In The Name Of God

APPROACH TO CYANOSIS IN THE NEWBORN

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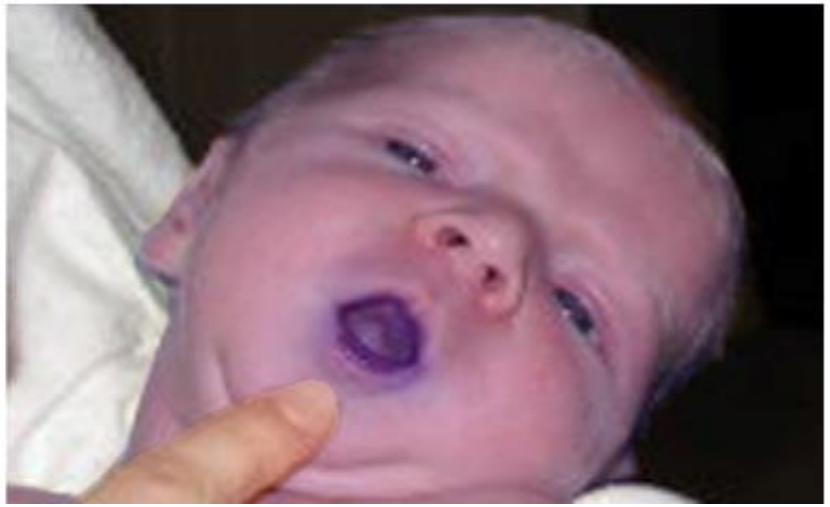
TITLES

- Definition
- Classification
- Pathophysiology
- Causes
- Evaluation
- Diagnostic tests
- Pulse oximetry screening

CYANOSIS

- A bluish discoloration of the tissues when the absolute level of deoxygenated hemoglobin in the capillary bed exceeds 3-5 g/dL.
- Two types of cyanosis:
  - Central cyanosis
  - Peripheral cyanosis



PERIPHERAL CYANOSIS

- The concentration of deoxygenated hemoglobin on the venous side of the capillary bed is increased, whereas the systemic arterial oxygen saturation is normal.
  - Due to increased tissue oxygen extraction
  - Peripheral cyanosis may be associated with peripheral vasoconstriction
  - It typically affects the distal extremities and sometimes the circumoral or periorbital areas
- In neonates, the mucus membranes remain pink, which differentiates it from central cyanosis
- It can be a **benign** (eg, **acrocyanosis**) or **pathologic** finding
- Causes include: cold exposure, sepsis, shock, venous obstruction, and polycythemia

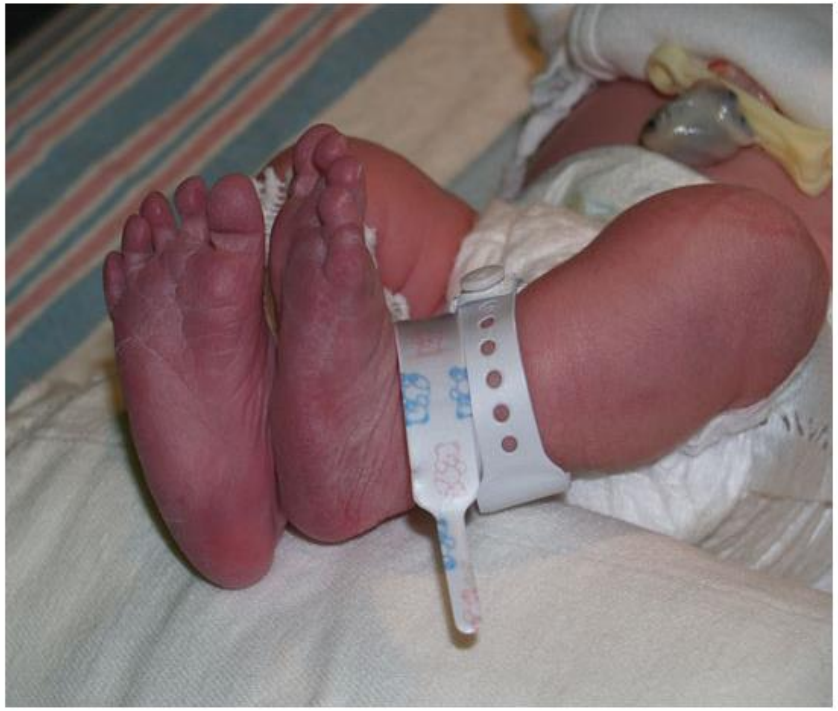
ACROCYANOSIS

It is a benign peripheral cyanosis around the mouth and the extremities caused by vasomotor changes result in peripheral vasoconstriction and increased tissue oxygen extraction

Acrocyanosis is differentiated from pathologic causes of peripheral cyanosis (eg, septic shock) by its clinical course.

It occurs in otherwise healthy infants immediately after delivery and does not persist beyond 24 to 48 hours after birth.

Neonatal acrocyanosis



Acrocyanosis is often seen in healthy newborns and refers to peripheral cyanosis around the mouth and the hands and feet, as shown in this picture. It is a benign condition caused by vasomotor changes resulting from the transition from fetal to extrauterine life. Acrocyanosis is differentiated from pathologic causes of peripheral cyanosis (eg, septic shock) by its clinical course. It occurs in otherwise healthy infants immediately after delivery and typically does not persist beyond 24 to 48 hours after birth.

CENTRAL CYANOSIS

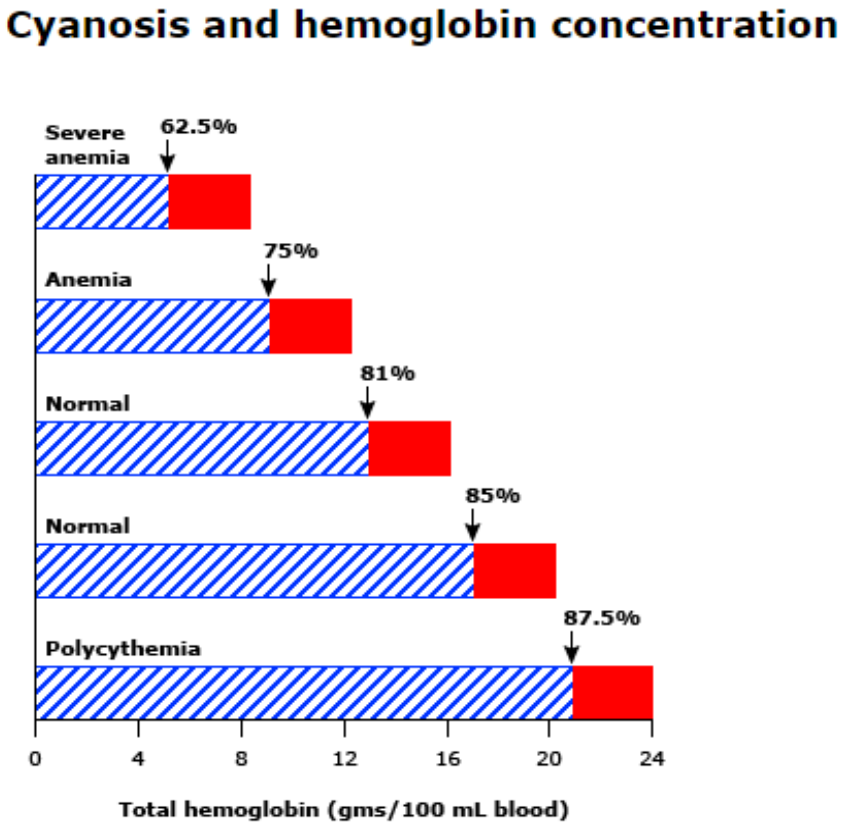
- Reduced oxygen saturation in the arterial circulation.
- Newborn infants normally have central cyanosis until up to 5 to 10 minutes after birth, as the oxygen saturation rises to 85 to 95 percent by 10 minutes of age
- Persistent central cyanosis is always pathologic and should be evaluated and treated promptly.

PATHOPHYSIOLOGY OF CENTRAL CYANOSIS

- **Alveolar hypoventilation:**
  - It can cause hypercarbia, hypoxemia and cyanosis.
  - Causes of hypoventilation: CNS depression (eg, perinatal asphyxia), airway obstruction (choanal atresia), or neuromuscular disorders (eg, SMA type 1).
- **Ventilation-perfusion mismatch:**
  - neonatal pneumonia, pneumothorax
- **Right-to-left shunt:**
  - intracardiac (eg, cyanotic congenital heart disease [CCHD])
  - through the ductus arteriosus (eg, persistent pulmonary hypertension)
  - intrapulmonary (eg, perfusion of non-ventilated areas of the lung)
- **Diffusion impairment:**
  - pulmonary edema Interferes with alveolar-arterial diffusion

FACTORS THAT AFFECT CYANOSIS DETECTION

- **Hemoglobin concentration** affects **the level of oxygen saturation at which cyanosis is perceptible.**
  - The perception of cyanosis depends upon the absolute concentration of deoxygenated hemoglobin, not the ratio of deoxygenated to oxygenated hemoglobin.
  - In polycythemia, cyanosis can be detected at higher oxygen saturations; whereas an anemic patient may not have perceptible cyanosis despite significant hypoxemia.



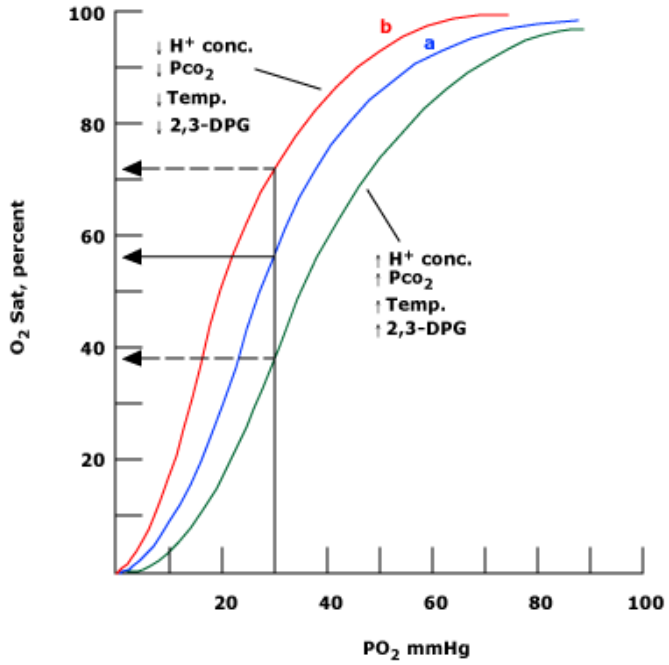
The arterial oxygen saturation level at which cyanosis is detectable at different total hemoglobin concentrations is illustrated above. The solid, red portion of each bar represents 3 g/dL reduced hemoglobin.

- **Fetal hemoglobin :** cyanosis is detected at a lower PaO2 in newborns who have predominantly fetal hemoglobin compared with older patients.
- **Skin pigmentation:** Cyanosis is often less apparent in patients with darker skin pigmentation. For this reason, examination should include the nail beds, tongue, and mucous membranes.
- **Factors that increase the affinity of hemoglobin for oxygen:**

alkalosis, hyperventilation (low PCO2), cold temperature, and low levels of 2,3 diphosphoglycerate

- **Factors that decrease the affinity of hemoglobin for oxygen:** acidosis, fever, or increased concentration of adult hemoglobin

Factors that affect the neonatal oxygen-dissociation curve



The oxygen-dissociation curve of human blood and the effects of changes in the H^+ ion concentration, Pco_2, temperature, and level of 2,3-diposphoglycerate (2,3-DPG) are depicted above. For fetal hemoglobin, the normal curve (a) is shifted to the left (b).

CAUSES OF PERIPHERAL CYANOSIS

- Cold exposure and benign acrocyanosis
- Shock
- Sepsis
- Elevated venous pressure or venous obstruction (eg, venous thrombosis)
- Polycythemia

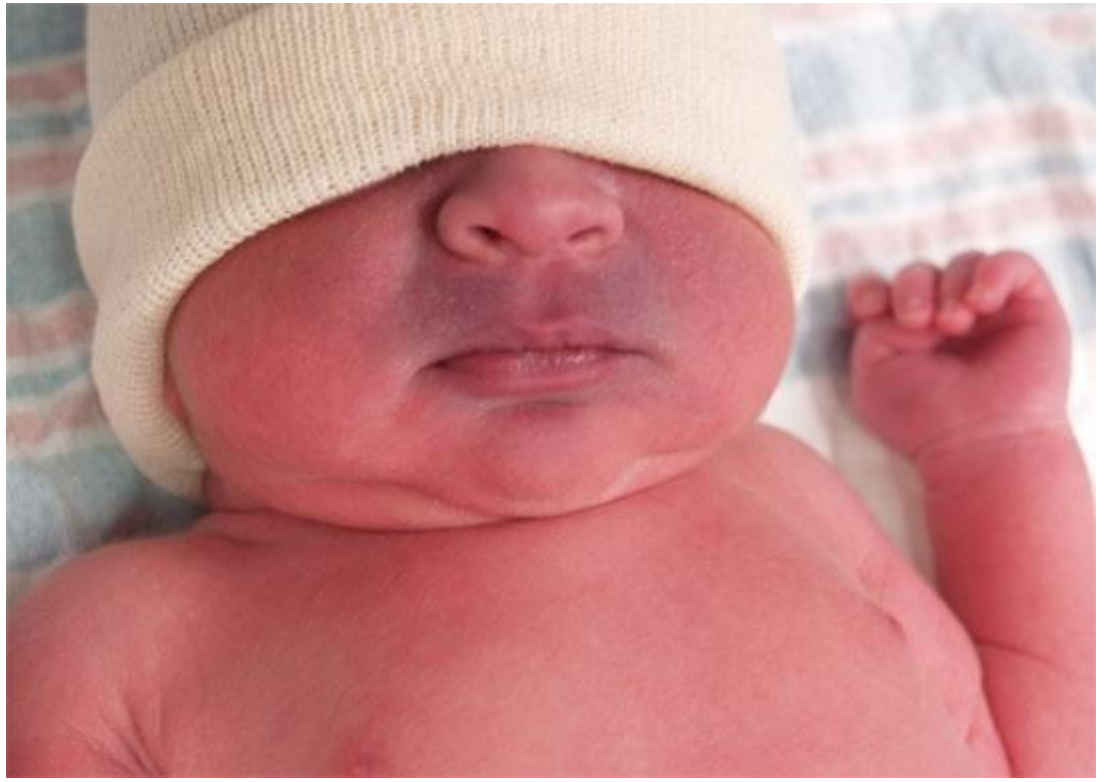
ETIOLOGIES OF PERSISTENT CENTRAL CYANOSIS

- Cardiac
- Metabolic
- Neurologic
- Infectious
- Hematologic
- Parenchymal and non-parenchymal pulmonary disorders

Causes of central cyanosis in the neonate

Disease category	Primary underlying mechanism
Airway obstruction	
Choanal atresia	Hypoventilation
Laryngotracheomalacia	
Macroglossia	
Micrognathia or retrognathia (eg, Pierre-Robin syndrome)	
Cardiac	
Congenital cyanotic heart disease	Right-to-left shunting
Heart failure/pulmonary edema	Impaired alveolar-arterial diffusion and V/Q mismatch
Hematologic	
Hemoglobinopathies (eg, methemoglobinemia)	Impaired oxygen saturation
Polycythemia	Elevated hemoglobin resulting in low oxygen saturation
Metabolic	
Severe hypoglycemia	Hypoventilation due to decreased or absent respiratory effort secondary to lethargy, seizures, and/or apnea
Inborn errors of metabolism	
Neurologic	
Central nervous system depression	
Apnea of prematurity	Hypoventilation
Infection (eg, meningitis, encephalitis)	
Intraventricular hemorrhage	
Maternal sedation	
Seizure	
Neuromuscular disorder	
Neonatal myasthenia gravis	Hypoventilation
Phrenic nerve injury	
Spinal muscular atrophy type 1 (Wernig-Hoffman disease)	
Pulmonary	
Parenchymal disease	
Atelectasis	V/Q mismatch
Alveolar capillary dysplasia	
Lobar emphysema	
Pneumonia	
Pulmonary hypoplasia	
Pulmonary hemorrhage	
Respiratory distress syndrome (Hyaline membrane disease)	
Transient tachypnea of the newborn	
Pulmonary fibrosis	Impaired alveolar-arterial diffusion
Pulmonary edema	Impaired alveolar-arterial diffusion and V/Q mismatch
Nonparenchymal disease	
Pleural effusion	V/Q mismatch
Pneumothorax	
Other	
Persistent pulmonary hypertension of the newborn	Right-to-left shunting

CAUSES OF CENTRAL CYANOSIS BASED ON ITS MECHANISM

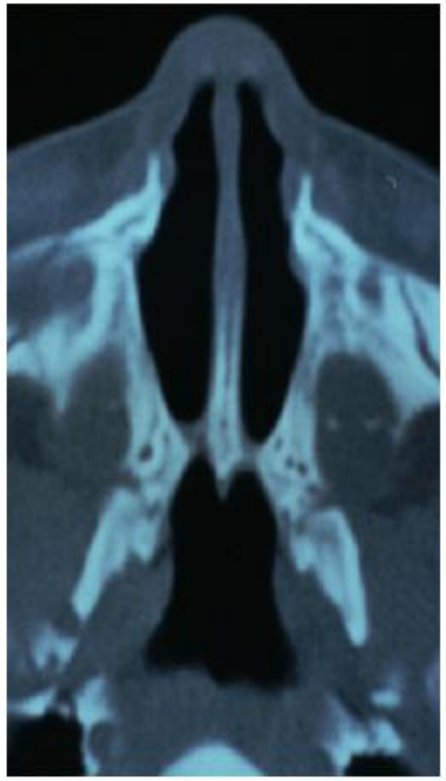


①HYPOVENTILATORY DISORDERS

Airway abnormalities:

- **Choanal atresia:**
  - ❖ usually unilateral
  - ❖ bilateral atresia will present immediately after birth with respiratory distress and **cyanosis** while in a **quiet** state but becomes pink while crying.
  - ❖ computed tomography will confirm the diagnosis
- **Micrognathia or retrognathia:**
  - ❖ Airway obstruction is caused by the posterior tongue obstructing the retropharyngeal airway while the infant is supine
- **Laryngeal and tracheal abnormalities:**
  - ❖ congenital laryngomalacia, vocal cord paralysis, tracheal stenosis, and vascular rings
  - ❖ all present soon after birth with airway obstruction, stridor, and **cyanosis** especially evident while the neonate is **crying.**

CT image of choanal atresia



Axial CT image of choanal atresia. Note the bony narrowing of the posterior nose.

HYPOVENTILATORY DISORDERS

- **Neurologic disorders:**
  - ❖may cause hypoventilation and apnea resulting in hypoxemia and cyanosis**.**
  - ❖hypoxic ischemic encephalopathy, intracranial hemorrhage, or seizures
- **Metabolic disorders :**
  - ❖may be complicated by apnea leading to intermittent episodes of hypoxemia and cyanosis (eg, severe hypoglycemia).

②PULMONARY DISORDERS

Ventilation-perfusion mismatch:

- The most common cause of neonatal cyanosis
- almost always have some degree of respiratory distress
- Specific causes: Respiratory distress syndrome (RDS), Transient tachypnea of the newborn, Meconium aspiration syndrome, Neonatal pneumonia, Air leak syndromes, Congenital abnormalities of the lung and diaphragm (congenital diaphragmatic hernia and cystic adenomatoid malformation)

Impaired alveolar-arterial diffusion:

- Pulmonary edema (associated with both pulmonary and non pulmonary disease) is the major cause
- ❖Examples of non pulmonary causes of pulmonary edema include:
- ●Sepsis: capillary leak may result in pulmonary edema in the later stages of sepsis
- ●Arteriovenous or venous malformations may cause high-output cardiac failure and pulmonary edema (eg, Vein of Galen malformation)
- ●Heart failure in patients with cyanotic congenital heart disease (CCHD)

③RIGHT-TO-LEFT SHUNT

Intracardiac:

- cyanotic congenital heart disease (CCHD)

Most of the time present with cyanosis without R/D

CCHD may also develop heart failure → pulmonary edema → impaired alveolar-arterial diffusion → cyanosis

Through the ductus arteriosus:

Persistent Pulmonary Hypertension

Intrapulmonary:

right to left shunting due to impaired ventilation/perfusion of affected alveoli

HEMATOLOGIC CAUSES OF CYANOSIS IN NEWBORN

Hemoglobinopathies:

Hemoglobinopathies that inadequately transport oxygen → cyanosis

Methemoglobinemia:

- A genetic disorder
- The iron of heme is oxidized to the ferric state
- Unable to bind oxygen

- Mechanism: ④**Diffusion impairment**

Polycythemia:

- defined as a **hematocrit >65 percent** or a hemoglobin **concentration >22 g/dL**
- **RFs:** infants of diabetic mothers**,** delayed cord clamping, chronic fetal hypoxia, fetal growth restriction
- Polycythemia → Hyperviscosity → Interfere with pulmonary perfusion → **PPHN**

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

- The normal circulatory transition from fetal to newborn circulation fails to occur
- Elevated pulmonary vascular resistance → right to left shunting through ductus arteriosus and foramen ovale → severe hypoxemia and cyanosis
- PPHN is most frequently associated with parenchymal lung disease :
  - meconium aspiration syndrome, neonatal pneumonia, and RDS.
  - Clinical presentation: respiratory distress and cyanosis
- **Idiopathic PPHN** may also occur

EVALUATION

EVALUATION

History

Maternal diabetes

Polyhydramnios

Oligohydramnios

Prolonged rupture of the fetal membranes

Meconium staining of the amniotic fluid

Family history of CHD or underlying hemoglobinopathy

Associations

CHD, polycythemia, hypoglycemia

fetal airway, esophageal, neurological conditions

renal defects, pulmonary hypoplasia

neonatal sepsis

meconium aspiration syndrome and pulmonary hypertension of the newborn (PPHN)

Physical examination

signs of respiratory distress :

- pulmonary disease, obstructed TAPVR and left-sided obstructive disease.

presence of R/D does not rule out congenital heart disease

Neonates with cardiac tachypnea frequently lack increased work of breathing at rest (sometimes referred to as "**happy**" or "**comfortable**" tachypnea), and they become more distressed with feeding

Any critically ill infant with respiratory distress, cyanosis, poor perfusion and/or shock:

- CHD (Left-sided obstructive lesions with ductal closure) and sepsis should be considered

DIAGNOSTIC TESTS

- **Pulse oximetry :** confirm hypoxemia and asses the severity
- **Arterial blood gas :** PaO2, PaCO2, pH, base excess, calculated bicarbonate level
  - Methemoglobinemia: low oxygen saturation + normal PaO_2
- **Hyperoxia testing** : measuring the PaO2 with and without 100 percent oxygen
  - It was used in the past to distinguish cyanotic CHD from pulmonary disorders.
  - The hyperoxia test should only be used if reliable echocardiography is not immediately available.
- **Complete blood count** (CBC)
- **Blood glucose :** Cyanosis due to apnea and poor perfusion can be seen in severe hypoglycemia.
- **Blood culture** : in all neonates with clinically significant cyanosis (sepsis is an important potential cause)
- **Chest radiograph**
- **Echocardiography**

Findings Suggestive Of Cardiac Disease In Chest Radiograph

- **Abnormal configurations** : dextrocardia, right aortic arch, situs inversus
- **Cardiac size and shape :**
  - Tetralogy of Fallot ("boot-shaped" heart)
  - transposition of the great arteries ("egg-on-a-string"-shaped heart)
- **Pulmonary vascular markings** : Increased or decreased

When Echocardiography Should Be Performed In Infants With Cyanosis

- Cyanosis **out of proportion to lung pathology** on chest radiography
- **Persistent cyanosis** despite supplemental oxygen and/or positive pressure ventilation
- Findings on physical exam and/or chest radiography suggestive of heart disease
- **Poor perfusion or shock**

CONFIRMING HYPOXEMIA (PULSE OXIMETRY)

- The ideal oxygen saturation target range is currently unknown.
- The revised American Academy of Pediatrics guidelines state that target oxygen saturations of 90%-95% may be safer than 85%-89%.
- A difference of **≥4** percent between the preductal (right hand) and postductal (either foot) SpO2 suggests either **congenital heart disease** (eg, **critical aortic stenosis** or **coarctation of the aorta**) or **persistent pulmonary hypertension** of the newborn (PPHN).
- In infants with PPHN, if right-to-left shunting is predominantly through the **foramen ovale** rather than the ductus, pre- and postductal saturations may not be different. (difficult to differentiate from cyanotic heart disease)

HYPEROXIA TEST

- The hyperoxia test aids in differentiating between **primary lung disease** and **CHD with right-to-left shunting**.
- The test is performed by placing the infant in **100% oxygen for 5-10 minutes** followed by monitoring oxygenation by arterial blood gas or noninvasive measures.
- In **primary lung disease**, oxygen should diffuse into the poorly ventilated areas and improve oxygenation.
- **Persistent hypoxemia** would suggest the presence of **right-to-left shunting**.
- With the advent of routine **pulse oximetry screening** for critical CHD and improved access to **echocardiography**, the hyperoxia test is usually **not** necessary.
- Hyperoxia testing **is not** definitive.
- Abnormal response → Echocardiography

HYPEROXIA TEST

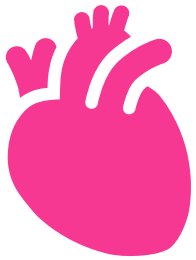
Formal hyperoxia testing (using ABGs)

- Measuring **PaO_2** in the right radial artery (**preducta**l) before and after administration of **100 %** inspired oxygen for **10 minutes**.
- An **increase** in the PaO_2 to a level **>150 mmHg** suggests **pulmonary disease**
- An increase to a value **<150 mmHg or no increase** is suggestive of **cyanotic CHD and PPHN**

Informal hyperoxia testing (using pulse oximetry)

- An increase in the oxygen saturation by **≥10%** with administration of **100 %** inspired oxygen suggests a **pulmonary cause** of cyanosis.
- This finding by itself is generally not sufficient to **forego** additional evaluation with echocardiography.

A rise in oxygen saturation and PaO_2 during the challenge does not exclude CHD and echocardiography should still be performed if clinical suspicion for CHD remains high



Hyperoxia test results in neonates with cyanosis

	PaO_2 (percent saturation) when FiO_2 = 0.21		PaO_2 (percent saturation) when FiO_2 = 1	$PaCO_2$
Normal	>70 (>95)		>300 (100)	35
Pulmonary disease	50 (85)		>150 (100)	50
Neurologic disease	50 (85)		>150 (100)	50
Methemoglobinemia	>70 (<85)		>200 (<85)	35
Cardiac disease				
Parallel circulation*	<40 (<75)		<50 (<85)	35
Mixing with reduced PBF¶	<40 (<75)		<50 (<85)	35
Mixing without restricted PBF△	40 to 60 (75 to 93)		<150 (<100)	35
	Preductal	**Postductal**		
Differential cyanosis◇	70 (95)	<40 (<75)	Variable	35 to 50
Reverse differential cyanosis§	<40 (<75)	>50 (>90)		

Hyperoxia test: The typical results of PaO_2 and percent of oxygen saturation following administration of room air (FiO_2 = 0.21) or 100% oxygen (FiO_2 = 1) to neonates with different causes of cyanosis.

HYPEROXIA WITH HYPERVENTILATION

- It can be used to distinguish between **structural congenital heart disease** and primary (or persistent) pulmonary hypertension of the newborn (**PPHN**), both of which have **right-to-left shunting**.
- In response to hyperventilation with 100% oxygen ($PaCO_2$ 25-30 mm Hg), more infants with PPHN achieve PaO_2 levels higher than 100 mm Hg.
- In contrast, patients with anatomically fixed right-to-left shunting rarely generate a PaO_2 well above 40-50 mm Hg, even with inhalation of 100% oxygen and hyperventilation.

All newborns should undergo routine pulse oximetry screening for critical congenital heart disease prior to discharge from the delivery hospital.

Congenital heart disease (CHD) is the most common type of congenital anomaly, with an overall prevalence of approximately 1 percent

About 25% of infants with critical congenital heart disease may not be symptomatic and diagnosed until after initial discharge from the newborn nursery if oxygen saturation screening is not performed.

IMPORTANT TERMS TO CHARACTERIZE CHD

Cyanotic CHD:

Entry of deoxygenated blood into the systemic circulation through an intracardiac or extracardiac shunt

Ductal-dependent CHD:

lesions are dependent upon a PDA to supply pulmonary or systemic blood flow or to allow adequate mixing between parallel circulations

- In critical right heart obstructive lesions, the PDA is necessary to supply blood flow to the lungs
- In critical left heart lesions, the PDA supplies systemic circulation
- In parallel circulations (eg, TGA), bidirectional flow in the PDA allows mixing between oxygenated and deoxygenated circuits

Critical CHD:

lesions requiring surgery or catheter-based intervention in the first year of life that includes:

- ductal-dependent and cyanotic lesions
- CHD that may not require surgery in the neonatal period but still require intervention: a large VSD or an AV canal defect

POSTNATAL DIAGNOSIS

- Infants with serious and life-threatening clinical findings may be diagnosed during the birth hospitalization.
- Some infants with CHD may appear normal on routine examination and signs of critical CHD may not be apparent until after discharge
- Prior to the routine use of pulse oximetry screening, approximately 30 percent of patients with critical CHD were discharged from the birth hospitalization undiagnosed
- The most commonly reported delayed diagnoses are COA , interrupted aortic arch , aortic stenosis, hypoplastic left heart syndrome , transposition of the great arteries , pulmonary valve stenosis, and tetralogy of Fallot.

- Pulse oximetry screening can identify infants with some, but not all, of these lesions.
- For infants with critical CHD who are not diagnosed during the birth hospitalization, the risk of mortality is as high as 30 percent especially for ductal-dependent lesions
- Studies have shown that pulse oximetry is an effective, though not infallible, screening measure.
- A cutoff SpO_2 value of <95 percent is used as it provides a sensitivity of around 75 percent and specificity >99 percent
- The American Academy of Pediatrics (AAP), the American Heart Association (AHA), and the American College of Cardiology Foundation (ACCF) have recommended universal screening of all newborns with pulse oximetry to improve the recognition of CHD

NEWBORN SCREENING FOR CRITICAL CONGENITAL HEART DISEASE USING PULSE OXIMETRY

Timing :

- Screening should be performed **after 24 hours** of life or as late as **possible** if early discharge is planned.

Technique :

- Oxygen saturation (**SpO_2**) is measured in the **right hand** (preductal) **and** **either foot** (postductal)

CRITERIA FOR POSITIVE SCREEN

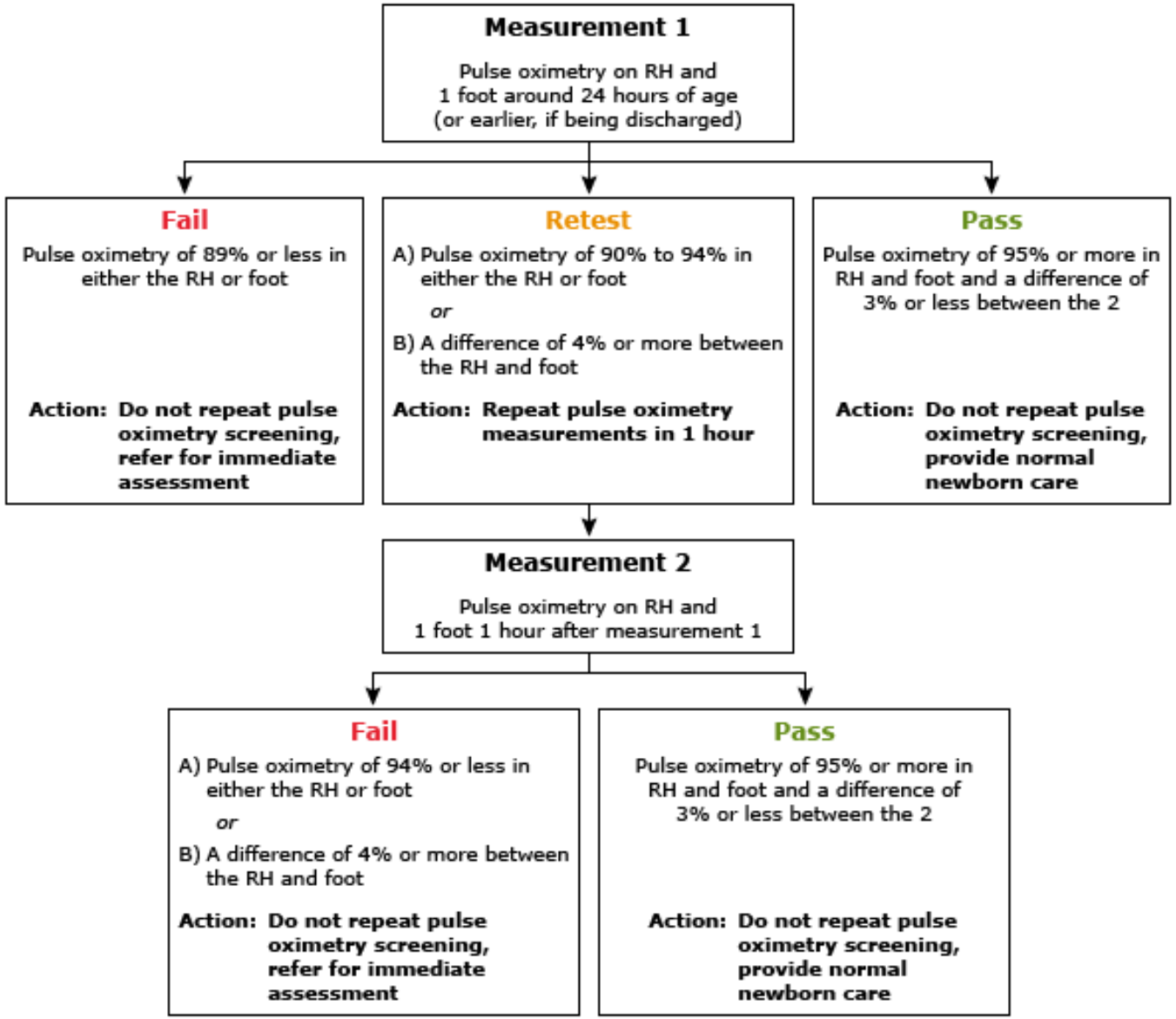
"FAILING" THE SCREEN

- Oxygen saturation (**SpO_2**) measurement **<90 percent** in **either extremity**

- **SpO_2** measurement **90 to 94 percent** in both **the right hand and** a **lower extremity** on two to three measurements, each separated by one hour

- **SpO_2 difference ≥4 percent** between the upper and lower extremities on two to three measurements, each separated by one hour

Modified algorithm for critical congenital heart disease screening with pulse oximetry



ASSESSMENT OF NEWBORNS WITH POSITIVE AND NEGATIVE SCREENS

positive screens:

- Evaluation to identify the cause of hypoxemia "Approach to cyanosis in the newborn“
- **Echocardiography** for evaluation of critical CHD if a noncardiac cause of the hypoxemia cannot be identified
- Evaluation of the baby with low SpO_2 using other means (eg, chest radiograph, blood work) should not be delayed while awaiting an echocardiogram.

NEGATIVE SCREEN:

- Clinically well newborns without signs concerning possible CHD (eg, cardiac murmur, weak femoral pulses) do not require additional evaluation
- However, universal newborn POS may miss as many cases of critical CHD as it detects
- POS cannot "rule out" the presence of critical CHD
- POS will not detect noncritical CHD lesions (eg, aortic stenosis, large atrial or ventricular defects)
- If there is clinical suspicion for CHD, additional evaluation should be pursued even in the setting of a normal pulse oximetry result.

Thank you for your attention