exceeding 25 mm Hg is abnormal and requires evaluation. Early treatment aimed at the underlying disease process may prevent progression. The prognosis is determined by the reversibility of the underlying disease process.

The World Health Organization (WHO) classification, initially proposed in 1998 and revised in 2003, categorizes different forms of PH based on similarities in pathophysiology, clinical presentation, and treatment (Table 1). Discussing all of the conditions listed in the WHO classification is beyond the scope of this review. Rather, we concentrate on a few select, but highly representative, forms of PH.

Persistent Pulmonary Hypertension of the Newborn

In the newborn, the most common cause of PH is persistent pulmonary hypertension of the newborn (PPHN). PPHN may be associated with acute neonatal respiratory conditions that result in persistently elevated pulmonary vascular resistance, with right-to-left shunting of blood across the foramen ovale, ductus arteriosus, or both, causing significant hypoxemia. Table 2 lists conditions during pregnancy and in the neonate that may predispose a newborn to PPHN. Alternatively, PPHN can occur without parenchymal lung disease (idiopathic). Overall, the incidence of PPHN is approximately 0.2% of term infants.

In the fetus, the highly vascular placenta serves as the organ for gas exchange and contributes to a lowered fetal systemic arterial pressure. Concurrently, the pulmonary vessels are constricted, making pulmonary and systemic arterial pressures nearly equal. This pressure state, in combination with an open ductus arteriosus and foramen ovale, results in 90% to 95% of cardiac output bypassing the fetal lungs.

At birth, the pulmonary artery pressure decreases to 50% of systemic artery pressure, and pulmonary blood flow in-

Abbreviations

cGMP: cyclic guanosine monophosphate
ECMO: extracorporeal membrane oxygenation
iNO: inhaled nitric oxide
OSAS: obstructive sleep apnea syndrome
PH: pulmonary hypertension
PPHN: persistent pulmonary hypertension of the newborn
WHO: World Health Organization

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Table 1. World Health Organization Diagnostic Classification of Pulmonary Hypertension

1. Pulmonary Artery Hypertension
   - 1.1 Idiopathic pulmonary hypertension
   - 1.2 Familial
   - 1.3 Pulmonary hypertension associated with
     - a. Collagen vascular disease
     - b. Congenital heart disease with a left-to-right shunt
     - c. Portal hypertension
     - d. Human immunodeficiency virus disease
     - e. Drugs, anorexigens, and other toxins
     - f. Thyroid disorders
     - g. Other entities: Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies
   - 1.4 Persistent pulmonary hypertension of the newborn
   - 1.5 Pulmonary veno-occlusive disease
2. Pulmonary Hypertension With Left Heart Disease
   - 2.1 Left atrial or left ventricular disease
   - 2.2 Left-sided valve disease
3. Pulmonary Hypertension With Respiratory Disorders
   - 3.1 Chronic obstructive lung disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation
   - 3.5 Chronic exposure to high altitude
   - 3.6 Neonatal lung disease
   - 3.7 Alveolar-capillary dysplasia
   - 3.8 Other
4. Pulmonary Hypertension Caused by Chronic Thrombotic/Embolic Disease
   - 4.1 Thrombotic obstruction of proximal pulmonary arteries
   - 4.2 Obstruction of distal pulmonary arteries, pulmonary embolism, or thrombus in situ thrombus
5. Miscellaneous

Table 2. Conditions Predisposing to Persistent Pulmonary Hypertension of the Newborn

Conditions in Pregnancy

- Abnormal fetal heart rate
- Absent prenatal care
- Diabetes
- High altitude
- Illicit drug use
- Low Apgar score
- Meconium-stained amniotic fluid
- Nonsteroidal anti-inflammatory drugs
- Post-date gestation
- Tobacco

Conditions in the Newborn

- Acute respiratory distress syndrome
- Asphyxia
- Congenital diaphragmatic hernia
- Hypoglycemia
- Hypothermia
- Meconium aspiration syndrome
- Pneumothorax
- Polycythemia
- Pulmonary hypoplasia
- Respiratory distress syndrome
- Sepsis/pneumonia
- Retained fetal lung liquid syndrome (transient tachypnea of newborn)

creases almost tenfold, primarily due to increased arterial pH and oxygen tension; the physical pulling open of capillaries accompanying lung inflation; local endogenous vasoregulatory mediators, especially vasodilatory prostaglandins and nitric oxide; and removal of the low-systemic vascular resistance placenta following clamping of the umbilical cord. The decline in pulmonary vascular resistance is greatest in the first 24 hours after birth and continues to fall over the first 2 postnatal weeks. Many processes, both pulmonary and systemic, may interrupt this normal transition and result in PPHN.

Most newborns who have PPHN have maladaptation, a term describing newborns who, despite normal pulmonary arterial number and muscularization, encounter a disruption in the decrease in pulmonary vascular resistance normally observed during transition. Maladaptation may be associated with perinatal asphyxia, sepsis, pneumonia, meconium aspiration, and acidosis. Maladaptation appears to be mediated by a complex imbalance in local vasodilatory and vasoconstrictor metabolites, including nitric oxide, prostaglandins, thromboxanes, leukotrienes, bradykinin, and inflammatory cytokines. Alternatively, PPHN may accompany chronic in utero hypoxia, marked by an increase and extension of medial muscle thickness; obstruction accompanying polycythemia or total anomalous pulmonary venous connection; pulmonary overflow following ductal narrowing; and a decrease in the number of pulmonary arteries, as seen in pulmonary hypoplasia, congenital diaphragmatic hernia,

or the oligohydramnios sequence. A reduced number of pulmonary arteries and capillaries, accompanied by abnormal arterial muscularization and a thickened alveolar septum, characterizes alveolar capillary dysplasia, a rare and often lethal form of PPHN.

Presentation

In the newborn, profound and labile hypoxemia, often out of proportion to the severity of parenchymal disease, as evidenced by radiography, is suggestive, but not diagnostic, of PPHN. Depending on the underlying cause, newborns may be acutely ill in the delivery room or may exhibit gradually escalating signs, including cyanosis, grunting, flaring, retractions, tachypnea, tachycardia, and shock. Clinically distinguishing the PH component from the underlying disease may be difficult. This dilemma is illustrated in meconium aspiration syndrome, in which atelectasis, hyperinflation, surfactant inactivation, and inflammation may be exacerbated by PH. In PH, the precordium usually is normoactive, whereas hyperactivity is more consistent with structural heart disease. In PH, the second heart sound by auscultation may appear single and loud, and there may be an accompanying systolic murmur from tricuspid insufficiency. Blood pressure and perfusion may be normal or there may be cardiogenic shock. The combination of hypoxemia and acidosis constricts the pulmonary vascular smooth muscle further, increases the PH, and creates a vicious cycle.

If the shunting associated with PPHN occurs exclusively at the ductus arteriosus, there is a gradient in the Pao_2 (the amount of oxygen dissolved in plasma) of greater than 20 mm Hg preductally and postductally, as measured at the right radial artery and left radial or umbilical artery, respectively. A similar gradient in oxygen saturation (the percentage of hemoglobin binding sites saturated with oxygen) may be observed, with a decrease in postductal oxygen saturation of greater than 5%. The absence of a gradient does not preclude the diagnosis of PPHN because shunting may be intermittent or at the atrial level.

Radiographic findings may reflect the underlying illness precipitating the PH (Table 2) or the images may appear remarkably clear, with diminished vascular markings and a slightly dilated heart suggestive of idiopathic PPHN. Electrocardiographic findings usually are normal. Echocardiography is essential to exclude cyanotic heart disease as the cause of hypoxemia and acidosis. Characteristic findings of PPHN include right-to-left shunting across the foramen ovale or ductus arteriosus, deviation of the atrial septum from right-to-left, right atrial enlargement, and tricuspid regurgitation.

Treatment

Treatment of PPHN is aimed at preventing end-organ injury from hypoxia, ischemia, and barotrauma. This goal is accomplished by correcting any contributing disturbances, including hypoglycemia, polycythemia, hypothermia, or pneumothorax, while maintaining systemic resistance and selectively lowering pulmonary vascular resistance.

Systemic vascular resistance is maintained with volume (crystalloid or colloid) and inotropic (dopamine and dobutamine) support, aiming at a mid- to high-normal systemic blood pressure. Such therapy decreases the pulmonary-to-systemic pressure gradient, reduces the shunt across fetal channels, and improves tissue oxygenation. Pulmonary vascular resistance is lowered by administering generous concentrations of oxygen. For refractory hypoxemia, inhaled nitric oxide (iNO) may be administered, which activates soluble guanylate cyclase, increases cyclic guanosine monophosphate (cGMP) production, and activates a cascade causing calcium efflux, with resultant vascular smooth muscle relaxation. By nature of its rapid binding and deactivation by reduced hemoglobin, iNO exhibits virtually no systemic vasodilatory affects. Although several clinical trials in newborns who had PPHN have shown that iNO improves oxygenation and decreases the need for extracorporeal membrane oxygenation (ECMO) by approximately 40%, this therapy has not reduced mortality. Between 25% and 33% of newborns who have PPHN, particularly those who have poor lung inflation, pulmonary hypoplasia/dysplasia, myocardial dysfunction, and pulmonary vascular structural disease, fail to show a sustained response to iNO. This lack of response is particularly evident in newborns who have congenital diaphragmatic hernia, in which iNO has not decreased ECMO use or mortality rate.

For infants whose hearts or lungs are unable to support them despite these therapies, ECMO provides cardiorespiratory support while the heart, lungs, and vasculature recover. With new therapies, particularly iNO, high-frequency ventilation, and the administration of surfactant, the use of ECMO in newborns suffering PPHN has declined. At the same time, such adjunctive therapies have changed the profile of newborns requiring ECMO such that only the sickest patients not responding to these alternative treatment modalities eventually receive ECMO. Similarly, delays in referral to ECMO centers, longer ECMO run times, increased age at initiation of ECMO, and increased rates of ECMO complications have been observed since the introduction of these adjunctive therapies. Cumulatively, these factors

may have a negative impact on the mortality associated with ECMO. Although overall survival with ECMO is approximately 80%, survival varies with disease, ranging from as low as 50% in congenital diaphragmatic hernia to as high as 95% in meconium aspiration syndrome. Several studies have demonstrated improved survival for patients who have PPHN and receive ECMO, but the procedure is invasive and is associated with complications that include intraventricular hemorrhage, bleeding, stroke, emboli, and infection.

Outcomes

Survival in PPHN varies with the underlying disorder, severity of hypoxemia, and resultant encephalopathy. Generally, newborns whose parenchymal lung disease is reversible have the best prognosis; those who have primary maldevelopment of the pulmonary parenchyma and vasculature have the worst, despite modern therapies. Survivors of PPHN have an increased incidence of neurodevelopmental impairment, neurosensory hearing loss, behavioral problems (including hyperactivity and conduct disabilities), and respiratory difficulties (including reactive airway disease and rehospitalizations due to respiratory complications). It is believed that the cerebral hypoxia resulting from the underlying condition, such as birth asphyxia, perinatal hypoxia, and systemic hypotension, rather than from the treatment itself, is responsible for the neurodevelopmental handicaps observed in survivors of PPHN.

PH in Infants and Children

The underlying disease resulting in PH varies with age. The most common causes of PH in children are congenital heart disease and pulmonary disease.

Presentation

In infants and children, the signs and symptoms of PH initially are subtle, are nonspecific, and may be overshadowed by the underlying disease process. Dyspnea on exertion and fatigue may be observed initially because the right heart is unable to increase cardiac output with activity. Such right heart impairment may manifest as tiring with feedings and failure to thrive. With disease progression, symptoms may occur at rest. Eventually, signs of overt right-sided heart failure occur, such as peripheral edema, ascites, and hepatomegaly. Syncope on exertion is an ominous sign that warrants a cardiac evaluation because patients who have PH can be prone to sudden death. Death may result from hypoperfusion of the subendocardial tissue due to increased wall stress and increased myocardial demand or from compression of the left main coronary artery by an enlarged pulmonary artery. Cardiac evaluation may reveal jugular venous distention and a palpable right ventricular impulse. In summary, the diagnosis of PH should be considered for any patient who complains of chest pain, dyspnea, or syncope on exertion or who has any of the previously noted physical findings, and the patient should undergo a baseline assessment, including chest radiography and electrocardiography.

Diagnostic Studies

In infants and children, the chest radiograph, although generally not revealing, may demonstrate underlying lung disease and further direct the evaluation. In advanced stages of disease, a prominent right ventricular contour and poorly vascularized lungs (oligemic lung fields) may be evident, but these observations may be subtle and easily missed.

Electrocardiography for infants and children who have PH often shows evidence of right ventricular hypertrophy and perhaps cor pulmonale (Figure). Cor pulmonale is defined as an alteration in the right ventricular

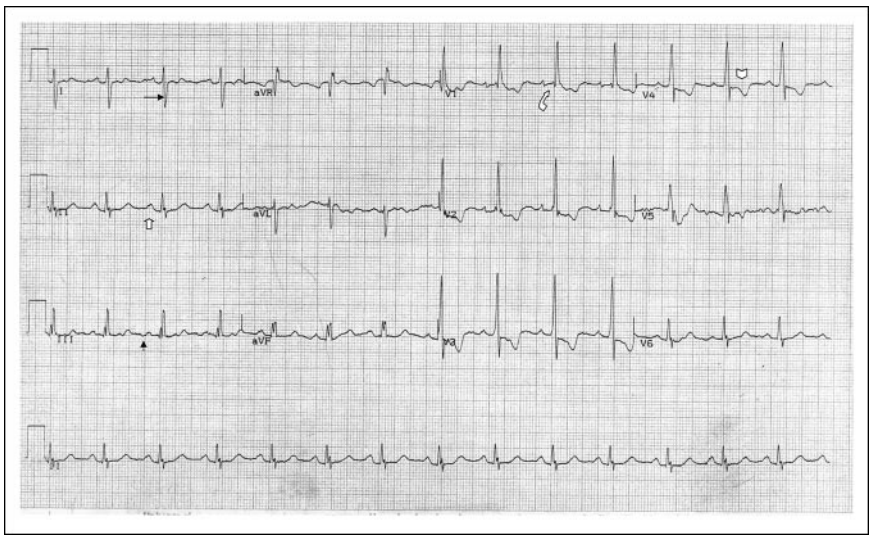

Figure. Electrocardiography in a patient who has pulmonary hypertension demonstrating evidence of right ventricular hypertrophy with strain (white chevron), right axis deviation (black arrow), right atrial enlargement (white arrow), and incomplete right bundle branch block (curved white arrow).

structure and function due to PH caused by disease affecting the lung or its vascular bed. The definition does not include left-sided heart failure. Therefore, congenital heart disease or acquired left-sided heart disease must be excluded prior to diagnosing cor pulmonale. If either chest radiography or electrocardiography indicates the presence of right ventricular hypertrophy, a cardiology evaluation with echocardiography is indicated.

Two-dimensional echocardiography with Doppler evaluation is the confirmatory test and can detect structural heart disease, if present. The tricuspid valve regurgitant jet velocity added to the estimated right atrial pressure allows for estimation of the right ventricular pressure. In the absence of pulmonary valve stenosis, this measurement equals pulmonary arterial pressure and provides the clinician with an estimate of disease severity as well as a response to treatment. Indicators for disease severity and ultimate prognosis include not only the degree of right ventricular pressure elevation, but also the reversibility of the PH. The latter can be determined by demonstrating a decrease in the right ventricular pressure in response to oxygen vasodilator therapy.

Congenital Heart Disease

PH occurs as a consequence of congenital heart disease when the pulmonary blood flow is increased, the pulmonary vascular resistance is increased, or some other factor increases downstream resistance to blood flow through the lungs (such as pulmonary venous obstruction, mitral stenosis, or left ventricular dysfunction).

In the pediatric age group, pulmonary arterial hypertension is the most common mechanism. Any congenital heart lesion that creates a significant shunt from the systemic to the pulmonary vascular bed results in PH. These conditions include large intracardiac defects in the atrial or ventricular septa or the endocardial cushion as well as large extracardiac shunts such as a patent ductus arteriosus or aortopulmonary window. Initially, the left-to-right shunt increases flow in the pulmonary vascular bed, creating PH. Such hyperkinetic PH is due to changes in shear stress on the endothelial wall, with resultant pulmonary arteriolar endothelial dysfunction. With time, the smooth muscle of the arteriolar beds proliferates and hypertrophies, and eventually the PH becomes both irreversible and progressive.

Once the pulmonary pressure exceeds the systemic vascular resistance, the left-to-right shunt reverses, and cyanosis develops due to the presence of a right-to-left shunt. This state is known as Eisenmenger syndrome, for which supportive care is the only treatment. Fortunately, with surgical repair of large shunts in the first year after birth, Eisenmenger syndrome now is considered a preventable disease.

PH may accompany obstruction of pulmonary venous flow. Pulmonary venous hypertension can be subcategorized into left-sided atrial or ventricular disease, left-sided valvular disease, and pulmonary venous obstruction. In left-sided ventricular disease, an increase in left ventricular end-diastolic pressure results in primary left ventricular failure. This condition is uncommon in the pediatric age group and usually is related to diseases of the myocardium, such as viral myocarditis. Treatments range from medical support to cardiac transplantation. Left-sided valvular disease and extrinsic compression of the pulmonary veins, by virtue of surgical or catheter intervention, are reversible causes of pulmonary venous obstruction. The same is not true, unfortunately, for pulmonary vein stenosis, for which supportive care is the only treatment.

Idiopathic PH

The cause of idiopathic PH is, by definition, unknown. This condition is characterized by a progressive elevation in the pulmonary arterial pressure that eventually leads to right ventricular failure and is a primary disorder rather than a secondary response to chronic illness. Idiopathic PH is rare and has a female preponderance in a 1.7:1 ratio. Between 6% and 10% of cases are familial, with an autosomal dominant inheritance pattern as well as an association with a genetic mutation in the *BMPR-2* gene. The pathogenesis involves three processes. First, vasoconstriction results from an imbalance in mediators of pulmonary vasodilation and vasoconstriction. Second, vascular remodeling occurs due to proliferation of endothelial cells and vascular smooth muscle. Third, thrombosis occurs due to coagulation abnormalities.

Unfortunately, idiopathic PH progresses rapidly without treatment. Current therapies, although not consistently successful, have improved survival. Treating the pulmonary vasculopathy while targeting symptoms of right ventricular failure and thrombosis is the primary approach. Conventional therapy includes administration of digoxin, furosemide, and warfarin, and if chronic hypoxemia is present, oxygen therapy.

Catheterization of the right heart is indicated if targeted vasodilator therapy is being considered. At the time of catheterization, an atrial septostomy may be performed for patients who have severe right ventricular failure or recurrent syncope. By creating a right-to-left shunt across the atrial septum, the obstructed pulmonary vascular bed may be bypassed, thereby increasing cardiac

output. In addition, the patient's response to iNO directs vasodilator therapy. Responders are treated with conventional therapy, including calcium channel blockers, which have been found to improve 5-year survival rates. Nonresponders are treated with prostacyclin analogs, such as iloprost, rather than with calcium channel blockers because the latter drugs have been associated with systemic hypotension and right ventricular failure in nonresponders. All patients, regardless of their initial response to vasodilator therapy, require ongoing monitoring to assess their responses to medical therapy and to determine if additional therapies are needed.

For patients who do not respond to conventional therapy or demonstrate no response to iNO, newer therapies are available. These treatments often are used in combination and target different mechanisms of action, including inhibition of the potent endogenous vasoconstrictor endothelin (bosentan) and the breakdown by phosphodiesterase of the vasodilator cGMP generated in the NO pathway (sildenafil).

Respiratory Disorders

Disorders of the respiratory system and hypoxemia are common causes of PH. Signs and symptoms relate to the underlying disease. The prognosis is determined by the underlying respiratory disease, with the presence of PH representing an unfavorable sign. Hypoxemia results in remodeling of the vascular wall, with increases in intimal, medial, and adventitial thickness and proliferation of fibroblasts, which leads to increased pulmonary vascular resistance. Right ventricular enlargement with signs of right-sided heart failure may develop. As discussed, pulmonary heart disease, or cor pulmonale, results from acute or chronic PH and manifests as right ventricular enlargement.

Chronic obstructive and interstitial lung diseases, although listed in the WHO classification, primarily are diseases of adults. The mechanisms leading to PH in these disorders include hypoxic vasoconstriction, compression, possibly destruction of blood vessels by fibrosis, and low lung volumes.

More common in the pediatric age group are alveolar hypoventilation syndromes associated with thoracic cage abnormalities such as kyphoscoliosis and neuromuscular diseases. Loss of lung volume causes alveolar hypoventilation and subsequent hypoxemia and hypercapnia. Such gas exchange abnormalities result in pulmonary vasoconstriction and PH. The PH associated with exposure to high altitude is characterized by vascular wall remodeling due to hypoxia. Polycythemia may aggravate PH.

Sleep-disordered breathing, as it relates to obstructive sleep apnea syndrome (OSAS), may cause PH. The incidence of OSAS is estimated to be 2% to 3% in young children. The increasing prevalence in children is largely attributable to the obesity epidemic. OSAS also may accompany adenotonsillar hypertrophy, craniofacial abnormalities, and neurologic disorders affecting upper airway dynamics and patency. Overnight polysomnography provides a definitive diagnostic approach for OSAS.

OSAS is characterized by repeated episodes of partial or complete upper airway obstruction during sleep, resulting in abnormalities of gas exchange and disruption of sleep patterns. The changes in respiratory mechanics and homeostasis during sleep are magnified further by upper airway obstruction and manifested as increased work of breathing, sleep fragmentation, episodic hypoxemia, and hypercapnia. Frequent oxygen desaturations during sleep occur in children who have OSAS. Hypoxia-induced pulmonary vasoconstriction results in elevation of pulmonary artery pressure and can lead to cor pulmonale. Episodic nocturnal hypoxia also is speculated to result in changes in the physical properties of resistance vessels and may lead to systemic hypertension.

Treatment of OSAS, although beyond the scope of this article, is aimed at preventing the complication of PH and cor pulmonale. Reversal of hypoxemia is intimately linked to normalization of pulmonary artery pressures.

In general, treatment of patients who have secondary PH rests on correcting the underlying respiratory system abnormality and relieving the hypoxemia and hypercapnia that contribute to pulmonary vasoconstriction. Supplemental oxygen can correct arterial hypoxemia and reduce pulmonary artery pressure. Therapies, including pulmonary vasodilation with prostacyclin and NO and calcium-channel blockers, also have been used.

Thrombotic or Embolic Disease

PH caused by chronic thrombotic or embolic disease occurs when pulmonary artery pressure is elevated due to obstruction of blood flow through large pulmonary arteries by a venous clot. The mainstay of management is anticoagulation therapy.

Disorders of Pulmonary Vasculature

PH resulting from disorders directly affecting the pulmonary vasculature is uncommon in the pediatric age group. Examples include pulmonary histiocytosis X and sarcoidosis. Pulmonary histiocytosis X is an interstitial pulmonary disease complicated by severe PH from fibrosis of pulmonary arteries and veins. Sarcoidosis, a multiorgan granulomatous disorder, results in destructive vasculitis involving the muscular layers of arteries and veins.

Summary

- PPHN causes profound hypoxemia that is labile and varies pre- and postductally and may exacerbate newborn illnesses such as meconium aspiration.
- Treatment and possible reversal of PH often begins with correction of the underlying disorder that is causing hypoxemia.
- Diagnostic electrocardiographic criteria for cor pulmonale include right ventricular hypertrophy, right axis deviation, right atrial enlargement, and incomplete right bundle branch block.
- For children who have OSAS, early diagnostic evaluation (including polysomnography) and treatment may reverse the hypoxemia that is causing PH or exacerbating existing cor pulmonale.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

1. All of the following conditions are associated with a difference in pre- and postductal oxygen saturation *except*:

   A. Atrial septal defect.
   B. D-transposition of the great arteries.
   C. D-transposition of the great arteries and coarctation of the aorta.
   D. Interrupted aortic arch type-B.
   E. PPHN.

2. All of the following treatments are valuable in the treatment of PPHN *except*:

   A. Blood transfusion.
   B. ECMO.
   C. iNO.
   D. Oxygen.
   E. Sodium nitroprusside

3. A 6-year-old girl complains of exertional fatigue, and examination reveals a precordial bulge and a loud second heart sound. You consider the diagnosis of idiopathic PH. The *first* laboratory test to obtain is:

   A. Cardiac magnetic resonance imaging.
   B. Chest radiography.
   C. Echocardiography.
   D. Electrocardiography.
   E. Electrocardiography and chest radiography.

4. Electrocardiography for a 4-year-old boy who has Down syndrome shows right ventricular hypertrophy with strain, right axis deviation, right atrial enlargement, and right bundle branch block. Previous echocardiography demonstrated a large atrial septal defect. The *best* next step is to:

   A. Begin nighttime oxygen therapy.
   B. Obtain a sleep study.
   C. Order chest radiography.
   D. Perform a tonsillectomy and adenoidectomy.
   E. Perform cardiac catheterization.

5. Which of the following patients is *most* likely to suffer from irreversible PH?

   A. A 3-month-old boy who has Down syndrome, an atrioventricular septal defect, high pulmonary vascular resistance, and decreased pulmonary blood flow.
   B. A 3-year-old girl who has a structurally normal heart, normal pulmonary blood flow, and high pulmonary resistance.
   C. A 3-year-old girl who has a large ventricular septal defect, systemic pulmonary artery pressure, and increased pulmonary blood flow.
   D. A 3-year-old girl who has pulmonary hypertension and severe mitral stenosis.
   E. A 30-year-old man who has a large atrial septal defect and increased pulmonary blood flow.

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