Diagnostic Considerations in Infants and Children with Cyanosis

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Abstract

Cyanosis is defined by bluish discoloration of the skin and mucosa. It is a clinical manifestation of desaturation of arterial or capillary blood and may indicate serious hemodynamic abnormality. The goal of this article is to help the reader understand the etiology and pathophysiology of cyanosis and to formulate an approach to its differential diagnosis. **[*Pediatr Ann.* 2015;44(2):76-80.]**

It is important to distinguish the terms "cyanosis," "hypoxia," and "hypoxemia." Hypoxemia is a condition in which arterial oxygen content is low. It is usually defined as an arterial oxygen tension (partial pressure of oxygen in systemic artery [PaO_2]) that is below normal (normal PaO_2 is 80-100 mm Hg) and usually associated with systemic arterial desaturation. The relationship between PaO_2 and saturation is defined by the oxygen dissociation curve and the various factors that influence it.[1] Hypoxia is defined as the failure of oxygenation at the tissue level and usually manifests as metabolic acidosis due to anaerobic metabolism.[2] Cyanosis is the clinical manifestation of bluish discoloration of skin or mucosa resulting from the presence of deoxygenated hemoglobin in the circulation.

Cyanosis, hypoxemia, and hypoxemia, although interrelated, can each exist independently of the others. For example, an infant or a child with cyanotic congenital heart disease could have hypoxemia and cyanosis but no hypoxia as long as the cardiac output or hemoglobin is adequately increased. On the other hand, an infant or a child with decreased cardiac function or severe anemia may have normal saturations but evidence of tissue hypoxia due to decrease in total oxygen delivery. Some cases of abnormal hemoglobin or methemoglobinemia can have clinical cyanosis but normal saturations and oxygen content.[3] The goal of the clinician is to detect hypoxemia (either by low pulse oximetery in mild desaturation or by clinical cyanosis when severely desaturated). Pediatric patients suspected of having cyanosis should be assessed promptly by a pediatric cardiologist or by pediatric pulmonologist as dictated by clinical situation.

PATHOPHYSIOLOGY OF CYANOSIS

Normal partial pressure of oxygen in alveoli (PAO_2) is approximately 100 mm Hg at sea level in room air. Partial pressure of oxygen in systemic artery (PaO_2) is approximately 80 mm Hg at sea level in room air. Thus, the normal alveolar-arterial oxygen gradient (the "A-a gradient," which is defined as PAO_2 minus PaO_2) is about 20 mm Hg and results from baseline physiological atelectasis. Oxygen capacity is a combination of oxygen that is bound to hemoglobin (normally this is 1.34 mL of oxygen per gram of hemoglobin at 38°C) and dissolved oxygen (0.003 mL of oxygen per 100 mL of plasma). The dissolved component is a small fraction of oxygen content at room air and normal hemoglobin concentration. These data are usually ignored but become very important when a patient needs supplemental oxygen or has anemia. The oxygen content could be lower than the oxygen capacity depending on the degree of desaturation. Total oxygen delivery is a product of oxygen content and cardiac output. When oxygen content decreases (either due to anemia or desaturation), the cardiac output is increased appropriately to maintain oxygen delivery.

Cyanosis is discernible to the human eye when the deoxygenated hemoglobin

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content is 3-5 g/dL.[2,4] It is sometimes difficult to detect clinically due to factors such as skin color, exposure to light, or presence of jaundice. Normal arterial saturation as measured by pulse oximetery is ≥95%. Depending on the hemoglobin concentration, the degree of desaturation required to produce the same amount of cyanosis varies considerably. For example, an infant or a child with hemoglobin of 20 g/dL will exhibit cyanosis at a saturation of 85% (15% of 20 g/dL is 3 g/dL of deoxygenated hemoglobin), whereas an infant or a child with hemoglobin of 10 g/dL will not exhibit clinical cyanosis until saturation drops to as low as 70% (30% of 10 g/dL is 3 g/dL of desaturated hemoglobin). Thus, in children with anemia with hypoxemia, clinical cyanosis may not be recognized until saturations drop below 85%. Cyanosis may become apparent only during episodes of crying or feeding, when the saturations decrease further.[5] It is for this reason that pulse oximetery plays a very important role in screening for congenital heart disease and is recommended to be done on all neonates before discharge from the nursery.[5-7] The American Academy of Pediatrics suggests using saturation of <95% in a lower extremity after 24 hours of life as an indication for further evaluation.[7]

MECHANISMS OF CYANOSIS/ HYPOXEMIA

Cyanosis/hypoxemia in children results from one of the following physiological mechanisms: (1) pulmonary venous desaturation; (2) extrapulmonary right to left shunting; (3) transposition physiology; or (4) hemoglobin disorders affecting affinity to oxygen. The different causes and physiological mechanisms are summarized in **Figure 1** and **Table 1**.[1,8]

Pulmonary Venous Desaturation

Pulmonary venous desaturation can result from three broad mechanisms: (1) hypoventilation; (2) parenchymal or extra-parenchymal lung disease; and (3) intrapulmonary right to left shunt.

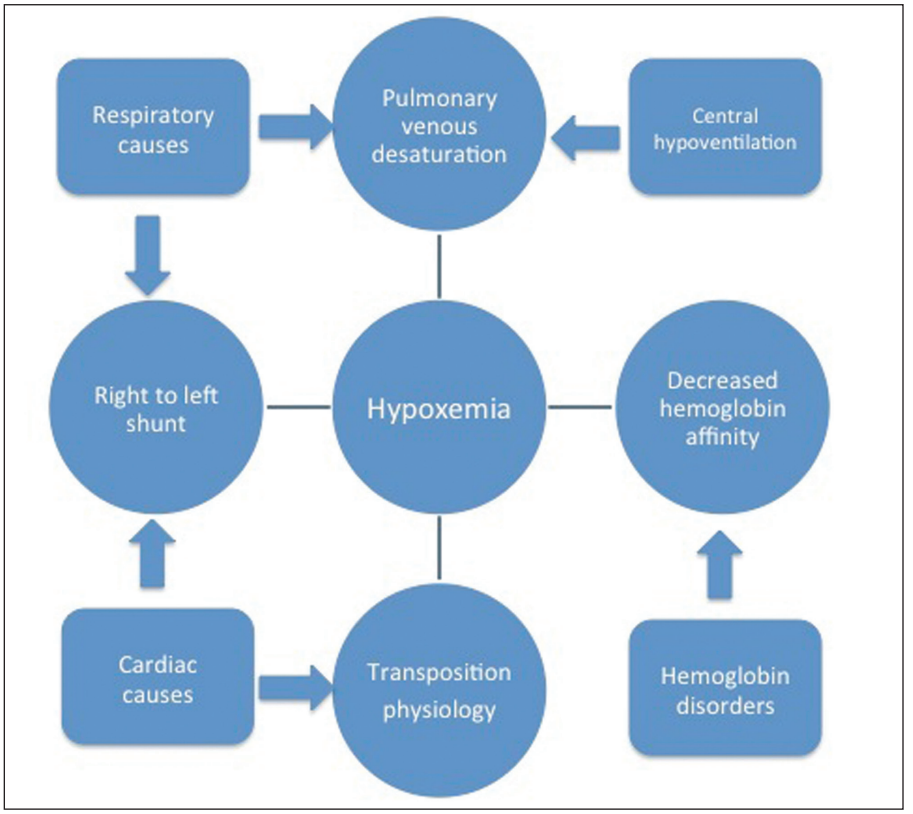

Figure 1. Physiological mechanisms of hypoxemia.

Hypoventilation can be secondary to central nervous system (CNS) infection, injury, inflammation, malformation,[9] or due to drug overdose (eg, opiod, sedatives).[2,9] Associated findings in such patients may include low A-a gradient, apnea, hypoventilation, lethargy, and hypotonia, and arterial blood gas will show hypercarbia in addition to hypoxia.

Parenchymal or interstitial lung disease results in pulmonary venous desaturation, respiratory distress, abnormal chest X-ray, and variable (usually low) A-a gradient depending on the disease severity.

Intrapulmonary right to left shunting results from ventilation perfusion mismatch or arteriovenous (AV) malformations that are seen in liver failure or Glenn physiology. In Glenn physiology, the pulmonary artery is directly anastomosed to the superior vena cava and disconnected from the heart (as part of staged surgical single ventricle palliation), resulting in hepatic blood flow diverted away from the lungs. These patients develop AV malformations due to lack of the yet-to-be characterized "hepatic factor."[10] AV malformations can be diagnosed with a positive bubble study on transthoracic echocardiogram.

Extrapulmonary Right to Left Shunting

In the second group of lesions involving extrapulmonary right to left shunt, the two main lesions are cyanotic congenital heart lesions and pulmonary hypertension. The pulmonary venous saturation is normal in this group, but systemic arterial desaturation results from deoxygenated blood shunting from the systemic venous side to systemic circulation. The heart lesions have right-sided obstruction or insufficiency

TABLE 1.

Causes of Hypoxemia in Children

- **Pulmonary venous desaturation**
  - With high A-a gradient
    - Severe parenchymal lung disease (eg, acute respiratory distress syndrome, pulmonary hemorrhage)
    - Lung disease with diffusion impairment (eg, interstitial lung disease)
    - Intrapulmonary right to left shunting (eg, atelectasis, pulmonary arteriovenous malformations
  - With low A-a gradient (eg, central hypoventilation, opioid overdose, parenchymal lung disease such as pneumonia)
- **Extrapulmonary right to left shunting**
  - Cyanotic congenital heart disease with decreased pulmonary blood flow and right to left shunting (eg, tetralogy of Fallot, pulmonary atresia)
  - Pulmonary hypertension, primary or secondary, with right to left shunt at the level of ductus or patent foramen ovale (eg, primary pulmonary hypertension, Eisenmenger syndrome)
- **Transposition physiology**
  - (eg, D-transposition of great arteries, double outlet right ventricle with malposed great vessels and subpulmonary ventricular septal defects)
- **Hemoglobin disorders with decreased oxygen affinity**
  - (eg, methemoglobinemia)

as a common finding, resulting in decreased pulmonary blood flow. Examples include tricuspid atresia, Ebstein's anomaly, pulmonary atresia, tetralogy of Fallot, absent pulmonary valve syndrome, and critical pulmonary stenosis. In general, they present a few hours to days after birth with "hypoxemia without respiratory distress" as the ductus starts to close. These lesions could be ductal dependent based on severity of obstruction, so timely initiation of prostaglandin is crucial.

The pulmonary hypertension group presents with hypoxemia if there is a communication to allow right to left shunt at the atrial, ventricular, or ductal level. This is typically seen in a newborn baby with persistent primary pulmonary hypertension (PPHN) where right to left shunt at atrial or ductal level leads to hypoxemia. If the shunt is at the ductal level, it will manifest with differential cyanosis; the saturations will be normal in right upper limb but lower in the legs due to right to left shunt. If there is no patent ductus arteriosus, right to left shunt at the patent foramen ovale (PFO) leads to uniform desaturation in both upper and lower body. It is important to understand that sometimes the right subclavian is aberrant and originates distal to the ductus (hence is postductal). In such a situation, there would be no differential saturations between right upper limb and lower limbs even though there is a right to left shunt at the ductus. Saturations in the right ear lobe are always preductal and should be checked when in doubt.[5]

Transposition Physiology

Transposition physiology occurs when systemic and pulmonary circulations are arranged in parallel rather than in series due to ventriculo-arterial discordance. D-transposition of great arteries is the typical example for such lesions. The fully saturated pulmonary venous blood is directed back into the pulmonary circulation, and systemic venous blood is directed to the systemic arterial circulation. Survival depends on some pulmonary venous blood shunting to the systemic side at the atrial, ventricular, or ductal level, and hence some of these patients need urgent balloon atrial septostomy and a prostaglandin infusion before surgery.[8,11] The hypoxemia in such a physiology presents immediately at birth, unlike the cases with decreased pulmonary blood flow.[8] Clinical exam usually shows a single and loud second heart sound (because the great vessels are anterior-posterior), prominent right ventricular impulse (because right ventricle is the systemic ventricle), and differential cyanosis with higher postductal saturations than preductal saturations.

Hemoglobin Disorders Affecting Affinity to Oxygen

Methemoglobinemia or other hemoglobin disorders of oxygen affinity should be suspected in an otherwise asymptomatic infant or a child with cyanosis and discrepancy between PaO_2, saturation, and clinical assessment.[3,12] The primary pathology is in the decreased affinity of the hemoglobin to oxygen, resulting from multiple mechanisms. Saturations by pulse oximetry could be normal or low, but as a group all patients exhibit normal PaO_2. Family history is usually positive in hemoglobin disorders.

DIAGNOSTIC APPROACH TO CYANOSIS

Careful history and detailed clinical exam usually guide the physician to the etiology of the cyanosis. Laboratory evaluation, such as complete blood count, arterial blood gas, co-oximetry, chest X-ray, and echocardiogram, helps in confirming the clinical suspicion (**Table 2**). History should include detailed perinatal history, such as asphyxia, maternal ingestion of nonsteroidal medications (resulting in premature ductal

TABLE 2.

Diagnostic Testing of Cyanosis in Children

Test	Pulmonary Parenchymal Disease	Intra- or Extrapulmonary Right to Left Shunt	Central Hypoventilation	Transposition Physiology	Hemoglobin Disorders
Respiratory distress	Present; may have fever	No	No; apnea/hypoventilation	Mild distress, usually tachypnea due to increased PBF	No
Cardiac examination	Normal	May have single S2, RV heave, thrill, and murmurs	Normal	Single S2, flow murmur, RV heave	Normal
Chest X-ray	Pulmonary pathology	Variable cardiac silhouette; usually clear lung fields	Normal	Egg-on-end appearance, pulmonary venous congestion +/-	Normal
Differential saturation (preductal vs postductal)	Absent	Present if right to left shunt at ductus; postductal < preductal	Absent	Postductal > preductal	Absent
Complete blood count	Elevated white cell count	Polycythemia if chronic	Normal	Polycythemia if chronic	Normal
Arterial blood gas on 100% FiO_2	PaO_2>150 mm Hg PCO_2 variable	PaO_2<150 mm Hg Normal PCO_2	PaO_2>150 mm Hg, usually much higher; elevated PCO_2	PaO_2<150 mm Hg, usually <50 mm Hg; normal PCO_2	Normal PaO_2 and PCO_2

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in a systemic artery; PBF, pulmonary blood flow; PCO_2, partial pressure of carbon dioxide; RV, right ventricle.

closure), and meconium aspiration, that would increase the risk for PPHN. Presence of fever and respiratory distress on clinical exam would suggest respiratory pathology. Timing of presentation would help differentiate ductal-dependent decreased pulmonary blood flow lesions versus transposition physiology.

Clinical exam should include careful examination of skin, mucosa, as well as cardiac and respiratory systems. Acrocyanosis is the bluish discoloration of extremities, often seen in newborns (and sometimes in older patients) exposed to cold stress, and it results from peripheral vasoconstriction. It is benign and should be differentiated from central cyanosis in which the entire skin and mucosa are bluish. Clubbing of the fingers suggests chronic hypoxemia. Central hypoventilation presents with shallow breathing/apnea, pulmonary pathology presents with respiratory distress, and most cardiac causes have normal respiratory exam. The presence of abnormal cardiac impulse/heave, abnormal second heart sound, or murmur or thrills points to cardiac etiology.

The hyperoxia test is a useful tool to help differentiate the different causes of hypoxemia.[4,12,13] It is a simplified way of differentiating lesions with high A-a gradient from lesions with low A-a gradient. In this test, the patient is placed on 100% oxygen for 10-15 minutes. An arterial blood gas is obtained from a preductal artery (usually from the right upper extremity). This is important because the natural tendency is to obtain a blood gas from the existing umbilical arterial line, which could be more or less saturated, rather than the preductal artery depending on the relationship of the great arteries and the direction of ductal shunting. With 100% oxygen, the alveolar PAO_2 at sea level is greater than 500 mm Hg (PAO_2 = 760 × fraction of inspired oxygen [FiO_2] – 1.2 × partial pressure of carbon dioxide [$PaCO_2$)]). If the A-a gradient is normal (approximately 20 mm Hg), then the pulmonary venous partial pressure of oxygen (PO_2)should be close to 500 mm Hg. In pulmonary parenchymal disease, depending upon the severity of diffusion abnormality, the pulmonary venous partial PO_2 and hence the systemic arterial PO_2 are decreased but usually >150 mm Hg. In case of right to left shunting or transposition physiology, the systemic arterial PO_2 (referred to as PaO_2) is much lower (usually <150 mm Hg) depending on the severity of shunt and mixing (**Table 2**).

Chest X-ray is helpful in confirming a pulmonary pathology such as consolidation, pleural effusion, or congenital malformations of lungs. Complete blood count may show elevated white cell count in infections, and polycythemia suggests chronic state of hypoxemia. Echocardiogram is diagnostic in excluding or confirming cardiac pathology.

MANAGEMENT

Management of hypoxemia depends on the etiology; pulmonary pathology

and central hypoventilation need ventilatory support whereas cardiac causes may require treatment with prostaglandins and/or surgery.

SUMMARY

Central cyanosis can result from a variety of conditions involving pulmonary, cardiac, hematological, or central nervous system etiologies. Understanding the pathophysiology of hypoxemia is important. A careful history, complete physical exam, and focused laboratory evaluation are usually sufficient for determining the cause and initiating treatment.

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