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A 3-hour-old term infant has cyanosis, no cardiac murmur, tachypnea, and no retractions. Pulse oximetry reveals an oxygen saturation of 60% in the right hand and 75% in the right foot.

Of the following, the MOST likely cause of the cyanosis is

1	group B streptococcal sepsis
2	persistent fetal circulation
3	pulmonary valve atresia
4	tetralogy of Fallot
5	transposition of the great vessels

You selected 2, the correct answer is 5.

The absence of a cardiac murmur does not exclude serious cyanotic congenital heart disease. Abnormal murmurs result from high blood flow velocities causing turbulent blood flow, which is produced when blood flows across an obstruction, such as with valvular stenosis. Flow from a higher-pressure chamber or vessel to a lower-pressure chamber or vessel through a restrictive communication also causes high-velocity, turbulent blood flow.

Transposition of the great arteries and pulmonary atresia are two types of congenital heart diseases in which there are no abnormal murmurs. With transposed great arteries, blood flow from the right ventricle to the aorta and flow from the left ventricle to the pulmonary artery are unobstructed. In pulmonary atresia, there is no flow across the right ventricular outflow tract, which would be the case in pulmonary stenosis. Both of these congenital lesions can result in severe cyanosis in the newborn. The findings on physical examination that suggest cardiac disease may be very subtle and may include a single second heart sound of increased intensity and an abnormally active precordial impulse to palpation. The ductus arteriosus usually is patent, but it does not result in a cardiac murmur because the pressure in the pulmonary artery is almost the same as that in the aorta when affected infants present with cyanosis.

Some infants who have transposition of the great vessels will have early pulmonary hypertension, with shunting of pulmonary arterial blood into the descending aorta across a patent ductus arteriosus. Because the pulmonary artery carries oxygenated blood from the left ventricle, the ductal shunting results in reverse differential cyanosis. In this type of cyanosis, oximetry values measured in the feet are consistently higher than the preductal oximetry readings from the right hand, as described for the infant in the vignette. Not all cyanotic infants who have transposition of the great vessels will have reverse differential cyanosis, but its presence makes the diagnosis extremely likely. In contrast, although pulmonary atresia can mimic transposition with cyanosis, a single second heart sound, and no cardiac murmur, ductal shunting in either direction will not cause reverse differential cyanosis.

Primary pulmonary hypertension, sometimes called **persistent fetal circulation**

(PFC), also causes cyanosis in newborns who do not have congenital heart disease. Severely increased pulmonary vascular resistance results in inadequate pulmonary blood flow and in right-to-left shunting of deoxygenated pulmonary arterial blood into the descending aorta through the open ductus arteriosus and from the right atrium to the left atrium through a patent foramen ovale.

PFC may follow perinatal asphyxia or significant meconium aspiration at the time of delivery. It also may occur in newborns who have sepsis, such as with early-onset group B streptococcal infection. PFC may occur in apparently well term infants discovered to have cyanosis in the newborn nursery after an uneventful delivery. As with the cyanotic infant who has transposed great vessels or pulmonary atresia, there may be an abnormal second heart sound and precordial impulse, in this case due to pulmonary and right ventricular hypertension. Ductal patency in these infants also results in no murmur because the pulmonary artery pressure is essentially the same as the aortic pressure. If there is significant shunting of pulmonary arterial blood into the descending aorta across a patent arterial duct, differential cyanosis will occur. Pulse oximetry values will be lower in the feet than preductal oximetry values measured in the right hand. This may suggest that the cause of cyanosis is isolated pulmonary hypertension rather than congenital heart disease. Nevertheless, any infant who has cyanosis and is suspected of having PFC must undergo echocardiography to exclude cyanotic congenital heart disease.

Group B streptococcal sepsis and PFC without obvious severe meconium aspiration can mimic transposition of the great vessels in clinical presentation, but reverse differential cyanosis will not be present. If there is an oximetry difference, postductal oxygen saturation measurements will be lower.

Infants who have **tetralogy of Fallot** almost always have a loud murmur and no obvious cyanosis in the early neonatal period. This is because the degree of infundibular pulmonic stenosis present in the right ventricular outflow tract usually is not severe enough to result in significant right-to-left shunting through the ventricular septal defect. Normal pulmonary blood flow through the stenotic outflow causes a loud murmur. In the infrequent case of tetralogy of Fallot that also involves pulmonary atresia, the clinical presentation may include cyanosis and no appreciable murmur, but reverse differential cyanosis will not be present.

References:

Abman SH. Abnormal vasoreactivity in the pathophysiology of persistent pulmonary hypertension of the newborn. Pediatr Rev. 1999;20:e103-e109. Available at: http://pedsinreview.aapjournals.org/cgi/content/full/20/11/e103

Kinsella JP, Neish SR, Abman S, Wolfe RR. Therapy for pulmonary hypertension. In: Garson A Jr, Bricker JT, Fisher DJ, Neish SR, eds. The Science and Practice of Pediatric Cardiology. 2nd ed. Baltimore, Md: Williams & Wilkins; 1998:2345-2366

Neches WH, Park SC, Ettedgui JA. Transposition of the great arteries. In: Garson A Jr, Bricker JT, Fisher DJ, Neish SR, eds. The Science and Practice of Pediatric Cardiology. 2nd ed. Baltimore, Md: Williams & Wilkins; 1998:1463-1504

Tingelstad J. Consultation with the specialist: nonrespiratory cyanosis. Pediatr Rev. 1999;20:350-352

Content Specification(s):

Understand the pathophysiology, recognize the clinical, laboratory, and radiographic features, and formulate a differential diagnosis of a cyanotic neonate

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An infant is delivered by emergent cesarean section because of fetal distress from acute placental abruption. The Apgar scores are 1 and 3 at 1 and 5 minutes, respectively. The cord pH is 6.98, and the base deficit is 20 mEq/L. The infant is resuscitated and admitted to the neonatal intensive care unit for observation of potential injury to the brain and other organs.

Of the following, the MOST frequent complication of perinatal asphyxia is

1	hepatic cholestasis
2	myocardial dysfunction
3	necrotizing enterocolitis
4	pulmonary hemorrhage
5	renal failure

You selected 4, the correct answer is 5.

The clinical history, cord blood acidemia, and low Apgar scores reported for the infant in the vignette suggest the diagnosis of perinatal asphyxia. In addition to the brain, the organ most frequently affected by perinatal asphyxia is the kidney. Renal failure occurs in 40% to 70% of cases. The clinical spectrum varies from oliguria to azotemia, depending on the severity of the insult. Monitoring of urine output, serum electrolytes and creatinine, and urinalysis for hematuria and myoglobinuria are important in the evaluation and management of affected infants.

Hepatic cholestasis occurs in approximately 10% of cases of perinatal asphyxia. Liver injury from perinatal asphyxia results in an increase in liver enzymes, hypoproteinemia, and abnormal liver-dependent coagulation factors. A rise in liver enzyme levels indicates hepatocyte necrosis or dysfunction. Hypoproteinemia is caused by impaired hepatic albumin production. Consumption of coagulation factors, thrombocytopenia from decreased platelet production or increased consumption, platelet dysfunction, and vascular endothelial damage are consequences of perinatal asphyxia that result in disseminated intravascular coagulopathy.

Myocardial dysfunction occurs in approximately 30% of cases of perinatal asphyxia. Early right heart failure with tricuspid regurgitation or global heart failure with cardiogenic shock characterizes the myocardial dysfunction. The dysfunction can be evaluated with a chest radiograph for cardiomegaly, arterial blood sampling for metabolic acidosis, and electrocardiography for evidence of myocardial hypoxia. An echocardiogram is useful for evaluating contractility of the heart, valvular incompetence, cardiac shunts, filling pressures, and volume status.

Necrotizing enterocolitis from hypoxic-ischemic injury of the gut is a potential complication of perinatal asphyxia. The onset of necrotizing enterocolitis is typically delayed until after enteral feedings are initiated. Accordingly, enteral feedings usually are delayed for several days after the initial injury to ensure recovery of the gut.

Pulmonary hemorrhage is an infrequent complication of perinatal asphyxia. Pulmonary edema from left heart failure, disruption of the pulmonary capillary bed from hypoxia, and coagulopathy associated with perinatal asphyxia contribute to

pulmonary hemorrhage.

References:

Piazza AJ. Postasphyxial management of the newborn. ***Clin Perinatol***. 1999;26:749-765 Abstract

Rivkin MJ, Volpe JJ. Asphyxia and brain injury. In: Spitzer AR, ed. ***Intensive Care of the Fetus and Neonate***. St. Louis, Mo: Mosby; 1996:685-695

Content Specification(s):

Understand the pathophysiology, recognize the clinical, laboratory, and radiographic features, and formulate a differential diagnosis of a cyanotic neonate

PREVIOUS NEXT

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Please remember that you must answer all 10 of the questions in order to claim CME credit for this month.

A term newborn has tachypnea, rales, tachycardia, audible gallop, and diminished arm and leg pulses. Echocardiography shows enlargement of both ventricular chambers, with good systolic function and no congenital heart disease.

Of the following, the MOST likely diagnosis is

1	carnitine deficiency
2	hyperthyroidism
3	hypoglycemia
4	intracranial arteriovenous malformation
5	pheochromocytoma

You selected 3, the correct answer is 4.

Congenital arteriovenous malformations are unusual vascular malformations that allow excessive shunting of systemic arterial blood to the systemic venous system, bypassing the vascular capillary bed. If the malformation is significant, the work of the heart is increased markedly by the increased return to the right heart. Both the normal systemic venous return and the excess oxygenated blood that bypassed the capillary bed in the organ where the malformation is located return to the right heart. Pulmonary blood flow, therefore, is excessive, resulting in pulmonary vascular congestion and tachypnea. This excess flow returns to the left ventricle, which becomes enlarged from the excess preload. Affected infants have signs and symptoms of congestive heart failure but no evidence of congenital heart disease on echocardiography. In the early stages of congestive heart failure, left ventricular function will be normal; in latter stages, left ventricular function may decrease, but in many cases function is preserved.

The most common sites of significant systemic arteriovenous malformation in neonates are the liver and the cerebral vasculature. Abnormal bruits over the head or liver may occur in some, but not all infants who have systemic arteriovenous malformation. When the vascular shunt is in the head, the systemic output of the aorta is "stolen" up the carotid artery, and downstream pulses in the arms and legs may be diminished, as described for the newborn in the vignette. The left ventricular output is high, but the cardiac output to the body downstream of the head is diminished.

Preserved systolic function in the presence of clinical congestive heart failure is not consistent with a dilated cardiomyopathy due to a metabolic defect, such as carnitine deficiency.

Cardiomegaly and signs of congestive heart failure may occur in newborns who have significant hypoglycemia. In some cases, echocardiography reveals that the cardiomegaly is due to a hypertrophic cardiomyopathy that has developed in the fetus in response to maternal hyperglycemia. Fetal hyperinsulinemia appears to

contribute to the abnormal hypertrophy of the heart and is responsible for the neonatal hypoglycemia. Postnatally this form of hypertrophic cardiomyopathy resolves as insulin levels decrease in the infant. The lack of severe left ventricular hypertrophy in the infant described in the vignette makes hypoglycemia unlikely. Some infants who have neonatal hypoglycemia without transient hypertrophic cardiomyopathy have poor systolic function that improves with effective treatment of the hypoglycemia.

Hyperthyroidism can cause a high-output form of neonatal heart failure. Late findings may include diminished ventricular function, but increased systolic performance and chamber enlargement would be evident before this occurs. In the early stages of hyperthyroid-associated high-output heart failure, pulses are brisk rather than diminished.

Pheochromocytoma is extremely unlikely in a newborn. Severe, often paroxysmal hypertension is the hallmark finding in patients who have pheochromocytomas, which are adrenal tissue tumors that secrete excessive catecholamine and catecholamine precursors. Symptomatic congestive heart failure can occur in newborns who have severe hypertension, but this usually is due to etiologies other than pheochromocytoma. One such cause is renal arterial stenosis or occlusion after umbilical artery catheter use. When neonatal hypertension causes heart failure, the cardiac systolic performance is poor. Pheochromocytoma is not a likely possibility for the infant in the vignette.

References:

Heymann MA. Systemic arteriovenous fistula. In: Rudolph AM, Hoffman JIE, Rudolph CD, eds. Rudolph's Pediatrics. 20th ed. Stamford, Conn: Appleton & Lange; 1996:1465

McMahon WS. Arteriovenous fistulae. In: Garson A Jr, Bricker JT, Fisher DJ, Neish SR, eds. The Science and Practice of Pediatric Cardiology. 2nd ed. Baltimore, Md: Williams & Wilkins; 1998:1677-1690

Content Specification(s):

Understand the pathophysiology, recognize the clinical, laboratory, and radiographic features, and formulate a differential diagnosis of an acyanotic neonate with a left-to-right shunt lesion

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A 2-day-old 4.1-kg male infant is referred to you for evaluation of tachypnea that began 15 hours after birth. Pregnancy, labor, and vaginal delivery were uncomplicated. The respiratory rate is 75 breaths/min, but there are no retractions or nasal flaring. The infant appears pink, and the oxygen saturation is 97% in both upper and lower extremities. Physical examination reveals a grade II/VI systolic murmur, mild hepatomegaly, equal pulses, bobbing of the head, petechiae, and irritability. When he is awake, he can fix and follow movement, and muscle tone appears normal. The abdomen is slightly distended but soft and has active bowel sounds. You place an umbilical venous line and confirm that it is located just into the right atrium. Results of laboratory studies are: platelet count, 44 × 10^3/mcL (44 × 10^9/L); hematocrit, 31% (0.31); white blood cell count, 8 ×10^3/mcL (8 × 10^9/L) with 38% polymorphonuclear lymphocytes and 62% lymphocytes. Arterial blood gases with an Fio_2 of 1.0 by mask are: pH, 7.33; Pco_2, 36 mm Hg; Po_2, 240 mm Hg; base excess, -1 mEq/L. Umbilical venous blood gases with an Fio_2 of 1.0 by mask are: pH, 7.28; Pco_2, 41 mm Hg; Po_2, 190 mm Hg; base excess, -3 mEq/L.

Of the following, the MOST likely diagnosis for this infant is:

1	meconium aspiration syndrome
2	subgaleal hemorrhage
3	transient tachypnea of the newborn
4	transposition of great arteries
5	vein of Galen aneurysm

You selected 2, the correct answer is 5.

Approximately 40% to 60% of vein of Galen aneurysms present during the neonatal period. Anatomically, the aneurysm involves the persistent embryologic median prosencephalic vein of Markowski, which lies immediately anterior to the vein of Galen. Despite this finding, the term "vein of Galen" malformation is entrenched in the literature and applied to this entity. The most common feeding arteries are the posterior choroidal, anterior cerebral, middle cerebral, anterior choroidal, and posterior cerebral. Persistence of the transient venous structure called the falcine sinus often accompanies this malformation and, with the straight sinus, serves to drain the aneurysm. Neurologic effects frequently are associated with ischemic infarction, hemorrhage, or mass effect on brain structures. Congestive heart failure develops to compensate for the large proportion of cardiac output that may flow through the aneurysm. In fact, approximately 95% of affected neonates present with congestive heart failure; the remainder present with hydrocephalus or intracranial hemorrhage. Physical findings include bounding carotid pulses that may cause bobbing of the head, cranial bruit, and signs of congestive heart failure, as reported for the infant in the vignette. Older infants usually present with seizures and other neurologic findings. Among neonatal patients who survive, developmental delays, abnormal neurologic signs, and seizures occur due to mass effect and intracranial hemorrhage. The diagnosis is established in neonates who have unexplained high-output heart failure with head ultrasonography, computed tomography, or preferentially, magnetic resonance imaging. Thrombocytopenia and disseminated intravascular coagulation may result from consumption of platelets and clotting factors within the aneurysm. Right atrial oxygenation may be significantly elevated

due to the return of arterial blood that has flowed through the aneurysm without passing through capillary beds where oxygen is consumed. Improved embolization techniques have resulted in increasing survival rates, but the prognosis remains guarded, with only 40% to 65% of survivors having favorable outcomes.

Meconium aspiration often presents with hypoxic respiratory failure and pulmonary hypertension. Although congestive cardiomyopathy may accompany meconium aspiration, hypotension usually is due to poor myocardial function, not a hyperdynamic high-output state. The absence of meconium, complicated delivery, hypoxic respiratory failure, and preductal/postductal oxygenation difference for the infant described in the vignette argues against meconium aspiration complicated by pulmonary hypertension. Right atrial oxygenation is not significantly increased above venous levels in meconium aspiration.

Subgaleal hemorrhage describes bleeding into the aponeurosis covering the scalp, which lies between the subcutaneous tissue and skull bone periosteum. Blood in this aponeurosis may spread beneath the entire scalp and subcutaneous tissues of the neck and present as a firm, fluctuant mass that increases in size after birth. A large amount of blood loss and consumptive coagulopathy may occur, which can result in respiratory distress, hypotension, shock, and disseminated intravascular coagulation. Progression can be rapid and result in death unless recognized and treated early. Hypotension and shock are due to hypovolemia rather than heart failure unless the shock is advanced; high-output cardiac failure is not present. Hyperbilirubinemia may complicate the recovery phase. Right atrial oxygenation is not increased, and neurologic signs become apparent only if associated with intracranial bleeding or advanced stages of shock.

Transient tachypnea of the newborn most often presents immediately after birth rather than during subsequent hours and days. Cardiomegaly, heart murmur, and increased vascular markings on chest radiographs may suggest congestive heart failure, although blood pressure and pulse pressure are typically normal. Bounding pulses usually are not found with transient tachypnea. Right atrial oxygenation, as with meconium aspiration, is not increased significantly above venous levels.

Transposition of great arteries is a cyanotic congenital heart lesion. The usual presentation is cyanosis. High-output congestive heart failure is unusual. If coarctation of the aorta accompanies transposition of great arteries, full pulses may be present in the upper extremities and neck, similar to that found with high-output congestive heart failure. However, cyanosis and lack of elevated right atrial oxygenation reported for the infant in the vignette argue against transposition.

References:

Miller MJ, Fanaroff AA, Martin RJ. Respiratory disorders in preterm and term infants. In: Fanaroff AA, Martin RJ, eds. ***Neonatal-Perinatal Medicine***. 7th ed. St. Louis, Mo: Mosby; 2002:1025-1028, 1030-1031

Volpe JJ. Brain tumors and vein of Galen malformations. In: ***Neurology of the Newborn***. 4th ed. Philadelphia, Pa: WB Saunders Co; 2001:849-854

Volpe JJ. Injuries of extracranial, cranial, intracranial, spinal cord and peripheral nervous system structures. In: ***Neurology of the Newborn***. 4th ed. Philadelphia, Pa: WB Saunders Co; 2001:813-815

Zahka KG, Patel CR. Congenital defects. In: Fanaroff AA, Martin RJ, eds. ***Neonatal-Perinatal Medicine***. 7th ed. St. Louis, Mo: Mosby; 2002:1120-1122

Content Specifications:

Understand the clinical features and evaluation of arteriovenous malformations

Understand the management, complications of management, and outcome of arteriovenous malformations

Understand the diagnosis, clinical and radiographic features of extracranial hemorrhage, including cephalohematoma and subgaleal hemorrhage

PREVIOUS NEXT

You are viewing the autopsy of a term male infant who died six days after birth. He was admitted for cyanosis secondary to persistent pulmonary hypertension. The infant was born by emergent cesarean section for severe fetal bradycardia; amniotic fluid was meconium-stained. Cyanosis at birth was treated with 100% oxygen, high-frequency oscillation, inhaled nitric oxide and sedation. Pre- and postductal SaO_2s were 76%. Chest radiograph showed a mildly enlarged heart and dark lung fields. Echocardiogram two hours after birth was reported to show right-to-left shunting at the atrial level, bowing of the ventricular septum into the left ventricle, right ventricular hypertrophy and tricuspid valve jet indicative of suprasystemic pulmonary arterial pressure. The study was abbreviated because of worsening hypoxemia (SaO_2, 63%).

Transfer arrangements were made for extracorporeal membrane oxygenation (ECMO), which was initiated emergently upon arrival in your neonatal intensive care unit. Within minutes, perfusion worsened, pulse pressure narrowed to less than 5 torr and blood pressure measured in an umbilical arterial catheter fell to 31 mmHg. Repeat echocardiogram indicated poor biventricular function and findings not visualized previously. The infant's parents requested withdrawal of ECMO, and the infant died within minutes.

Gross inspection of the heart revealed a small hypertrophied right ventricle, thickened and nodular coronary arteries, dimples on the epicardial surface (consistent with ventriculocoronary sinusoidal connections), and absent coronary artery origins from the proximal aorta.

Of the following, the autopsy diagnosis MOST likely to be confirmed in this infant is:

1	pulmonary atresia with intact ventricular septum
2	total anomalous pulmonary venous return
3	transposition of the great arteries
4	tricuspid atresia with ventricular septal defect
5	truncus arteriosus

You selected 5, the correct answer is 1.

The infant in the vignette is most likely to have pulmonary atresia with intact ventricular septum (PA-IVS). This condition accounts for only 1% to 3% of all congenital heart defects, although it is one of the more frequent defects that presents as cyanosis in neonates. A variable spectrum of findings is included in this disorder, with two predominant pathophysiologic patterns categorized as either Type I or Type II. Type I pulmonary atresia with intact septum is characterized by the association of abnormal ventriculocoronary sinusoidal connections, abnormal coronary artery anatomy, atretic pulmonary valve, competent tricuspid valve, small hypertrophied right ventricle with suprasystemic pressure and, in some cases, right ventricular-dependent coronary artery circulation. Type II is characterized by anomalous tricuspid valve and insufficiency, retrograde blood flow through the right atrium and atrial septal defect, and a normal or dilated, thinned, low-pressure right ventricle. Type II may be associated with hydrops fetalis and fetal loss when severe tricuspid insufficiency is present in utero.

Type I PA-IVS is anticipated in the repeat echocardiogram and autopsy of the infant in the vignette. In Type I, myocardial dysfunction or infarction occurs due to venous blood supplying an abnormal coronary circulation; this is worsened with unloading of the right ventricular pressure head that drives coronary perfusion. Right ventricular pressure was acutely decreased during initiation of ECMO in the infant in this vignette. This coronary artery steal phenomenon is better understood by tracing the circulation of venous blood from the hypertrophic blind right

ventricle in patients with Type I PA-IVS. Suprasytemic pressure in the blind right ventricle functions to force venous blood into intramyocardial sinusoids that anastomose with the coronary artery circulation. The high blood flow through the coronary arteries induces morphologic changes characterized by endothelial irregularity, stenosis and obstruction. Coronary artery blood then flows into the coronary veins, coronary sinus and right atrium. From the right atrium, venous blood flows through the anomalous tricuspid valve back into the hypertrophic right ventricle thereby completing a circular pattern of blood flow. This pattern does not include flow through the lung. The result is desaturated blood flowing through the coronary circulation. If the anomalous coronary circulation is only perfused by right ventriculocoronary sinusoids and not supplemented from a source of oxygenated blood (left to right shunt through an atrial septal defect or patent foramen ovale), a high risk for myocardial ischemia exists. This ischemic risk is increased because of coronary artery stenosis and obstruction.

In the infant in the vignette, the cause for cyanosis was thought to be persistent pulmonary hypertension of the newborn due to a history of fetal distress, meconium-stained amniotic fluid, cyanosis and suggestive echocardiographic evidence. However, the infant developed severe myocardial dysfunction soon after beginning venoarterial extracorporeal membrane oxygenation (VA ECMO). Myocardial dysfunction after initiation of VA ECMO most often is due to myocardial stun, the mechanism of which is unknown. Myocardial stun is also more common during venoarterial rather than venovenous cardiopulmonary bypass. The mechanism for the rapid onset of myocardial dysfunction in the infant in this vignette with PA-IVS is an acute reduction in driving pressure and blood flow into the right ventricular-dependent coronary circulation during ECMO initiation. This acute decrease in coronary blood flow in a coronary circulation already compromised by perfusion with poorly saturated venous blood precipitated severe myocardial dysfunction; in the infant in this vignette, the ischemia was considered lethal, and additional cardiovascular interventions were not undertaken.

This case is unusual but demonstrates the value of echocardiography before ECMO initiation. Although the clinical history and abbreviated initial echocardiogram suggested persistent pulmonary hypertension of the newborn, persistent low oxygen saturations and unresponsiveness to interventions, including ECMO, indicated that congenital heart disease was possible. ECMO also is used to stabilize some critically unstable infants with congenital heart diseases before surgical treatment. Most of these cardiac anomalies do not have right ventricular-dependent coronary blood flow so are not at high risk for myocardial ischemia when right ventricular pressure is reduced. Type I PA-IVS is also an uncommon form of congenital heart disease as is a right ventricular-dependent coronary circulation. The odds of this condition being present in the infant in this vignette are low. Although valuable, echocardiography may not identify ventriculocoronary sinusoidal connections and right ventricular-dependent coronary flow unless the sinusoidal connections are large. Cardiac catheterization often is required to establish this diagnosis as well as the coronary anatomy. The infant in this vignette was in extremis on arrival, so ECMO was initiated emergently before repeat echocardiography and catheterization could be performed.

Total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia with ventricular septal defect and truncus arteriosus are congenital heart lesions that most often present as cyanosis during the neonatal period. None of these disorders is associated with right ventriculocoronary sinusoidal connections, coronary artery stenosis and obstruction and right ventricular-dependent coronary circulation. Therefore, none of these would be found on echocardiography or autopsy in the infant in this vignette.

An example of PA-IVS , demonstrated by right ventricular injection of dye during a cardiac catheterization of a child with pulmonary atresia and intact ventricular septum, is demonstrated on the video clip. Pause or slow the clip to notice retrograde filling of coronary vessels immediately after right ventricular injection in the lower right quadrant at the beginning of the clip. During the remainder of the clip, coronary vessels continue to be filled from the right ventricular-coronary connections (sinusoids in the right ventricular wall).

References:

Baschat AA, Love JC, Stewart PA, Bembruch U, Harman CR. Prenatal diagnosis of

ventriculocoronary fistula. *Ultrasound. Obstet Gynecol.* 2001;18:39-43

Freedom RM, Nykanen DG. Pulmonary atresia and intact ventricular septum. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:845-863

Joffe G, Izquierdo LA, Del Valle GO, et al. Pulmonary valve atresia with intact ventricular septum, Type 1. Available at http://www.thetetus.net/page.php?id=62. Accessed April 8, 2005.

*Videoclip compliments of Robert Darragh, M.D., Indiana University School of Medicine.

Content Specifications:

Plan appropriate management for a neonate with a right-sided cardiac lesion and understand the potential adverse effects of specific therapeutic approaches

Understand the pathophysiology, including genetics, of a neonate with a right-sided cardiac lesion

Recognize the lab and radiographic findings of an infant with a right-sided cardiac lesion

PREVIOUS NEXT

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A 6-week-old infant, whose birthweight was 984 g and estimated gestational age at birth was 28 weeks, has a systolic blood pressure of 98 mm Hg and a diastolic blood pressure of 60 mm Hg. These measurements were obtained by oscillometric method, with the right arm, using an appropriately sized cuff, and while the infant was asleep. The neonatal history is significant for initial respiratory distress managed with brief mechanical ventilation and umbilical arterial catheterization, sedation with fentanyl during the first 10 days after birth, and a course of caffeine for apnea during the second and third weeks after birth. The infant is receiving full enteral feedings, is maintaining normal oxygen saturations in room air, and has normal physical examination findings, including vital signs.

Of the following, the diagnostic test MOST likely to confirm the cause of hypertension in this infant is:

1	chest radiography
2	echocardiography
3	head computed tomography
4	renal ultrasonography
5	thyroid radionuclide scan

You selected 1, the correct answer is 4.

The infant described in the vignette has systemic hypertension, which is defined as systolic and/or diastolic blood pressure equal to or greater than the 95th percentile adjusted for postmenstrual age. The oscillometric method of blood pressure measurement is based on the oscillation of the arterial wall as pulsatile blood flows through the artery during automatic deflation of the cuff after its initial inflation. The systolic blood pressure is identified at a point at which the amplitude of oscillations increases rapidly; the diastolic blood pressure is identified at a point at which the amplitude of oscillations decreases rapidly. The point of greatest average oscillation identifies the mean blood pressure, which can be estimated by the following equation: mean BP = diastolic BP + 1/3 (systolic BP - diastolic BP). For accuracy, the blood pressure measurements in neonates should be obtained on at least three separate occasions, using a cuff that has a cuff-width/arm-circumference ratio between 0.45 and 0.55, and while the infant is asleep. Consistent use of the extremity is important to avoid differences in measurements between the arm and the leg.

The causes of neonatal hypertension can be summarized using a mnemonic shown in the table. The most common cause of neonatal hypertension is related to renovascular and renal parenchymal disease. The renovascular cause commonly involves thromboembolism affecting either the aorta or the renal arteries associated with umbilical arterial catheterization. The incidence of thrombosis related to an umbilical arterial catheter may be influenced by several factors, including the size and type of catheter, the duration of catheter placement, the use of heparin through the catheter, the location of the catheter tip in the aorta, and the practice of infusing medications, blood products, hyperosmolar solutions, and calcium through the catheter. The mechanism of hypertension is believed to be disruption of vascular endothelium by the catheter, embolization of the renal artery, renal hypoperfusion, and release of renin. Other renovascular causes of neonatal hypertension include renal artery stenosis from fibromuscular dysplasia, renal vein thrombosis from polycythemia and hyperviscosity, and renal vascular abnormalities from metabolic and infectious causes.

Congenital renal parenchymal diseases that can result in neonatal hypertension include

polycystic kidney disease, multicystic/dysplastic/hypoplastic kidney, and obstructive uropathy. Acquired diseases that can be related to neonatal hypertension include acute tubular necrosis, renal cortical necrosis, and interstitial nephritis. The mechanism of hypertension in such instances is unclear, although the renin-angiotensin system has been implicated. The best modality for diagnosing renal parenchymal disease is renal ultrasonography. Assessment of renal blood flow and function by Doppler sonography, plasma renin activity, and renal radionuclide scan are useful in establishing the diagnosis of renovascular hypertension.

Neonatal hypertension is about two- to nine-fold more common among preterm infants who have bronchopulmonary dysplasia (BPD) compared with those who do not have lung disease. The incidence of neonatal hypertension varies with the severity of lung disease. The mechanism of hypertension in BPD remains unconfirmed. It may be related to the effects of chronic hypoxemia on peripheral vascular resistance; medications such as dexamethasone, xanthines, and bronchodilators; nephrocalcinosis from chronic furosemide therapy; or cor pulmonale with associated sodium retention. Although the infant described in the vignette was at risk for the development of BPD because of prematurity and initial lung disease, the lack of need for supplemental oxygen at the postmenstrual age of 34 weeks precludes that diagnosis. A chest radiograph, therefore, is unlikely to elucidate the cause of hypertension in this infant.

Congenital heart disease, specifically coarctation of the aorta with intact ventricular septum, is a cause of neonatal hypertension. The blood pressure is elevated moderately in the arms, and the brachial and radial pulses are readily palpable. Conversely, the blood pressure is reduced in the legs, and the femoral and dorsalis pedis pulses may be weak or absent. The infant usually becomes symptomatic within the first week or two after birth, a time coinciding with the spontaneous closure of the ductus arteriosus. Restlessness, irritability, and poor feeding are common, as are tachycardia and tachypnea. The infant may become severely compromised, with manifestations of lethargy, rales, cardiomegaly, hepatomegaly, poor perfusion, and metabolic acidosis. The absence of such symptoms and signs, coupled with a relatively advanced age at the time of diagnosis of hypertension, makes congenital heart disease unlikely in the infant in the vignette. Echocardiography, therefore, may not reveal the cause of hypertension.

Neurologic causes of neonatal hypertension include seizures, intracranial hemorrhage, intracranial hypertension, pain, and withdrawal from prolonged sedation or analgesia. The hypertension tends to be episodic and to manifest early in life when the infant is unstable during transition from intrauterine to extrauterine life. Although the infant described in the vignette is at risk for the development of germinal matrix hemorrhage because of prematurity and initial sickness, systemic hypertension is a rare primary manifestation of such hemorrhage. The brief use of sedation early in life also makes withdrawal from sedation or analgesia unlikely as a cause of hypertension in this infant. Head computed tomography, therefore, may not yield information pertinent to the cause of hypertension.

Neonatal hypertension due to endocrine disorders is unusual. The disorders include congenital adrenal hyperplasia, hyperaldosteronism, Cushing syndrome, and hyperthyroidism. Pheochromocytoma is an extremely rare cause of hypertension in neonates. Unless suspected on the basis of newborn metabolic screening, fluid-electrolyte abnormalities, or other clinical manifestations, evaluation for an endocrine disorder is not the first diagnostic measure to establish the cause of hypertension in a neonate. Thyroid radionuclide scan, therefore, is not warranted.

References:

Abman SH, Warady BA, Lum GM, Koops BL. Systemic hypertension in infants with bronchopulmonary dysplasia. J Pediatr. 1984;104:929-931

Alagappan A, Malloy MH. Systemic hypertension in very low-birth weight infants with bronchopulmonary dysplasia: incidence and risk factors. Am J Perinatol. 1998;15:3-8

Boo N, Wong N, Zulkifli S, Lye M. Risk factors associated with umbilical vascular catheter-associated thrombosis in newborn infants. J Paediatr Child Health. 1999;35:460-465

Flynn JT. Neonatal hypertension: diagnosis and management. Pediatr Nephrol. 2000;14:332-341

Jones JE, Jose PA. Neonatal blood pressure regulation. Semin Perinatol. 2004;28:141-148

Rudolph AM. Aortic arch obstruction. In: Congenital Diseases of the Heart: Clinical-Physiological Considerations. 2nd ed. Armonk, NY, Futura Publishing Company; 2001:367-412

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. J Perinatol. 1995;15:470-479

Content Specification(s):

Know how to diagnose and evaluate an infant with hypertension
Know the most common predisposing factors to hypertension in early infancy

PREVIOUS NEXT

Table. Shenai Mnemonic for Causes of Neonatal Hypertension

H:	Heart disease (coarctation, patent ductus arteriosus)
Y:	Yet undetermined (idiopathic)
P:	Pulmonary disease (bronchopulmonary dysplasia)
E:	Endocrine disorder (congenital adrenal hyperplasia, adrenal hemorrhage, hyperaldosteronism, hyperthyroidism, Cushing disease)
R:	Renal disease (renovascular thromboembolism, polycystic/multicystic/dysplastic/hypoplastic kidney, obstructive uropathy, acute tubular necrosis)
T:	Total parenteral nutrition (high calcium, high salt)
E:	Extracorporeal membrane oxygenation
N:	Neoplasm (Wilms tumor, mesoblastic nephroma, neuroblastoma, pheochromocytoma)
S:	Surgery (abdominal wall defect repair)
I:	Intoxication (dexamethasone, xanthines, adrenergic drugs, phenylephrine eye drops, cocaine)
O:	Opioid withdrawal (withdrawal from any sedation)
N:	Neurologic cause (seizures, pain, intracranial hemorrhage, intracranial hypertension)

You are asked to see a 10-day-old male term large-for-gestational age infant of a diabetic mother. Delivery was complicated by shoulder dystocia and perinatal depression, with Apgar scores of 1 and 6 at 1 and 5 minutes, respectively. The infant's early clinical course was complicated by respiratory failure, hypotension, hypoglycemia, and anuria. These problems have been resolved. The infant presents now with continuing indirect hyperbilirubinemia despite phototherapy. He also has persistent hypertension at rest, with systolic blood pressures of 110 to 120 mm Hg. Direct Coombs test result is negative, and there is no evidence of hemolysis. White blood cell and platelet counts are normal. Hematocrit is 32% (0.32). Urinalysis findings are normal. Results of abdominal examination are normal. Abdominal ultrasonography, obtained to evaluate the hypertension, reveals a right suprarenal complex mass measuring 3x3 cm (Figure).

Of the following, the MOST likely diagnosis is

1	adrenal hemorrhage
2	horseshoe kidney
3	neuroblastoma
4	renal vein thrombosis
5	Wilms tumor

You selected 5, the correct answer is 1.

Adrenal hemorrhage has been found in 10% of infants at autopsy and is diagnosed in 2 per 1,000 live births. In most instances, it is found incidentally by noting adrenal calcifications on radiographic studies for other indications. The neonatal adrenal gland is predisposed to hemorrhage and trauma by virtue of its increased size and vascularity compared with adults. Risk factors for hemorrhage include birth trauma, macrosomia, breech delivery, infection, dystocia, hemorrhagic disorders, and asphyxia. In most cases, bleeding is unilateral and generally right sided (70%). In 5% to 8% of cases, it presents as severe bilateral bleeding. Ipsilateral renal vein thrombosis may occur with adrenal hemorrhage on the left because the left adrenal vein is a tributary of the left renal vein. Thrombus then may be propagated from one vessel to the other. Symptoms are related to the size and severity of bleeding, with most infants remaining asymptomatic. With larger hemorrhages, the infant may have unexplained persistent jaundice (11%), hypertension, and mild anemia. Classic symptoms with more extensive hemorrhage include fever, tachypnea, pallor, hypotensive shock, flank mass, poor feeding, hypoglycemia, coma, and seizures. If peritoneal extension occurs, a scrotal hematoma may be seen in males. Radiologic evaluation confirms the diagnosis. Mass displacement of the stomach and intestine may be seen on plain radiograph. Ultrasonography can document evolution of the hemorrhage from a solid hyperechoic clot to central liquefaction necrosis followed by cystlike anechoic fibrosis and calcification. Calcifications along the walls of the hemorrhage begin as early as 12 days after the insult, gradually increasing and contracting as the hemorrhage is absorbed. If the diagnosis is in question, serial ultrasonography over several weeks can document these changes and distinguish adrenal hemorrhage from other solid tumors. Magnetic resonance imaging (MRI) and radionuclide renal scans also may help differentiate atypical adrenal hemorrhages from renal lesions. Treatment is supportive, with volume replacement in severe hemorrhage. Surgery is indicated only rarely unless blood loss is severe and uncontrolled or peritoneal blood is present. Adrenocorticotropic hormone stimulation testing is recommended to evaluate adrenal function and cortisol response. The infant described in the vignette had multiple risk factors for adrenal hemorrhage at birth and demonstrates mild

symptoms with jaundice and hypertension. Additionally, the characteristics on ultrasonography are consistent with this diagnosis, showing central clot and surrounding liquefaction. No calcifications are seen yet.

Horseshoe kidney, ectopic kidney, and fused kidneys are abnormalities in the position of the kidney that typically are asymptomatic and have no long-term consequences unless they are associated with other anomalies. Horseshoe kidney occurs in 1 in 500 births, more frequently in Turner syndrome. It is the most typical type of renal fusion and one of the most common renal anomalies. Coexisting urinary tract anomalies must be ruled out. Ultrasonographic diagnosis shows the renal parenchyma in the abnormal location, lower than normal in the lumbar area, and often with abnormal associated vascular supply. Renal scan, intravenous pyelography, and MRI are adjunctive diagnostic studies that can be undertaken when the anatomy is in question. This patient's symptoms and ultrasonographic findings are not consistent with horseshoe kidney.

Neuroblastoma is the most common malignant tumor in neonates, with 20% presenting before 6 months of age. The tumor arises from neural crest cells, which migrate to form the adrenal medulla and sympathetic ganglia. Therefore, the tumor may be anywhere, but the primary locus in most cases is in the abdomen. Metastatic lesions may be a presenting feature, with spread to liver and skin most common. Other sites include bone marrow, bone, lung, and central nervous system. Neonatal neuroblastoma presents most commonly as liver enlargement alone (65%) followed by subcutaneous metastases (32%). Clinical symptoms include diarrhea, hypertension, tachycardia, myoclonus-opsoclonus, respiratory distress, jaundice, anemia, or symptoms related to the site of metastases. Urinary catecholamine levels are elevated. Approximately 95% of affected patients have increased urinary excretion of homovanillic acid and vanillylmandelic acid. Bone marrow biopsy and/or biopsy of the primary tumor confirm the diagnosis. The history for this infant and his normal liver size and lack of metastatic disease make neuroblastoma less likely.

Renal vein thrombosis is decreasing in incidence, probably due to better obstetric management. Approximately 60% to 75% of affected patients are infants younger than 1 month of age. Clots start in the small intrarenal veins after injury and are propagated distally toward the main renal vein and ultimately the inferior vena cava. Risk factors include dehydration, hyperviscocity, asphyxia, hypercoagulable states, diabetes, and indwelling catheters. The classic triad of symptoms is flank mass, hematuria, and thrombocytopenia, although they rarely are seen in the neonate. Hypotension may occur early in the course, with hypertension developing days or weeks later. The diagnosis is confirmed by ultrasonography and Doppler blood flow studies that show nephromegaly and thrombus. Radionuclide uptake on renal scan may be diminished or absent. Normal urinalysis results and platelet count in addition to the ultrasonographic findings make renal vein thrombosis unlikely in the infant described in the vignette.

Wilms tumor is the most common intra-abdominal tumor of childhood, but it rarely presents before 1 month of age; 80% of patients are diagnosed between 1 and 5 years of age. Generally, the initial presentation is an abdominal mass or enlargement. Extrarenal Wilms tumors are very rare and are believed to be associated with displaced metanephric tissue. Fifteen percent of Wilms tumors are associated with other anomalies or syndromes, and genes on the 11th and 16th chromosomes have been implicated. Approximately 5% to 10% of cases may be bilateral. Microscopic hematuria may be seen. Hypertension, sometimes seen in older infants and children, has not been found in neonates. On ultrasonography, the tumor appears as a smooth, well-delineated mass of uniform texture. Hemorrhage within the tumor is uncommon. This patient's age and history, hypertensive symptoms, and nature and location of the mass above the kidney make Wilms tumor unlikely.

References

Isaacs H. Neuroblastoma. In: *Tumors of the Fetus and Newborn*. Philadelphia, Pa: WB Saunders; 1997:130-149

Isaacs H. Renal tumors. *Tumors of the Fetus and Newborn*. Philadelphia, Pa: WB Saunders; 1997:244-277

Kaplan BS. Developmental abnormalities of the kidneys. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1272-1281

Loh ML, Katherine KM. Congenital malignant disorders. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1437-1470

Mangurten HH. Birth injuries. In: Fanaroff AA, Martin RJ, eds. *Neonatal -Perinatal Medicine*. 7th ed. St. Louis, Mo: Mosby; 2002:460-487

Silverman FN, Kuhn JP. Disorders of adrenal glands retroperitoneal and pelvic masses. 1. Diseases of adrenal glands. In: *Caffey's Pediatric X-Ray Diagnosis*. 9th ed. St. Louis, Mo: Mosby; 1993:1421-1435

Silverman FN, Kuhn JP. Congenital renal anomalies and renal neoplasms. 2. Renal neoplasms. In: *Caffey's Pediatric X-Ray Diagnosis*. 9th ed. St. Louis, Mo: Mosby; 1993:1243-1253

Tulassay T, Ramanathan R, Evans JR. Renal vascular disease in the newborn. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1320-1333

Content Specifications

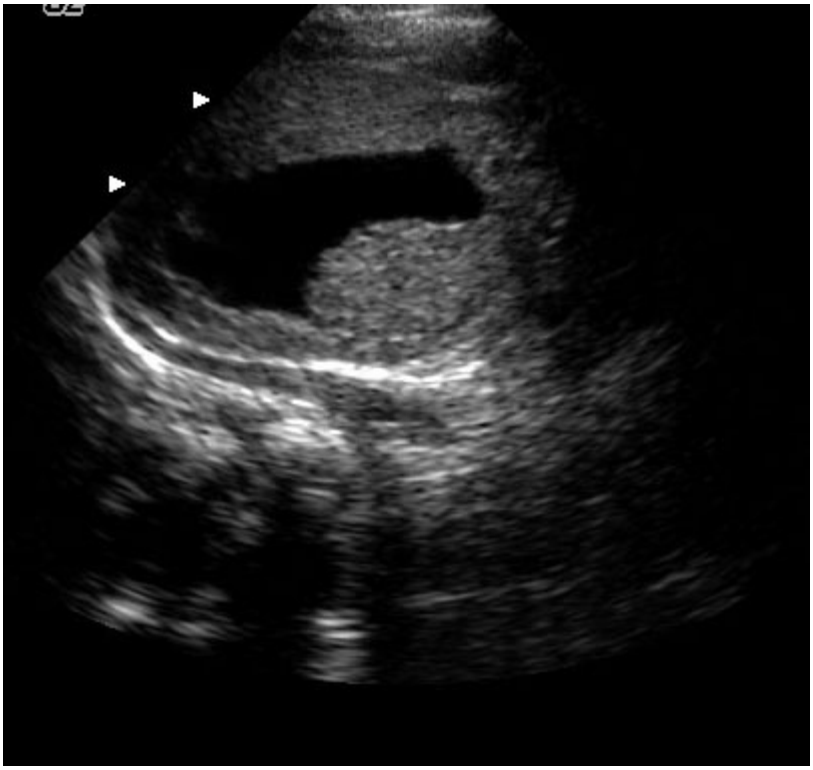
Know the etiology, clinical and laboratory features, and treatment of abdominal masses in the neonate.

Know the laboratory and radiographic features, the differential diagnosis, and the management of abdominal masses in the neonate

Recognize the clinical and laboratory features of neuroblastoma in the newborn

Recognize the clinical and laboratory features of Wilms tumor in the newborn

Know the etiology, clinical manifestations, laboratory features and management of renal vein thrombosis



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A 2-day-old infant has sudden tachycardia, with a heart rate of 240 beats/min. She remains hemodynamically stable. A bag of ice and water applied to the face restore normal heart rate quickly and easily. The maneuver is repeated twice more over the next day, each time with a stable child and an easy conversion. Between episodes, an electrocardiogram shows a short PR-interval and a delta-wave leading each R-wave (Figure 1).

Of the following, the class of antiarrhythmic drug MOST likely to benefit this child is

1	class Ia - sodium channel blocker, fast recovery
2	class Ic - sodium channel blocker, slow recovery
3	class II - beta blocker
4	class III - potassium channel blocker
5	class IV - calcium channel blocker

You selected 3, the correct answer is 3.

Symptomatic but hemodynamically stable Wolff-Parkinson-White syndrome (WPW) in a neonate, as seen in this vignette, is best treated with esmolol or propranolol, class II (beta-blocker) antiarrhythmic drugs.

WPW occurs in 0.1% to 0.3% of the general population and has been associated with defects on several chromosomes. Most cases are sporadic and nonfamilial, although the occurrence in first-degree relatives is 3%. Pre-excitation of the ventricles via an accessory pathway manifests in the electrocardiogram as a delta wave leading the R-wave. The aberrant conduction via the accessory pathway can cause supraventricular tachycardia (SVT), as in the infant in this vignette.

Immediate treatment is with vagal maneuvers, as in the vignette, or with intravenous adenosine. Although digoxin frequently is used in neonatal SVT, its use is controversial in pre-excitation syndromes such as WPW, in which the impairment to atrioventricular (AV) node conduction may be greater than any effect on the accessory pathway and may lead to atrial fibrillation and ventricular tachydysrhythmia. Initial treatment with a beta-blocker has a better chance of slowing conduction via the accessory pathway.

The antiarrhythmic drugs are classified by their site of major action Class I drugs block the sodium channels responsible for the rapid upward depolarization of the cardiac action potential. Class II drugs provide beta blockade. Class III drugs block the channels (mainly potassium channels) that shorten the action potential; these drugs prolong the action potential. Class IV drugs block calcium channels.

Class	Major Site of Action	Example
Class I	Sodium channel	Procainamide, lidocaine, flecainide
Class II	Beta adrenergic	Esmolol, propranolol
Class III	Potassium channel	Amiodarone
Class IV	Calcium channel	Verapamil

Digoxin and adenosine are not classified by this scheme. No drug has a purely single action, and these drugs often are combined for their secondary effects.

It may help to remember this classification scheme by associating the classes with their main effects on the cardiac myocyte action potential as illustrated in this drawing.

Class I drugs change the upstroke, classes II and III drugs work on the sustained depolarization phase, and class IV drugs affect depolarization.

Class I drugs (sodium-channel blockers) can be differentiated further by their rate of recovery from block into class Ia, Ib, and Ic for medium, fast, and slow recovery, respectively. Procainamide (class Ia) is useful in treating SVT and ventricular tachycardia. Toxicities can include vomiting, AV-block, or a lupus-like syndrome with fever, rash, and thrombocytopenia. Lidocaine (class Ib) is used for short-term treatment of ventricular arrhythmia and can cause convulsions or respiratory arrest. Flecainide (class Ic) is used to treat SVT and can cause bradycardia, ventricular tachycardia, and congestive heart failure.

Class II drugs, such as long-acting propranolol and short-acting esmolol, are helpful in the management of SVT, long QT syndrome, and some ventricular dysrhythmias. Toxic effects include hypotension, AV block, hypoglycemia, and bronchospasm. These adverse effects are less common in neonates than the adverse effects of other antiarrhythmics that might be used in WPW, such as procainamide or amiodarone. Their safety makes class II drugs the most appropriate choice for the infant in the vignette.

A class III drug, such as amiodarone, is useful in the treatment of SVT and ventricular tachycardia. Its adverse effects limit its use to dysrhythmias that are resistant to other drug regimens. These adverse effects include photosensitivity, corneal deposits, hyper- or hypothyroidism, weakness, peripheral neuropathy, and hepatitis.

A class IV drug, such as verapamil, is useful in some cases of SVT in some pediatric patients. It is contraindicated in children younger than age 1 year due to their greater sensitivity to its negative inotropic effects. Complete AV block also can be seen.

References:

Artman M. Pharmacologic therapy. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:333-349

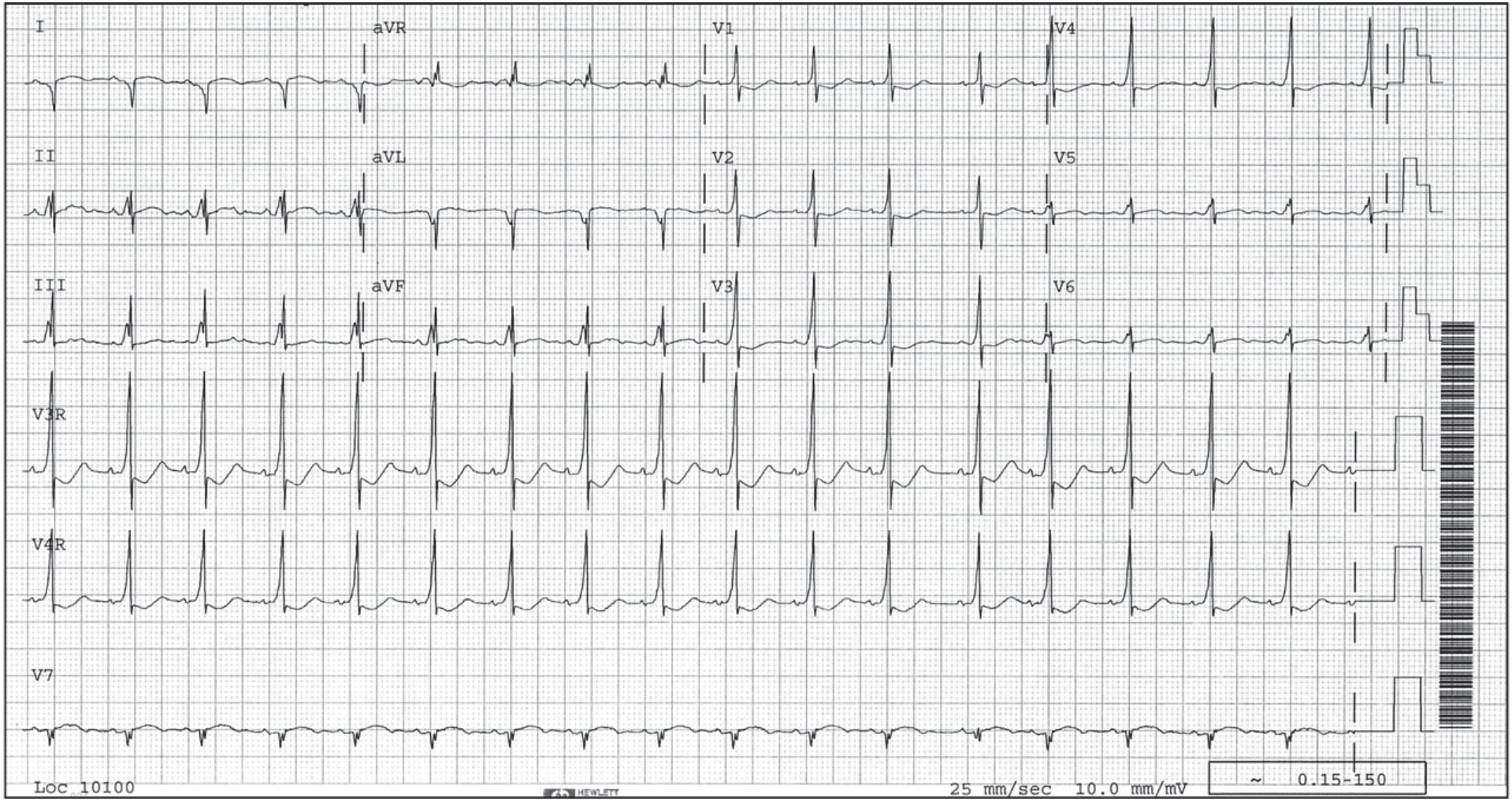
Cohen MI, Jedeikin R. Arrhythmias in the fetus and newborn. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:873-887

Roden DM. Antiarrhythmic drugs. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill; 2001:933-970

Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia. *NeoReviews* [serial online]. 2005;6:e339-e350. Available at: http://neoreviews.aappublications.org. Accessed August 16, 2005

Content Specification:

Plan appropriate management of a dysrhythmia in a newborn infant, including noninvasive and invasive management of electrophysiologic disturbances, and understand the potential adverse effects of approaches and drugs used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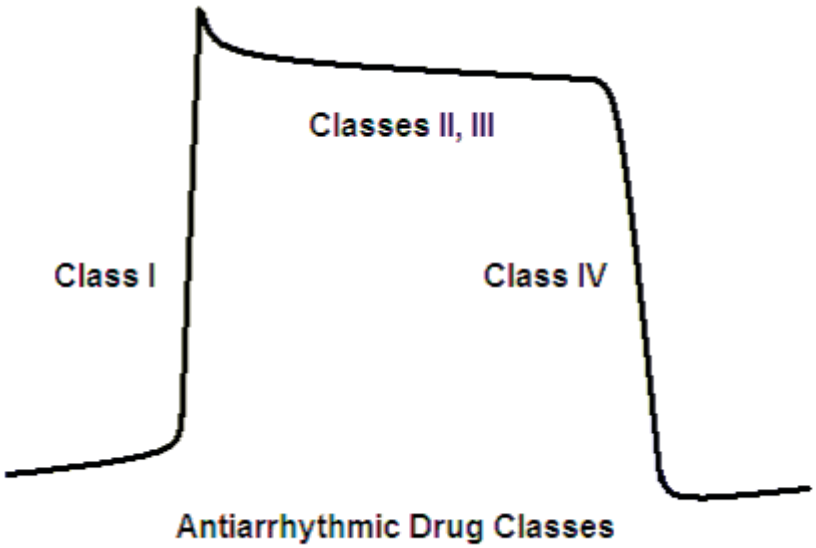

Classes II, III
Class I
Class IV
Antiarrhythmic Drug Classes

A 3-day-old infant is blue and feeding poorly. The heart rate is 190 beats/min. The liver is 2 cm below the right costal margin. A chest radiograph suggests a large right-heart silhouette. You suspect a right-sided cardiac lesion. A prostaglandin drip is started.

Of the following, the condition MOST typically associated with a large right-heart silhouette on a chest radiograph is:

1	critical pulmonary stenosis
2	Ebstein anomaly
3	pulmonary atresia with intact ventricular septum
4 (selected)	pulmonary atresia with ventricular septal defect
5	tricuspid atresia

You selected 4, the correct answer is 2.

Right-sided cardiac lesions have a variety of presentations. Obstruction to ventricular outflow results in increased right atrial pressure and shunting across the atrial septum, spilling deoxygenated blood into the left atrium and then into the systemic circulation, causing cyanosis. Right heart failure may cause an enlarged liver. Right atrial enlargement can affect heart conduction, causing supraventricular tachycardia. Of the given lesions, Ebstein anomaly is associated most typically with a large right heart on a chest radiograph.

Ebstein anomaly (Figure 1), first described in 1866, occurs in 1 in 25,000 live births and involves displacement of the tricuspid valve into the right ventricle. Maternal lithium exposure may be a risk factor. The marked right atrial enlargement is caused by a combination of tricuspid regurgitation and the abnormal contraction pattern of the atrialized portion of the right ventricle. The right atrial enlargement is associated with pulmonary hypoplasia, poor right ventricle output, supraventricular tachycardia, congestive heart failure, hypoxemia, and acidosis. Tachycardia, often seen, is associated with poor right ventricle filling but also may be caused by Wolff-Parkinson-White syndrome, found in up to 30% of patients with Ebstein anomaly. The most likely murmur is one of tricuspid insufficiency heard at the lower left sternal border. Pulmonary blood flow can be enhanced by using prostaglandin E1 to keep the ductus arteriosus patent. Respiratory alkalosis along with high inspired oxygen can lower pulmonary vascular resistance.

Critical pulmonary stenosis (Figure 2) was described by Morgagni in 1761. It results in right ventricular hypertrophy, right-to-left atrial shunting and hypoxemia, and pulmonary blood flow that are dependent on the patency of the ductus arteriosus. The ventricular wall hypertrophy narrows the lumen of the right ventricle. Right heart failure is prevented by atrial shunting, but at the cost of producing cyanosis. Low flow through the pulmonary valve gives only a soft heart murmur at the upper right sternal border. The right heart does not appear enlarged on chest radiography.

Pulmonary atresia with intact ventricular septum (Figure 3) occurs in approximately 1 in 12,000 live births. Blood exits the right atrium through the atrial septum. Pulmonary blood flow is dependent on patency of the ductus arteriosus. Right ventricular volume may be normal or reduced secondary to a hypertrophic right muscle mass. The coronary arteries can arise from the right ventricle, sometimes resulting in coronary insufficiency and myocardial infarction at birth. Isolated pulmonary atresia without tricuspid valve involvement does not exhibit a large right heart silhouette on chest radiography.

Pulmonary atresia with ventricular septal defect (Figure 4) occurs in approximately 1 in 14,000 live births. It can be associated with a microdeletion of region 22q11 or other chromosomal abnormalities. Pulmonary blood flow can come from the ductus arteriosus or aortopulmonary collateral arteries. Patients present with cyanosis and exhibit a single second heart sound. Right-sided heart failure and a large right heart on chest radiography rarely are seen until pulmonary vascular resistance decreases in the first four weeks after birth.

Tricuspid atresia (Figure 5) was described by Kreysig in 1817, and it occurs in approximately 1 in 20,000 live births. Incoming blood to the right atrium must exit via an atrial shunt, resulting in cyanosis. Pulmonary blood flow depends on a patent ductus arteriosus or a ventricular septal defect. More than 90% of cases have a ventricular septal defect, allowing filling of the right ventricle. In most of these cases, however, pulmonary stenosis often limits pulmonary blood flow unless the ductus arteriosus remains open. A closing ductus results in severe hypoxemia and acidosis. The right heart is not enlarged on chest radiography.

References:

Epstein ML. Congenital stenosis and insufficiency of the tricuspid valve. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:810-819

Epstein ML. Tricuspid atresia. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:799-809

Freedom RM, Nykanen DG. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:845-863

Latson LA, Prieto. Pulmonary stenosis. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:820-844

O'Leary PW, Mair DD, Edwards WD, Julsrud PR, Puga FJ. Pulmonary atresia and ventricular septal defect. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:864-879

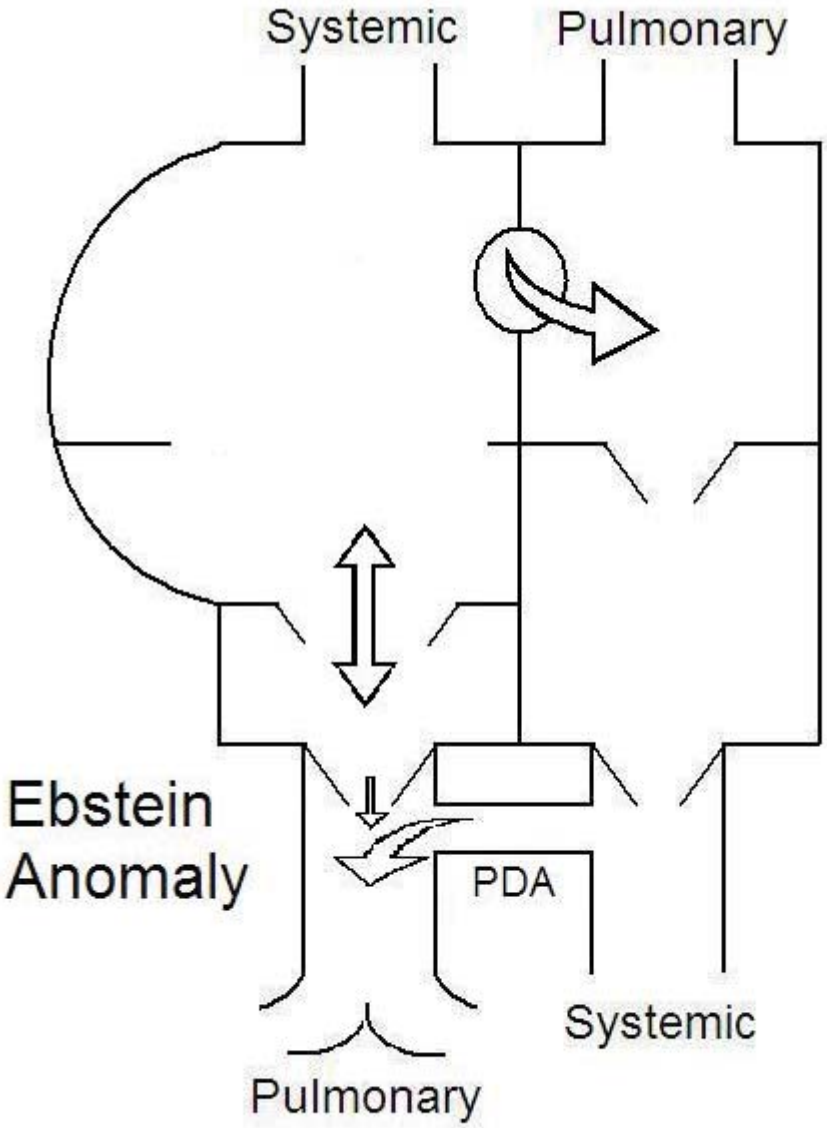
Wernovsky G, Gruber PJ. Common congenital heart disease: presentation, management, and outcomes. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:827-871

Content Specifications:

Recognize the clinical features of a neonate with a right-sided cardiac lesion

Formulate a differential diagnosis for a neonate with a right-sided cardiac lesion

PREVIOUS NEXT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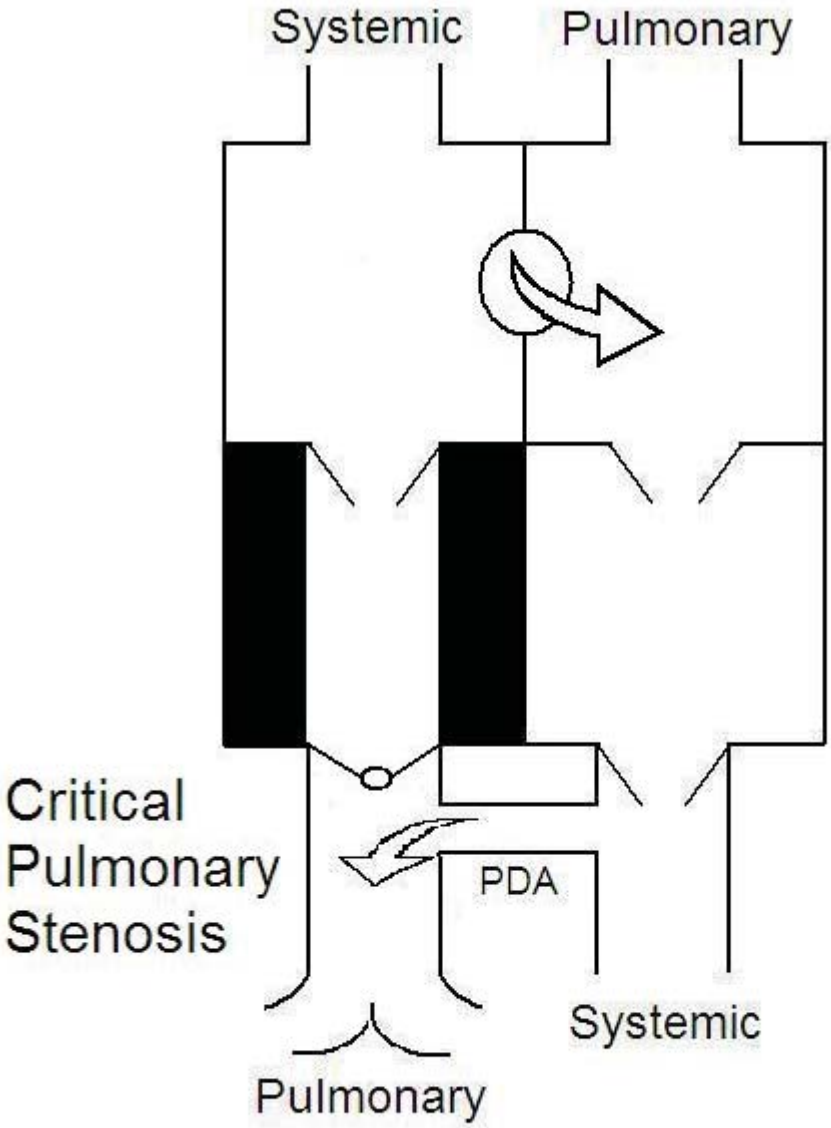
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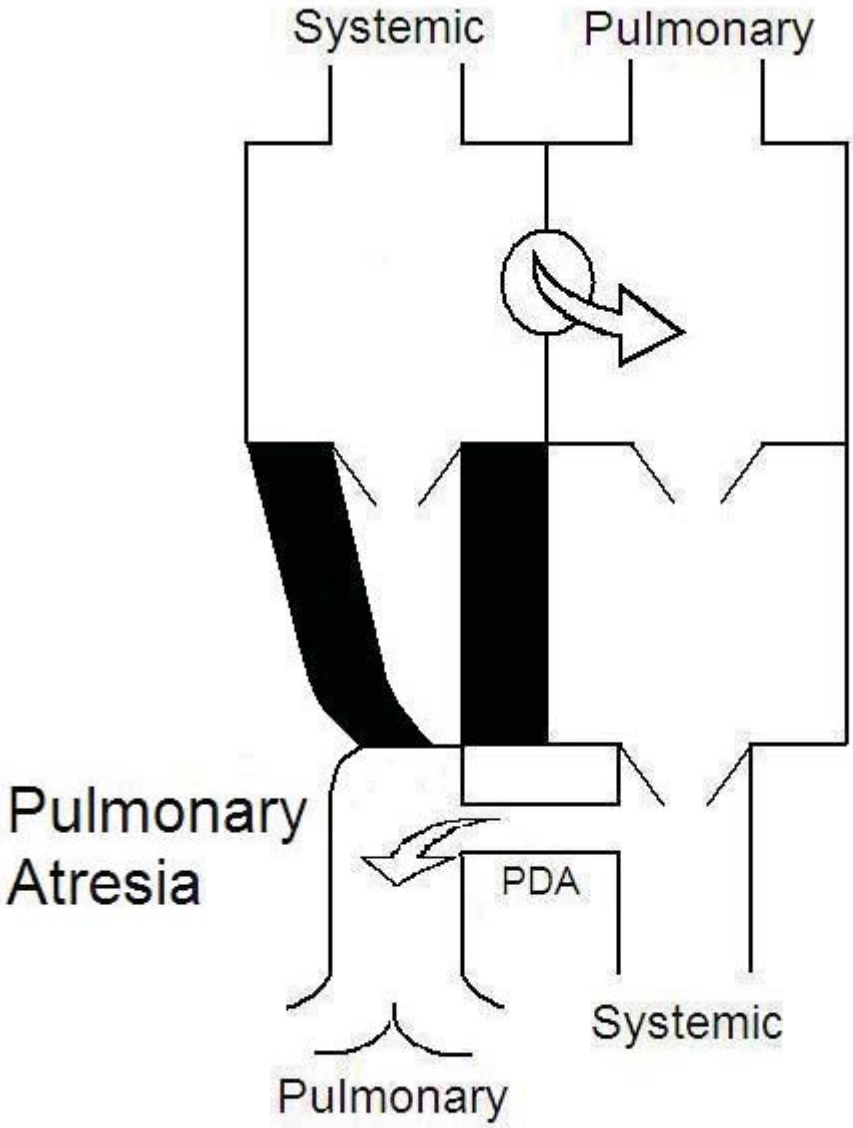
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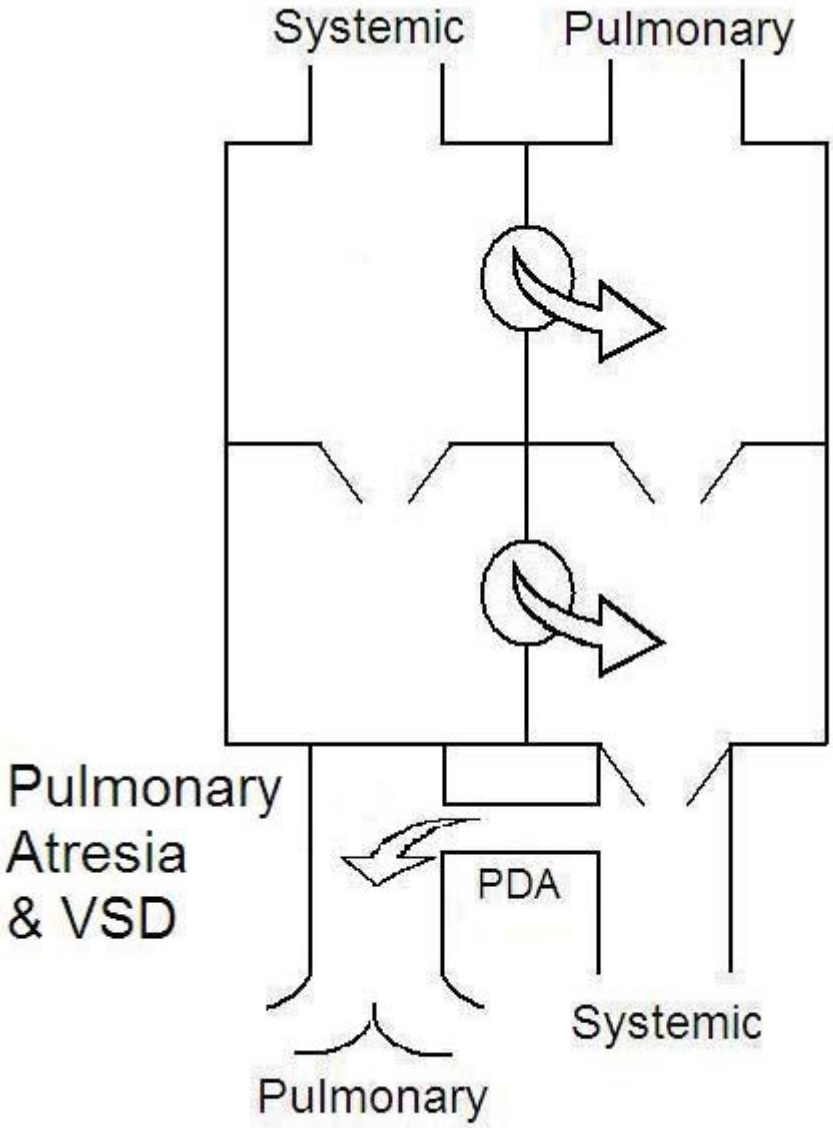
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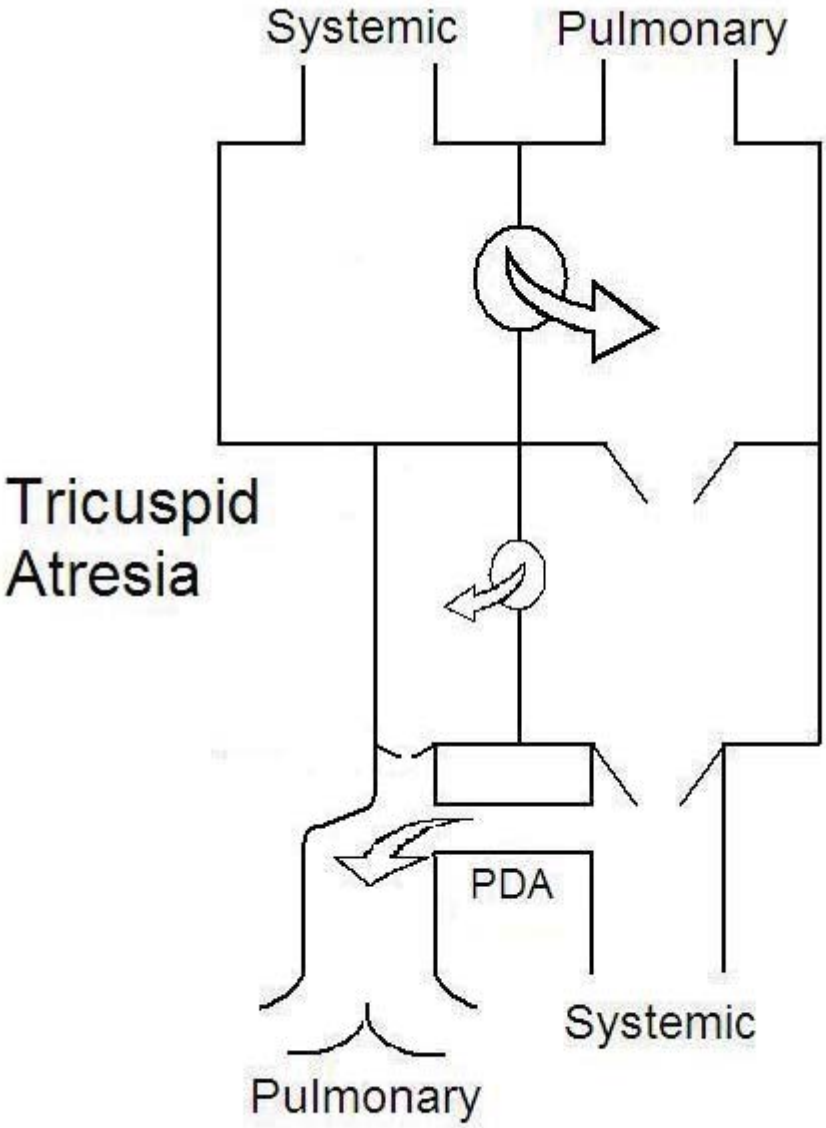
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As part of your collaboration with maternal-fetal medicine, you have prenatal consultations with women in the high-risk clinic, some of whom have a history of congenital heart disease. Many of the mothers' concerns revolve around the risk of congenital heart disease in their children.

Of the following, the maternal cardiac lesion MOST likely to be associated with congenital heart disease in an offspring is

1	anomalous pulmonary venous connection
2	atrioventricular septal defect
3	Ebstein anomaly of the tricuspid valve
4	tetralogy of Fallot
5	transposition of the great arteries

You selected 2, the correct answer is 2.

Children of parents who have a history of congenital heart disease (CHD) have an increased risk of having CHD. The overall risk ranges from 2.7% to 10.7% among different studies. In a study by Gill et al of 6,640 patients referred for fetal echocardiography based on family history, recurrence was noted 2.7% of the time and was similar for fetuses whose index case was the mother, the father, or another sibling . One population-based survey by Whittemore et al found a 10.7% risk among offspring, and a British collaborative study by Burn et al found that risk for offspring was 4.1% and 2.1% for siblings. The latter study found recurrence higher after maternal CHD (5.7%) than after paternal CHD (2.2%).

Although series and overall population data help in establishing some degree of increased risk, family history may refine your counseling. If CHD is part of a syndrome or chromosomal abnormality, recurrence risk of the underlying condition best reflects prognosis. If no genetic syndrome is recognized, the overall recurrence rate is 7%. If the cardiac anomaly is isolated, recurrence varies with the lesion and the severity of the lesion in the proband (more severe lesions have higher recurrence). In most studies, maternal CHD was more likely to recur than paternal. Recurrence is increased further if other first-degree relatives are affected.

Recurrence risk varies according to the specific anomaly of the affected parent. In the Gill et al fetal echocardiography study, a parent who had atrioventricular septal defect had a 7.8% risk, whereas a 10% risk was noted by Burn et al. These data are contrasted to lower risks for Ebstein anomaly (6%), anomalous pulmonary venous connection (3.7%), and tetralogy of Fallot (3.8%). Whereas no recurrences were noted with maternal d-transposition in the study by Burn et al, earlier reports found the risk to be in the 5% range. Recurrence risks for various lesions are noted in the Table. Recurrence rates vary considerably due to the relatively small numbers in most series, suggesting these rates be used to convey increased risk rather than to provide a more exact estimate.

If an offspring does have CHD, the risk for concordant CHD (having the same lesion as the parent) varies by the lesion as well. Ventricular septal defect has the highest concordance rate (55%), followed by hypoplastic left heart (33%), and coarctation of the aorta (13%).

References:

Burn J, Brennan P, Little J, et al. Recurrence risks in offspring of adults with major heart defects: results from first cohort of British collaborative study. *Lancet.* 1998;351:311-316

Driscoll DJ, Michels VV, Gersony WM, et al. Occurrence risk for congenital heart defect in

relatives of patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation.* 1993;87:114-120

Gill HK, Splitt M, Sharland GK, Simpson JM. Patterns of recurrence of congenital heart disease: an analysis of 6640 consecutive pregnancies evaluated by detailed fetal echocardiography. *J Am Coll Cardiol.* 2003;42:923-929

Goswami G, Ong K. eMedicine: Cardiovascular disease and pregnancy. Available at http://www.emedicine.com/med/topic3251.htm. Accessed April 17, 2005

Hoffman JL. Congenital heart disease: incidence and inheritance. *Pediatr Clin North Am.* 1990;37:25-43

Perloff JK. Pregnancy in women with congenital heart disease: general principles. Available at http://www.uptodate.com [subscription required]. Accessed March 28, 2005

Perloff JK. Pregnancy in women with congenital heart disease: specific lesions. Available at http://www.uptodate.com [subscription required]. Accessed March 28, 2005

Romano-Zelekha O, Hirsh R, Blieden L, Green MS, Shohat T. The risk for congenital heart defects in offspring of individuals with congenital heart defects. *Clin Genet.* 2001;59:325-329

Siu SC, Colman JM, Sorensen S, et al. Adverse neonatal and cardiac outcomes are more common in pregnant women with cardiac disease. *Circulation.* 2002;105:2179-2184

Siu SC, Sermer M, Colman JM, et al, for the Cardiac Disease in Pregnancy (CARPREG) Investigators. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001;104:515-521

Whittemore R, Wells JA, Castellsague X. A second-generation study of 427 probands with congenital heart disease and their 837 children. *J Am Coll Cardiol.* 1994;23:1459-1467

Content Specifications:

Know the effects of maternal cardiac disease and its treatment on the fetus

Understand the pathophysiology, including genetics, of a cyanotic neonate

Understand the pathophysiology, including genetics, of a neonate with a left-to-right shunt lesion

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

Understand the pathophysiology, including genetics, of a neonate with a right-sided cardiac lesion

PREVIOUS NEXT

Table

Table: Recurrence risk to offspring of mothers with congenital heart disease

Lesion	Recurrence risk-offspring(%)	Reference(s)
Aortic stenosis	1.2, 5-11.5	Driscoll, Hoffman
Atrial septal defect	4-14	Hoffman
Atrioventricular septal defect	5-10, 10	Hoffman, Burn
Coarctation of aorta	3-8	Hoffman
Double outlet right ventricle	4	Hoffman
Ebstein anomaly	5, 6	Hoffman, Perloff
Hypoplastic left heart	5-13.5	Hoffman
Hypoplastic right heart	5	Hoffman
Patent ductus arteriosus	3-11	Hoffman
Pulmonic stenosis (valvular)	6-9, 2.8	Hoffman, Driscoll
Single ventricle	5	Hoffman
Tetralogy of Fallot	4, 3.1	Hoffman, Burn
Total anomalous pulmonary venous return	5	Hoffman
Transposition (d)	5	Hoffman
Truncus arteriosus	7.7	Hoffman
Ventricular septal defect	4-22, 2.9	Hoffman, Driscoll

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You are called to see a 3.5-kg child born 20 minutes ago. The child has cyanosis, despite receiving 100% oxygen, and is in shock. Clinical examination reveals poor pulses, mottled appearance, oxygen saturation (SpO_2) 40%, and blood pressure 35/25 mmHg. The mother, whose prenatal care was not provided locally, tells you that some sort of congenital heart disease was suspected several months ago, but she cannot remember any specifics. You immediately start prostaglandin E_1 (PGE_1) at 0.1 mcg/kg per minute by intravenous route and call for an emergency echocardiogram. Over the next 20 minutes, the child worsens, with SpO_2 of 30% and blood pressure of 30/20 mmHg.

Of the following, the MOST likely explanation for this child's deterioration is

1	hypoplastic left heart syndrome with restricted atrial septum
2	interrupted aortic arch
3	total anomalous pulmonary venous return with obstruction of the common pulmonary vein
4	transposition of the great arteries with ventricular septal defect
✗ 5	viral myocarditis

You selected 5, the correct answer is 1.

Prostaglandin E_1 (PGE_1) often is used in infants suspected to have ductus-dependent congenital heart disease. PGE_1 is believed to exert its actions by two mechanisms: by activating adenylate cyclase in the vascular smooth muscle cells of the ductus arteriosus, thereby inhibiting the sensitivity of the contractile proteins to calcium; and by opening potassium channels to hyperpolarize the muscle cells, thereby reducing muscle tone. Due to its half-life of minutes, PGE_1 is given by constant infusion at doses of 0.01 to 0.4 mcg/kg per minute. Acute adverse effects include fever, apnea, hypotension, hypertonia, and irritability. Long-term adverse effects may include renal insufficiency, hypoglycemia, hypocalcemia, hyperostosis, obstructive gastropathy, thrombocytopenia, and seizures. Maternal inhibition of prostaglandin synthesis by chronic nonsteroidal anti-inflammatory drugs is associated with premature ductal closure and persistent pulmonary hypertension of the newborn.

Clinical deterioration once PGE_1 is started can be a useful sign of conditions in which there is obstruction to the pulmonary veins or to left atrial outflow. These conditions include total anomalous pulmonary venous return with pulmonary vein obstruction (TAPVR-PVO), hypoplastic left heart syndrome with restrictive atrial septum (HLV-RAS), mitral atresia with restrictive foramen ovale, and transposition of great arteries (TGA) with intact ventricular septum. Without the "pop-off" through the foramen ovale or atrial septal defect, pressure builds up in the left atrium and pulmonary veins to quickly cause pulmonary congestion, and markedly decreased pulmonary flow. The fully opened ductus would worsen the pulmonary overload.

Interrupted aortic arch usually presents as shock or congestive heart failure in the first fortnight. More than half the time, it is associated with a microdeletion of chromosome 22 and the DiGeorge syndrome. These children are dependent on a patent ductus arteriosus for blood flow to the descending aorta. Such a case would be expected to benefit from PGE_1 infusion.

TAPVR-PVO usually presents with cyanosis and tachypnea, often initially diagnosed as a primarily pulmonary problem. Delayed presentation until after age 12 hours helps differentiate it from respiratory distress syndrome. Physical findings, including murmurs, thrills or hyperactive pulses, seldom are found. Drainage often is below the diaphragm into the inferior vena cava.

TAPVR-PVO is difficult to find by echocardiogram, especially in the prenatal period; it is unlikely that the mother would have been warned about it.

HLV-IAS could present as in the vignette and fail to respond to PGE_1. The small size of the left ventricle would have been seen on prenatal echocardiogram and mentioned to the mother, as in the vignette. The severe obstruction to left-atrial outflow requires rapid palliation (atrial septostomy) or surgical intervention. Most other causes of left-sided obstruction should improve with PGE_1, including critical aortic stenosis, coarctation of the aorta, interrupted aortic arch, and HLV with atrial septal defect.

TGA with ventricular septal defect is likely to present with a higher SpO_2 than in the vignette. Improvement rather than deterioration is expected with PGE_1; the better mixing between the two parallel circulations would give even higher saturations.

Viral myocarditis might present with shock but would be unlikely to produce such low SpO_2 levels. The peripheral vasodilatation caused by PGE_1 might even help cardiac function by reducing afterload. Most cases should resolve over two months into either adequate cardiac function, or failure and death. It is unlikely that this was the problem the mother was told about prenatally.

References:

Clyman RI, Mechanisms regulating closure of the ductus arteriosus. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: Elsevier Saunders; 2004:743-748.

Fulton DR, Frees MD. Pathology, pathophysiology, recognition, and treatment of congenital heart disease. In Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's The Heart.* 11th ed. New York, NY: McGraw-Hill; 2004:1785-1850.

Marino BS, Wernovsky G. Stabilization and transport of the neonate with congenital heart disease. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:812-815.

Wernovsky G, Gruber PG. Common congenital heart disease: presentation, management, and outcomes. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:827-871.

Content Specifications:

For therapeutic drugs commonly used in the neonate, know the indications for their use, clinical effects, pharmacokinetics, adverse effects, and toxicity

Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion

Formulate a differential diagnosis of a neonate with a left-sided cardiac obstructive lesion

PREVIOUS NEXT

A 10-week-old female infant, whose birthweight was 690 g and estimated gestational age at birth was 26 weeks, has a systolic blood pressure of 92 mm Hg and a diastolic blood pressure of 68 mm Hg. Neonatal history is significant for initial respiratory distress managed with mechanical ventilation for 14 days, umbilical arterial catheterization for 7 days, and two courses of antimicrobial treatment for airway infection. The infant is breathing spontaneously, but she requires a fraction of inspired oxygen (Fio_2) of 0.42 to maintain adequate oxygen saturations. She is receiving full enteral feedings and daily oral doses of furosemide and hydrochlorothiazide. Renal ultrasonography with Doppler reveals normal renal architecture and reduced arterial blood flow to the left kidney. Findings on cranial ultrasonography are normal, as are measurements of serum electrolytes, blood urea nitrogen, and serum creatinine. You are planning treatment with an oral antihypertensive drug.

Of the following, the FIRST drug of choice for oral administration in the treatment of hypertension in this infant is

1	captopril
2	hydralazine
3	nifedipine
✗ 4	propranolol
5	spironolactone

You selected 4, the correct answer is 1.

The extremely low-birthweight infant described in the vignette has a clinical course and oxygen need at 36 weeks' postmenstrual age that are consistent with diagnoses of bronchopulmonary dysplasia (BPD) and renovascular hypertension. Neonatal hypertension is about two- to ninefold more common among preterm infants who have BPD than among those who have no lung disease, and its incidence varies with the severity of lung disease. Although the mechanism for hypertension in BPD remains unconfirmed, it may be related to chronic hypoxemia and its effects on peripheral vascular resistance; use of medications such as dexamethasone, xanthines, and bronchodilators and their effects on cardiovascular function; use of chronic diuretics and their effects on renal parenchyma; and chronic pulmonary hypertension with resultant cor pulmonale and its effects on salt-water homeostasis. Renovascular disorders are the most common cause for hypertension in neonates, especially in those treated with umbilical arterial catheters.

The oral drug of choice for the treatment of hypertension in the infant in the vignette is captopril, an angiotensin-converting enzyme (ACE) inhibitor. Understanding the mechanism of action of an ACE inhibitor in controlling hypertension requires an understanding of the renin-angiotensin system (Fig. 1). Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus in the kidney in response to various stimuli, principally a fall in renal perfusion pressure. Renin converts angiotensinogen, a plasma globulin synthesized in the liver, into a decapeptide, angiotensin I (Fig. 2). Angiotensin I has no appreciable activity, but is converted in the lungs by ACE to an octapeptide, angiotensin II. ACE is a membrane-bound enzyme on the surface of endothelial cells and is particularly abundant in the lung, which has a vast surface area of vascular endothelium. Angiotensin II is a potent vasoconstrictor, and its sustained action can result in vascular hyperplasia and hypertrophy. Angiotensin II is cleaved by aminopeptidase A into a heptapetide, angiotensin III, which is cleaved further by aminopeptidase

N into a hexapeptide, angiotensin IV. Angiotensin III is a potent stimulator of adlosterone secretion, which promotes sodium and water retention; angiotensin IV stimulates the release of plasminogen activator inhibitor-1 from the endothelium, which increases blood viscosity. The actions of angiotensins, specifically angiotensin II and angiotensin III, increase blood pressure through changes in vascular tone as well as intravascular volume. ACE inhibitors exert their antihypertensive action by reversing these trends. Moreover, ACE inhibitors can suppress the vasoactive peptides bradykinin and kallidin and promote vasodilatation, which adds to the antihypertensive effect.

Captopril is one of the first ACE inhibitors used in clinical practice. Its starting oral dose is 0.01 to 0.05 mg/kg per dose administered at 8- to 12-hour intervals. The dose and the interval are adjusted according to the clinical response. Adverse effects may occur at doses higher than 0.15 mg/kg and include neurologic symptoms from decreased cerebral blood flow, oliguria from decreased renal blood flow, hyperkalemia from aldosterone suppression, and cough. The pharmacokinetic, safety, and efficacy profiles make captopril an attractive choice for single-agent treatment of neonatal hypertension.

Hydralazine is an arterial/arteriolar vasodilator whose mechanism of action remains uncertain. The starting oral dose is 0.25 to 1.0 mg/kg per dose administered at 6- to 8-hour intervals, with the dose and interval adjusted based on the clinical response. At doses higher than approximately 2.0 mg/kg, adverse effects may occur, including retention of sodium and water, reflex tachycardia, and a lupuslike syndrome. Concurrent use of a beta-adrenoceptor antagonist and a diuretic may be needed to lessen the adverse effects. Additional adverse effects of hydralazine include gastrointestinal irritation and agranulocytosis. The bioavailability of oral hydralazine is low because of its extensive first-pass metabolism in the liver and intestines. The less favorable pharmacokinetic and safety profiles of hydralazine restrict its use largely to patients who have severe hypertension that is refractory to other pharmacologic therapies.

Nifedipine is a dihydropyridine that blocks cellular entry of calcium ions by preventing the opening of voltage-gated L-type calcium channels. It exerts its antihypertensive action by inducing generalized arterial/arteriolar vasodilatation. The starting oral dose is 0.1 to 0.25 mg/kg per dose administered at 12-hour intervals. The dose is adjusted based on the clinical response. Adverse effects may be seen at doses higher than 1.5 mg/kg per dose, including reflex tachycardia and rapid, profound, and transient drops in blood pressure. Nifedipine is available in a capsule from which the contents must be drawn up in a syringe for any dose less than 10 mg, making the drug difficult to administer in neonates and inadvertent dosing errors common.

Propranolol is a beta-adrenoceptor antagonist that exerts its antihypertensive action by at least three mechanisms. First, propranolol induces a reduction in heart rate and stroke volume, with a resultant decrease in cardiac output (negative chronotropic and inotropic effects). Second, it reduces systemic vascular resistance by decreasing vasomotor tone. Third, it reduces the secretion of renin from the kidney, with consequent suppression of angiotensins. The starting oral dose is 0.25 to 0.5 mg/kg per dose administered at 6-hour intervals, and the dose is adjusted according to the clinical response. Adverse effects may be seen at doses higher than 3.5 mg/kg, including cardiac failure, hypoglycemia, and bronchoconstriction. The latter is of particular concern in infants who have significant lung disease.

Spironolactone is an aldosterone receptor antagonist that exerts its antihypertensive action by inhibiting sodium and water retention. The starting oral dose is 0.5 to 1.5 mg/kg per dose administered at 12-hour intervals, and the dose is adjusted based on the clinical response. At higher doses, adverse effects may include hyponatremia and potentially life-threatening hyperkalemia. The primary indication for spironolactone is treatment of hypokalemia associated with the use of a loop diuretic in infants who have BPD. A thiazide diuretic often is used in combination with a loop diuretic to reduce potassium loss in the urine (potassium-sparing effect). The addition of spironolactone to a combination of a loop diuretic and a thiazide diuretic, as being used for the infant in the vignette, offers little, if any, additional benefit.

References:

Armstrong AW, Myers CW, Yeh DC, Rocco TP. Integrative cardiovascular pharmacology: hypertension, ischemic heart disease, and congestive heart failure. In: Golan DE, Tashjian Jr AH, Armstrong EJ, et al, eds. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:375-399

Boehm M, Nabel EG. Angiotensin-converting enzyme 2: a new cardiac regulator. *N Engl J Med*. 2002;347:1795-1797

Flynn JT. Neonatal hypertension: diagnosis and management. *Pediatr Nephrol*. 2000;14:332-341

Rang HP, Dale MM, Ritter JM, Moore PK. The vascular system. In: Rang HP, Dale MM, Rilter JM, Moore PK, eds. *Pharmacology*. 5th ed. Edinburgh, Scotland: Churchill Livingstone; 2003:285-305

Taketomo C, Hodding J, Kraus D. *Pediatric Dosage Handbook*. 11th ed. Hudson, Ohio: Lexi-Comp Inc; 2004:850-852

Young TE, Mangum B. *Neofax 2004*. 7th ed. Raleigh, NC: Acorn Publishing; 2004:101, 118-119, 129, 164

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. *J Perinatol*. 1995;15:470-479

Figure 1. Renin-angiotensin system.

Figure 2. Formation of angiotensins I through IV from precursor angiotensinogen.

Content Specification(s):

Know how to manage hypertension in an infant

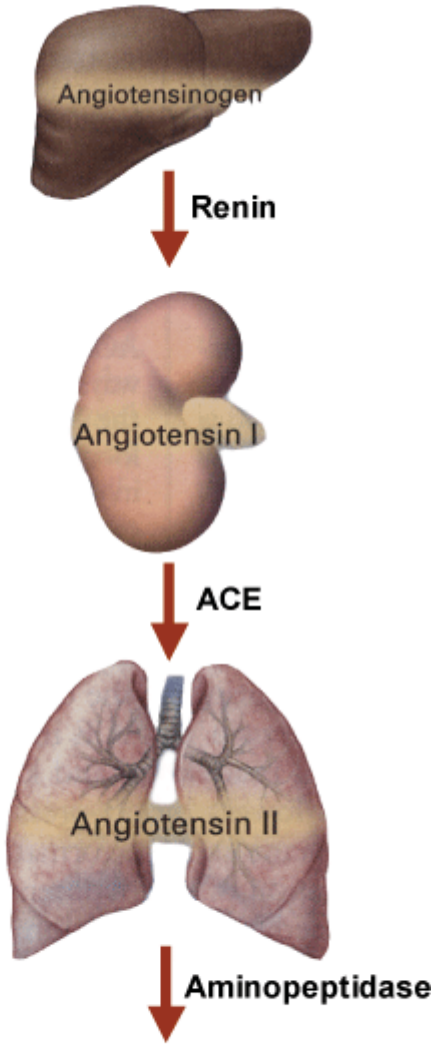


Fig. 1. Renin-angiotensin system.

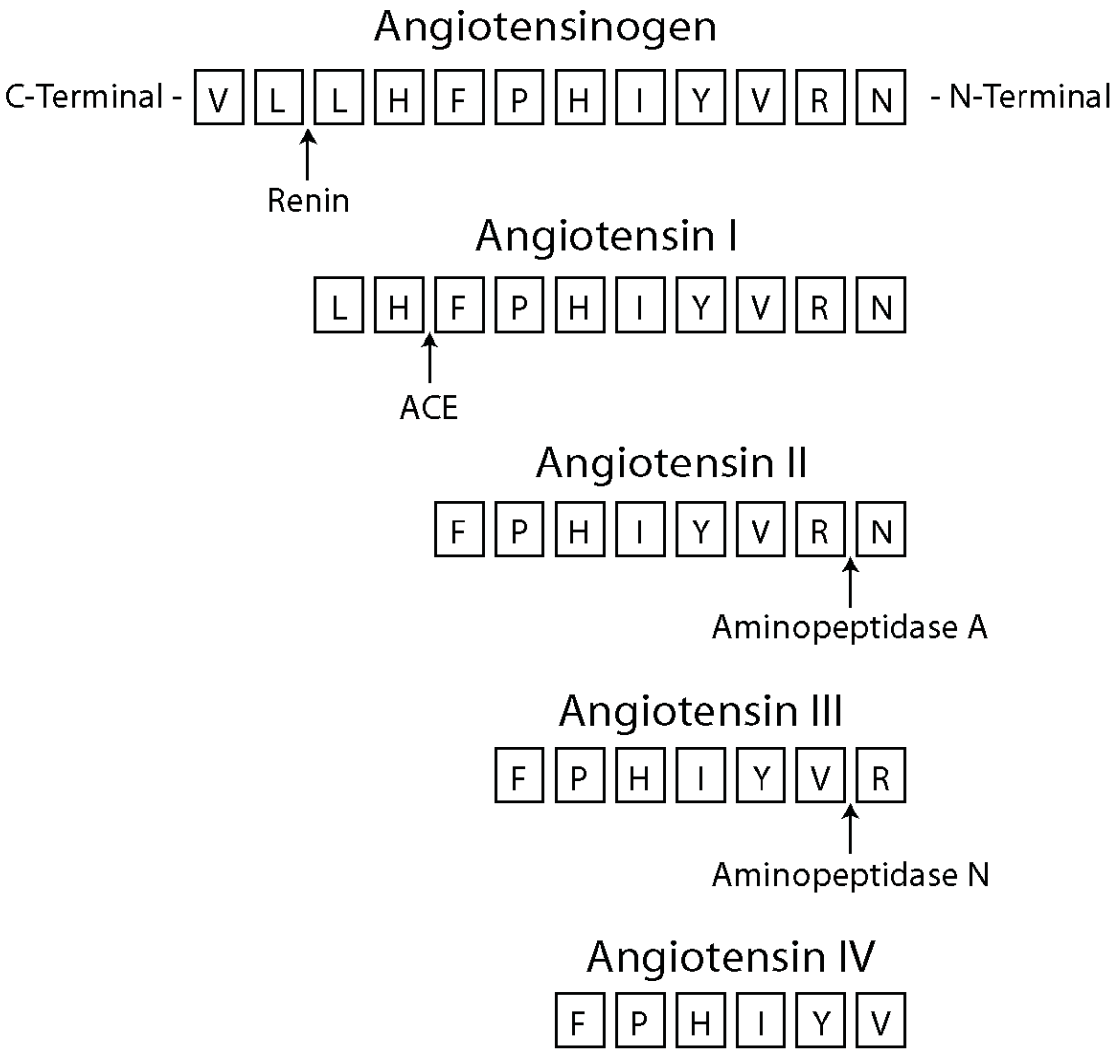


Figure 2: Formation of angiotensins I-IV from precursor angiotensinogen

A 24-year-old primiparous woman is admitted to the hospital at 32 weeks' gestation with a 1-week history of rapidly worsening hypertension and proteinuria. In your discussion with the residents and medical students regarding this case, you focus on the systemic endothelial dysfunction associated with pregnancy-induced hypertension (PIH). Specifically, you explain that binding of proangiogenic placental growth factor (PlGF) and vascular endothelial growth factor by an antiangiogenic protein, soluble fms-like tyrosine kinase 1 (sFlt1), lowers concentrations of PlGF, which causes endothelial dysfunction, followed by hypertension and proteinuria.

Of the following, the MOST accurate statement regarding urinary excretion of PlGF and its relationship to PIH is that

1	decreased urinary PlGF concentrations are noted by the end of the first trimester
2	female fetal sex results in higher urinary PlGF concentrations in PIH
3	gestational hypertension is predicted by lowered urinary PlGF concentrations in the second trimester of pregnancy
4	reduction in urinary PlGF is noted among normotensive mothers delivering small-for-gestational-age infants
5	severity of PIH correlates with the magnitude of urinary PlGF reduction

You selected 3, the correct answer is 5.

PIH is a common major complication of pregnancy that may result in severe maternal complications (seizures, coagulopathy, cerebral hemorrhage, renal failure) and fetal compromise (intrauterine growth restriction, preterm birth). PIH occurs in 4% of pregnancies that extend into the second trimester. Because the diagnostic signs of preeclampsia (edema, high blood pressure, proteinuria, retinal changes, and hyperreflexia) predate clinical symptoms (which may involve many organ systems), screening for PIH is a mainstay of prenatal care. Predictive testing may be useful in identifying patients before signs or symptoms arise.

The underlying systemic endothelial dysfunction manifests as hypertension and proteinuria. The only known cure for PIH is delivery of the placenta. Screening blood pressure and urinary protein concentrations are essential components of prenatal care, but the interval between the onset of PIH and the development of severe complications can be brief. Although there are no current therapeutic options for PIH that is detected early, monitoring can lead to more timely delivery and, in some cases, maternal referral to facilities better able to handle the preterm infant. Knowledge of the pathologic events of preeclampsia ultimately may result in treatments directed at these processes rather than early, emergent delivery.

Studies of angiogenic factors among pregnant women who subsequently developed PIH show elevations of sFlt1 about 5 weeks before the onset of clinical manifestations of PIH. Hypertension, proteinuria, and glomerular endotheliosis were noted among rats given sFlt1 experimentally. In the early second trimester, reduced serum concentrations of PlGF antedate the onset of clinical signs. Because PlGF is a small molecule that passes readily into the urine, reductions in urinary PlGF have been analyzed among women being followed for the development of PIH. No differences in urinary PlGF were noted until late second trimester and early third trimester, and increasing severity of PIH was associated with greater reductions in urinary PlGF excretion. For women in the lowest quartile of urinary PlGF, the odds ratio (based on urinary concentrations of PlGF) for developing PIH at less than 37 weeks' gestation was 31.3

(95% confidence interval, 5.6 to 174.7).

Urinary PlGF concentrations were unaffected by fetal sex. Mothers who manifested gestational hypertension (elevated blood pressure without proteinuria) and normotensive mothers whose infants were small for gestational age had urinary PlGF concentrations similar to those in the control group.

References:

Levine RJ, Thadhani R, Qian C, et al. Urinary placental growth factor and risk of preeclampsia. *JAMA*. 2005;293:77-85

Roberts JM. Pregnancy-related hypertension. In: Creasy RK, Resnik R, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa.: Saunders; 2004:859-899

Content Specification(s):

Know the effects on the fetus of mild preeclampsia and its management
Know the effects on the fetus of severe preeclampsia, including HELLP syndrome, and its management

PREVIOUS NEXT

You are asked to evaluate a 20-hour-old, 5-kg male with poor perfusion and tachypnea. The mother, who has diabetes, reports that the infant feeds poorly. On examination, the heart rate is 188 beats per minute, respiratory rate is 75 breaths per minute, and capillary refill time is 3 to 4 seconds. An ejection murmur is heard at the right upper sternal border. Oxygen saturation in room air is 92% in the right and left arms. Echocardiography shows a left-ventricle wall thickness of 10 mm (Figure).

Of the following, the drug most likely to be useful in this child is:

1	dobutamine
2	dopamine
3	furosemide
4	milrinone
5	propranolol

You selected 1, the correct answer is 5.

The infant in the vignette has signs of hypertrophic cardiomyopathy (HCM), sometimes known as obstructive cardiomyopathy. It may be seen during the neonatal period in up to 30% of infants of diabetic mothers, although other possible associations include Noonan syndrome, Pompe disease, and the mitochondrial diseases. Signs may include tachypnea or cyanosis from pulmonary congestion, poor perfusion, or feeding difficulties. A double or triple apical impulse may be felt, caused by ventricular contraction, exaggerated atrial contraction, and early ventricular filling. A systolic ejection murmur signifies aortic outflow obstruction and becomes louder with a larger subaortic gradient.

Alternatively, infants of diabetic mothers may have congestive cardiomyopathy without hypertrophy. These infants often respond to correction of underlying polycythemia, hypoglycemia, hypocalcemia, or hypomagnesemia. The thickened myocardium seen in the echocardiogram of the infant in the vignette makes this diagnosis less likely.

Treatment of obstructive HCM usually includes a beta-blocker such as propranolol. By reducing sympathetic stimulation, propranolol reduces ventricular contractility and heart rate. This effect reduces the subaortic outflow gradient and the oxygen demands on the thickened myocardium, and reduces the chance of myocardial ischemia and damage. Propranolol binds to a G-protein, which then is prevented from helping in the production of adenylate cyclase and cyclic adenosine monophosphate (cAMP), resulting in decreased activity of protein kinase-A and lowered intracellular calcium levels. Its toxicity often is related to its nonselective blocking of beta-1 and beta-2 adrenergic receptors; it is relatively contraindicated in bronchospasm (beta-2) and severe congestive heart failure (beta-1).

Inotropic agents such as dobutamine, dopamine, and milrinone, may increase subaortic outflow gradients and myocardial oxygen demands. These agents usually are not recommended in obstructive HCM.

Dobutamine binds to a and ß adrenergic receptors and works through G-proteins to increase cAMP levels, resulting in higher intracellular calcium availability. It has inotropic and limited chronotropic activity and also will lower peripheral vascular resistance (PVR). Coronary blood flow and myocardial oxygen delivery improve. Toxicities include arrhythmias, tremor, and vomiting.

Dopamine also binds to a and ß adrenergic receptors, but with more peripheral a effect, raising PVR. This gives a higher blood pressure than dobutamine, although long-term outcome data are not available to suggest the initial use of one agent over the other. The two often are used together. Some practitioners advocate dobutamine initially for the congestive cardiomyopathy of perinatal asphyxia, to reduce afterload. Similarly, dopamine often is started in septic shock to help increase PVR and stabilize the peripheral vascular derangements. Dopamine binds to receptors in the kidney and selectively reduces renal vascular resistance in premature infants. Available data suggest that dopamine and dobutamine reduce mesenteric vascular resistance equally. Toxicities of dopamine include arrhythmias, tremor, and vomiting. Subdermal extravasation can cause blanching and necrosis and can be treated with local infiltration of phentolamine, an alpha-agonist. Dopamine also inhibits thyrotropin release, delaying valid thyroid screening results.

Furosemide may be useful in congestive heart failure where volume overload needs to be relieved. In obstructive HCM, it may cause hypovolemia, poor ventricular filling, and a worsening of the subaortic gradient. Furosemide interferes at the chloride-binding site of the sodium-potassium-chloride cotransporter, inhibiting reabsorption of sodium and water in the ascending limb of the loop of Henle. Toxicities include hypokalemia, alkalosis, ototoxicity, nephrolithiasis, and renal failure.

Milrinone is another inotropic drug that increases cAMP levels. Instead of working through a cell-surface receptor, it works directly in the cell to inhibit the action of phosphodiesterase and so prevent the hydrolysis of cAMP. It has an inotropic effect on the heart and a dilating effect on veins and arterioles, effects that do not depend on neurotransmitter stores or receptors. It simultaneously can raise cardiac output and lower PVR, without increasing myocardial oxygen demand significantly. Toxicities include arrhythmias, tremor, thrombocytopenia, and vomiting. Milrinone is of benefit in right ventricular failure and in weaning cardiac surgery patients from cardiopulmonary bypass. Its role is being investigated in treating the early hypotension of the severely premature newborn.

References:

Chmait R, Moore TR. Endocrine disorders in pregnancy. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:71-86

Evans N, Seri I. Cardiovascular compromise in the newborn infant. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:398-409

Maron BJ. Hypertrophic cardiomyopathy. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:1167-1186

Padbury JF, Berg RA. Developmental pharmacology of adrenergic agents. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology.* 3rd ed. Philadelphia, Pa: Elsevier Saunders; 2004:227-233

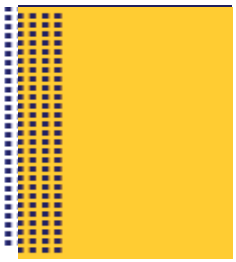
Rosenthal DN. Cardiomyopathy in infants: a brief overview. *NeoReviews.* 2000; 1:e139-e145

Content specifications:

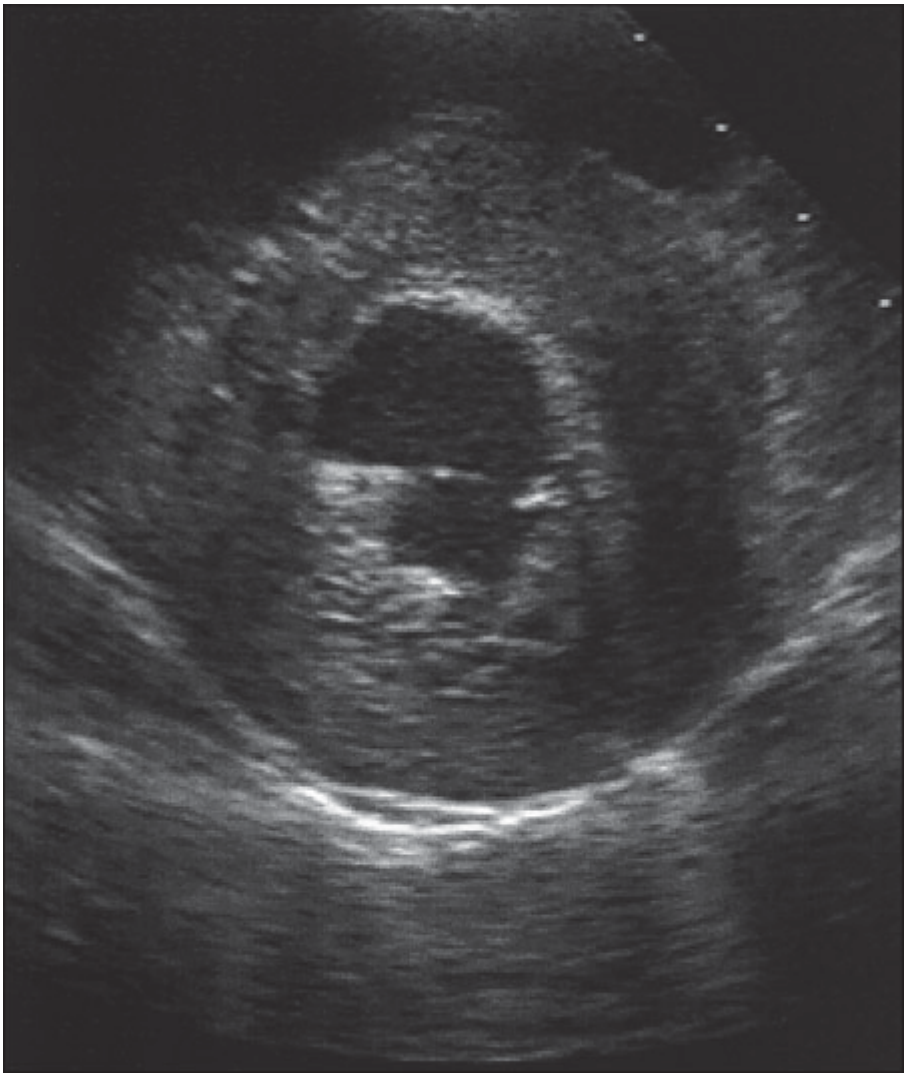
Recognize the therapeutic indications for and toxicity of inotropic agents in treating cardiovascular distress

Recognize the clinical features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Understand the mechanism of action of commonly used autonomic agonist and antagonist



drugs



As part of your collaboration with maternal-fetal medicine, you have prenatal consultations with women in the high-risk clinic, some of whom have a history of congenital or acquired heart disease. Maternal heart disease may influence a woman's tolerance to pregnancy, growth and development of the fetus, and tolerance for delivery and the postpartum period.

Of the following, the MOST significant predictor of maternal or fetal complications among pregnant women with congenital heart disease is

1	arrhythmia
2	coagulopathy
3	cyanosis
4	Eisenmenger syndrome
5	functional classification

You selected 4, the correct answer is 4.

Many women reach the child-bearing years after diagnosis and treatment for congenital heart disease. In most cases, careful management allows for pregnancy with no long-term adverse effects after delivery. Overall, pregnancy among women with congenital heart disease is associated with increased pregnancy loss, increased pregnancy complications (especially cardiac), higher cesarean section rate, and premature birth.

Tolerance for pregnancy varies depending on the specific cardiac lesion and its effects on cardiac and respiratory physiology in the individual patient. A number of factors influence the tolerance to pregnancy. Major hemodynamic changes during pregnancy include blood pressure decrease mediated by a decrease in peripheral vascular resistance starting in early gestation and reaching a low point in the second trimester, and increase in intravascular volume peaking in the first half of the third trimester. Cardiac output increases 30% to 50% during pregnancy, with half of this increase occurring by 8 weeks' gestation. The rise in cardiac output during early pregnancy is due to increased stroke volume, whereas the rise in cardiac output during later pregnancy is due to higher heart rate. Labor and delivery is associated with marked increase in cardiac output, up to a 50% increase by the end of the second stage of labor. Dramatic volume shifts occur with delivery: physiologic transfusion follows the release of venocaval obstruction and contraction of the uterus; and blood loss at delivery and postpartum can deplete blood volume. Any of these changes may be compromised by maternal congenital heart disease.

Maternal cardiac disease is associated with an increased cesarean section rate. The cesarean section rate for fetal distress, failure to progress, breech or prior cesarean delivery is not increased, but some procedures are performed due to maternal risks associated with labor. Neonatal complications are increased (odds ratio 2.3, 95% confidence intervals 1.4 - 4). In a controlled study, 15% of infants of mothers with congenital heart disease delivered at <37 weeks' gestation as compared to 5% among controls. Some 6% had either intraventricular hemorrhage, delivery at <34 weeks' gestation, or fetal/neonatal death contrasted with 2% in the control group. Of mothers whose cardiac disease was not part of a recognized syndrome, 8% of their infants had congenital heart disease.

The congenital cardiac condition most threatening to pregnant women and their fetuses is

pulmonary hypertension associated with Eisenmenger syndrome. Patients with pulmonary hypertension secondary to a nonrestrictive ventricular septal defect have right to left shunting, which is exacerbated by the decrease in systemic vascular resistance of pregnancy, resulting in worsening cyanosis because afterload is required to control the right to left shunt. Tolerance to pregnancy is poor, with increased susceptibility to spontaneous abortion, preeclampsia, intrauterine growth impairment, prematurity, and postpartum hemorrhage. From 20% to 40% of these pregnancies end in spontaneous abortions. Prematurity and fetal growth restriction complicate 50% of cases, and fewer than 25% of pregnancies go to term. Perinatal mortality ranges from 8% to 28%. Tolerance to labor is particularly poor, and most maternal deaths occur postpartum. As increases in systemic vascular resistance occur during labor secondary to uterine contractions and maternal effort, abrupt drops in cardiac output may result in maternal syncope, sometimes fatal. This complication is particularly troublesome in patients with Eisenmenger syndrome because of the dependence of cardiac output on adequate preload. The combination of these factors has resulted in maternal mortality of 30% to 50% for Eisenmenger syndrome, with most deaths due to thromboembolism, volume depletion, and preeclampsia. In spite of the risks of labor, cesarean section delivery offers a worse prognosis. Most experts believe that Eisenmenger syndrome is a contraindication to pregnancy. In the absence of Eisenmenger syndrome, pulmonary hypertension is not an independent predictor of risk due to its association with left heart obstruction or poor functional status, both of which are ominous signs during pregnancy.

Adverse consequences from arrhythmias are not major risk factors for either mother or fetus in most situations. Atrioventricular nodal reentrant tachycardia is the most common supraventricular tachycardia among women, pregnant or not. In the absence of structural heart disease, maternal or fetal problems are unusual. If structural heart disease is present, hemodynamic instability may result. Atrioventricular reentrant supraventricular tachycardia is less common but more likely to be symptomatic because of the rapidity of the heart rate. Approximately 25% of patients with Ebstein anomaly have accessory conduction pathways commonly associated with hemodynamic deterioration due to tachycardia. Other arrhythmias are unusual among pregnant women unless they are associated with cardiac structural abnormalities or previous cardiac surgery. Most antiarrhythmic medications are able to be used in pregnancy, but data on the individual medications should be obtained before use. Radiofrequency ablation is not recommended during pregnancy because of the associated need for fluoroscopy and radiation exposure. Women on antiarrhythmic medications can consider radiofrequency ablation prepregnancy so as to avoid both the arrhythmia and the medications when pregnant. Cardioversion has been used with success for acute tachyarrhythmias with hemodynamic deterioration during pregnancy. Implantable cardioverter-defibrillators have been used successfully during pregnancy with no adverse fetal effects.

Most congenital heart diseases do not require anticoagulant medications. Pregnancy is associated with a relative hypercoagulable state, with 20% reductions in the prothrombin time and in the activated partial thromboplastin time. Although these reductions protect against bleeding at delivery, thromboembolic disease can occur, leading to pulmonary embolic disease or arterial stroke if right to left shunting is present. These phenomena are not major consequences of pregnancy among most women with congenital heart disease but can lead to embolic disease due to suboptimal anticoagulation in women whose underlying cardiac disease requires anticoagulation (such as artificial heart valve).

Maternal cyanosis also predicts increased maternal and fetal risk. Postpartum cardiac complications occur among 90% of women with cyanotic congenital heart disease (CHD) versus 19% with acyanotic CHD. If oxygen saturation maintains above 90%, the risk decreases. Use of oxygen in cyanotic CHD has not been shown to benefit either mother or fetus. Maternal cyanosis also is complicated by high hematocrit and hyperviscosity, sometimes requiring phlebotomy.

Maternal functional cardiac classification is a major determinant of risk. Women whose cardiac disease is associated with severe limitation or inability to carry out ordinary physical activity

(Classes III or IV) are at significant risk for cardiac complications. A scoring system gives one point for each of the following four findings if present: functional class III or IV; previous heart failure, transient ischemic attack, stroke or arrhythmia; left heart obstruction (mitral valve area <2cm^2, aortic valve area <1.5 cm^2, or peak left ventricular outflow gradient >30 mmHg); and left ventricular systolic ejection fraction <40%. Zero points were associated with a 4% risk for maternal primary cardiac complications, such as pulmonary edema, arrhythmia requiring treatment, stroke, cardiac arrest, or death. A 1-point score raises the risk to 26%, and a >1 point score was associated with a 62% risk. Neonatal complications tripled compared to matched controls without heart disease.

References:

Blanchard DG, Shabetai R. Cardiac diseases. In: Creasy RK, Resnik R, Iams JD, eds. *Maternal-Fetal Medicine: Principles and Practice*. 5th ed. Philadelphia, Pa: Saunders; 2004:815-844

Garg M, Quick A. eMedicine: Atrioventricular nodal reentry tachycardia. Available at http://www.emedicine.com/med/topic2955.htm. Accessed April 18, 2005

Goswami G, Ong K. eMedicine: Cardiovascular disease and pregnancy. Available at http://www.emedicine.com/med/topic3251.htm. Accessed April 17, 2005

Perloff JK. Pregnancy in women with congenital heart disease: general principles. Available at http://www.uptodate.com [subscription required]. Accessed March 28, 2005

Perloff JK. Pregnancy in women with congenital heart disease: specific lesions. Available at http://www.uptodate.com [subscription required]. Accessed March 28, 2005

Podrid PJ. Arrhythmias and conduction disturbances associated with pregnancy. Available at http://www.uptodate.com [subscription required]. Accessed April 18, 2005

Podrid PJ. Management of arrhythmias in pregnancy. Available at http://www.uptodate.com [subscription required]. Accessed April 18, 2005

Content Specifications:

Know the effects of maternal cardiac disease and its treatment on the fetus

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April: Question 5

An 800-g newborn is delivered at 27 weeks' gestation. His hospital course includes use of umbilical vein and artery catheters for two days, a requirement for supplemental oxygen until 34 weeks' postmenstrual age (PMA), and administration of caffeine for apnea. At 38 weeks' PMA, he feeds poorly, and he has episodes between feedings of tachypnea and apnea. His blood pressure in the right arm is 120/80 mmHg.

Of the following, the MOST likely cause of this child's hypertension is:

1	adrenal hemorrhage
2	parenchymal damage
3	renal artery stenosis
4	renal artery thrombosis
5	renal vein thrombosis

You selected 4, the correct answer is 4.

Of the many causes of neonatal hypertension (Table below), the most common is renovascular disease. Less common causes include bronchopulmonary dysplasia, coarctation of the aorta, and hyperthyroidism. Within the renal category, the most common cause is renal artery thrombosis. The difficulty in setting an upper 95th percentile for normal neonatal blood pressure stems from disagreement over what constitutes a normal state, as well as an inability to identify a minimal hypertensive blood pressure at which damage to end organs occurs. The current consensus definition of neonatal hypertension was set arbitrarily in 1988 as "... persistent blood pressures exceeding by two SD, the mean values culled from the literature, a systolic and diastolic blood pressure greater than 90 mmHg and 60 mmHg, respectively, in the term newborn and greater than 80 mmHg and 50 mmHg, respectively, in the preterm infant (Adelman, 1988)."

Hypertension may present in the neonate with nonspecific symptoms, such as poor feeding, lethargy, or irritability. There may be apnea, skin mottling, or unexplained tachycardia. The presentation may be life-threatening, with seizures, congestive heart failure, or cardiogenic shock. Physical examination of a hypertensive neonate should include checking for dysmorphic features, (eg, congenital adrenal hypoplasia or Turner syndrome), measuring four-extremity blood pressures (eg, coarctation), palpation for femoral pulses (eg, coarctation) or flank masses (eg, ureteropelvic junction obstruction), and auscultation for epigastric bruits (eg, renal artery stenosis).

Renal artery thrombosis is the most frequent cause of neonatal hypertension. It is associated with umbilical artery catheter placement, although there are conflicting data on whether high- or low-lying catheters are safer. Damage to the vascular endothelium causes thrombus formation, which in turn causes arterial obstruction and emboli in the renal parenchyma. Factors that add to the risk of umbilical artery lines include dehydration, systemic infection, perinatal asphyxia, maternal diabetes, and polycythemia. In the absence of an umbilical artery catheter, hypercoagulable conditions, such as factor V Leiden with resistance to activated protein C, are risk factors for thrombosis and hypertension.

Adrenal hemorrhage can be associated with birth trauma, perinatal asphyxia, shock, or infection. It also may occur without any symptoms or associations. Only 5% to 8% of cases are bilateral, but those cases are more likely to present with hypoglycemia and hypotension. Clinical findings with unilateral bleeding are often nonspecific but may include mild anemia, persistent jaundice, abdominal mass, or scrotal hematoma. Adrenal hemorrhage patients most often are asymptomatic or hypotensive and rarely may be hypertensive.

Renal parenchymal damage can take several forms. Autosomal dominant polycystic kidney disease, and the more severe autosomal recessive polycystic kidney disease, can present with abdominal masses and hypertension, but both conditions are rare. Renal cortical and medullary necrosis is associated with severe perinatal stress and hypotension. Congenital ureteropelvic junction obstruction may present with hypertension, but such a presentation is unusual.

Renal artery stenosis is an uncommon disorder most often caused by fibromuscular dysplasia and associated with midaortic coarctation and cerebral vascular stenoses.

The classic triad of renal vein thrombosis includes hypertension, hematuria, and an abdominal mass. The usual presentation is a new flank mass with hypotension and clinical deterioration of the child. Risk factors include dehydration, asphyxia, infection, umbilical or central catheters, and maternal diabetes. Inherited thrombotic states, such as factor V Leiden and polymorphisms in methylene tetrahydrofolate reductase, may predispose an infant to venous thrombosis. Mild hypertension may be seen late in the course.

References:

Adelman RD. The hypertensive neonate. *Clin Perinatol.* 1988;15:567-585

Ettinger LM, Flynn JT. Hypertension in the neonate. *NeoReviews* 2002;3:e151-e156

Flynn JT. Neonatal hypertension: diagnosis and management. *Pediatr Nephrol.* 2000;14:332-341

Schieken RM. Systemic hypertension. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:1400-1412

Tulassay T, Ramanathan R, Evans JR, Seri I. Renal vascular disease in the newborn. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1320-1333

Table. Hypertension in Neonates (after Ettinger and Flynn 2002)

Renovascular Thromboembolism Renal artery stenosis Renal venous thrombosis Compression of renal artery Cardiac Coarctation of the aorta Pulmonary Bronchopulmonary dysplasia Renal Disease Congenital Polycystic kidney disease Multicystic-dysplastic kidney Ureteropelvic junction obstruction Acquired Acute tubular necrosis Hemolytic-uremic syndrome Obstruction by tumor Endocrine Congenital adrenal hyperplasia Pseudohypoaldosdosteronism type II	Medications/Intoxications Maternal Opioids (cocaine, heroin) Infant Dexamethasone Theophylline Caffeine Pancuronium Phenylephrine Neoplasms Pheochromocytoma Wilms tumor Mesoblastic nephroma Neuroblastoma Neurologic Pain Intracranial hypertension Seizures Miscellaneous Closure of abdominal wall defect Adrenal hemorrhage Hypercalcemia Extracorporeal membrane oxygenation Birth asphyxia

Content specification(s):

Recognize the clinical features of an infant with a condition affecting systemic blood pressure, such as shock or hypertension

Formulate a differential diagnosis of an infant with a condition affecting systemic blood pressure, such as shock or hypertension

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August: Question 9

You are evaluating a 12-day-old term infant with gastroesophageal reflux. A contrast study of the esophagus demonstrates a nonobstructive, oblique, posterior indentation of the esophagus. A chest radiograph reveals a left-sided aortic arch.

Of the following variations of the branching pattern of the aortic arch, the MOST likely cause of the incidental finding in the contrast study of the esophagus is:

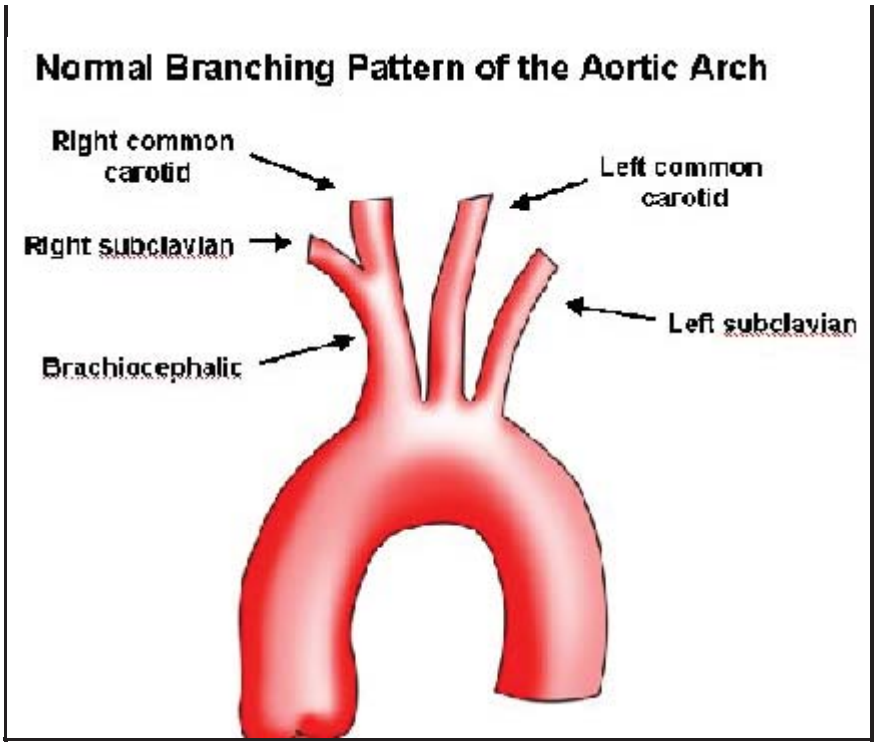
1	an aberrant right subclavian artery
2	an absent brachiocephalic trunk with right and left common carotid and subclavian arteries originating independently
3	the left common carotid originating from the brachiocephalic trunk
4	the left vertebral artery originating from the arch of aorta
5	the presence of a right and left brachiocephalic trunk

You selected 3, the correct answer is 1.

The arch of the aorta is the curved continuation of the ascending aorta that begins at the level of the second right sternocostal joint, and arches superiorly, posteriorly, and to the left in front of the trachea. The usual, left-sided, aortic arch crosses the left mainstem bronchus and reaches its apex at the left side of the trachea and esophagus as it passes over the root of the left lung. The arch descends posteriorly and becomes the descending aorta at the left side of the fourth thoracic vertebra. The normal order of the three branches of the aortic arch is the brachiocephalic trunk (which divides into the right common carotid and right subclavian arteries), followed by the left common carotid artery, and then the left subclavian artery (Figure 1). This pattern of branches occurs in 65% to 75% of people.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Figure 1



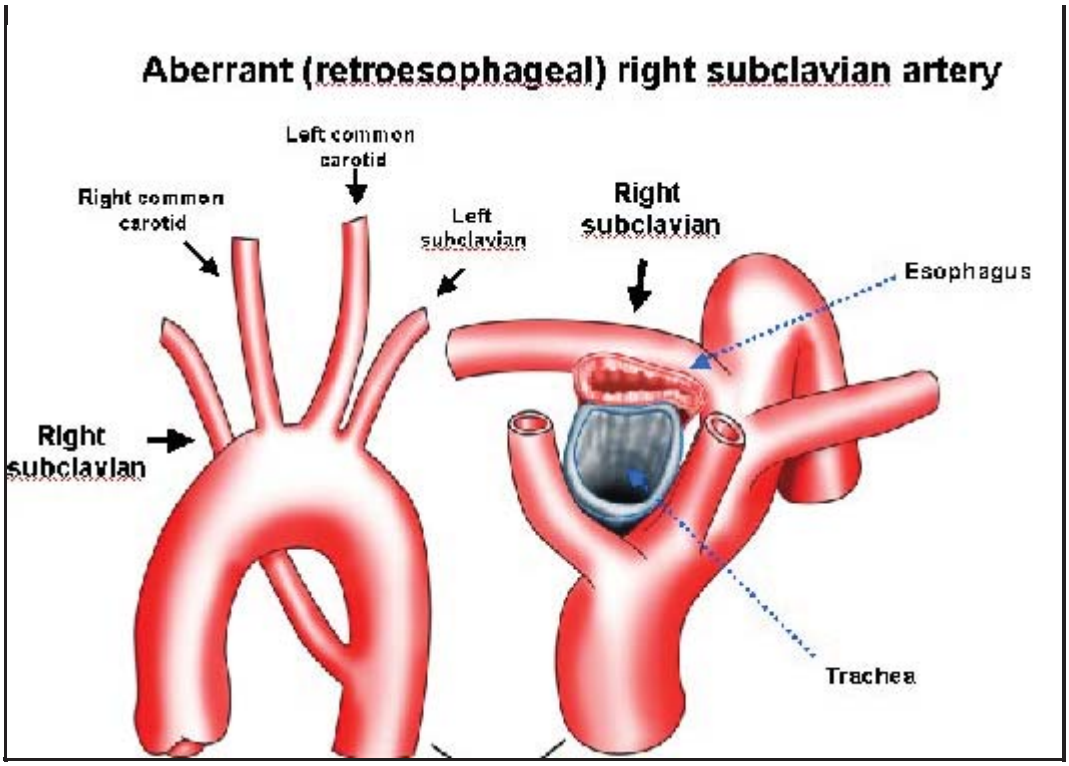
There are many variations in the number and position of vessels arising from the aortic arch. The number of vessels arising from the arch can range from as few as one to as many as six. Variations in the branching pattern of a left-sided aortic arch rarely are clinically significant. In contrast, abnormal branching patterns of a right-sided aortic arch result in vascular rings that cause compression of the trachea or bronchi leading to stridor and respiratory distress.

The development of the aortic arch is a complex process that involves the sequential appearance, followed by regression or persistence, of six paired vessels connecting the embryonic heart tube with the paired dorsal aortae. Each of the six paired vessels corresponds to a branchial pouch. Variations of the branches of the aortic arch occur when the dissolution or persistence of one of these six paired vessels is altered. The mechanism that determines dissolution or persistence of a given aortic arch component likely involves migration of neural crest cells into the region. Microdeletion of chromosome 22q11 is associated with a number of aortic arch anomalies.

A right-sided aortic arch is defined as an arch that crosses the right mainstem bronchus and reaches its apex at the right side of the trachea. A right-sided aortic arch is caused by the persistence of the fourth right arch rather than the usual fourth left arch.

An aberrant right subclavian artery, sometimes referred to as a retroesophageal subclavian artery, arises as the last (most left-sided) branch of the arch of the aorta (Figure 2).

Figure 2

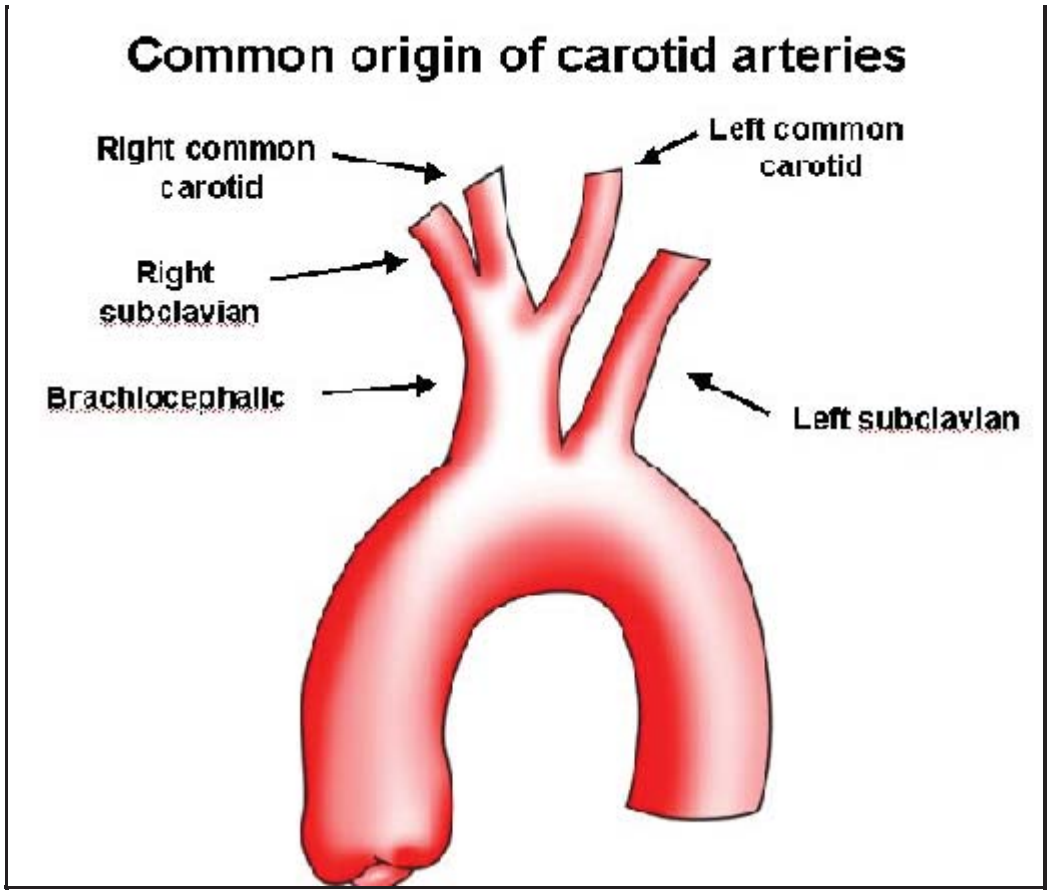


This anomalous distal origin of the right subclavian artery causes it to pass obliquely, posterior to the trachea and esophagus, to supply the right arm. An aberrant retroesophageal right subclavian artery always results in a vascular ring around the trachea and esophagus.

Esophageal compression caused by the vascular ring from an aberrant right subclavian artery can result in difficulty swallowing, which is called dysphagia lusoria, or "trick of nature." Dysphagia lusoria usually does not become symptomatic until adulthood, when the rigidity of the esophagus and subclavian artery increases. An aberrant right subclavian artery may be incidentally discovered in a newborn who undergoes a contrast esophagogram or echocardiogram. An aberrant right subclavian artery also may be suspected if a chest radiograph demonstrates an umbilical artery catheter in an oblique angle across the thorax toward the right arm.

In 10% to 25% of people, the left common carotid artery originates from the brachiocephalic trunk (Figure 3).

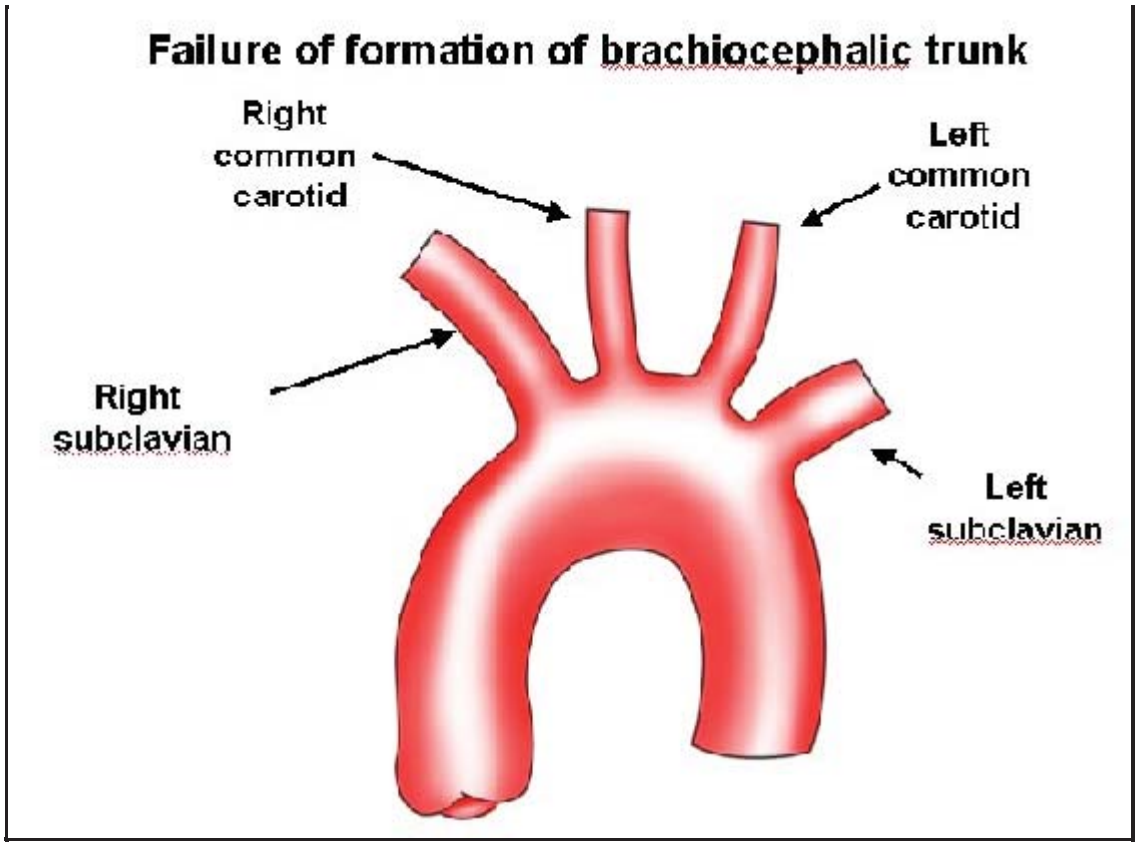
Figure 3



This aortic arch variant sometimes is referred to as a common origin of the carotid arteries because both the right and left common carotid arteries arise from a shortened brachiocephalic trunk. African Americans and patients with tracheoesophageal fistula and DiGeorge syndrome experience an increased incidence of a common origin of the carotid arteries. A common origin of the carotid arteries is usually asymptomatic; however, crowding of the mediastinum can lead to stridor or respiratory distress. This variant theoretically poses an increased risk of adverse neurologic sequelae after venoarterial extracorporeal membrane oxygenation (ECMO) because of potential occlusion of both carotid arteries by the arterial cannula. However, a recent study by Lamers and colleagues found no difference in neurologic outcome after ECMO in newborns with common origin of the carotid arteries.

The other aortic arch variants described in the vignette do not impinge upon the esophagus and are not associated with adverse consequences. In 2% of people, a brachiocephalic trunk fails to form, and the right and left common carotid and subclavian arteries originate independently (Figure 4).

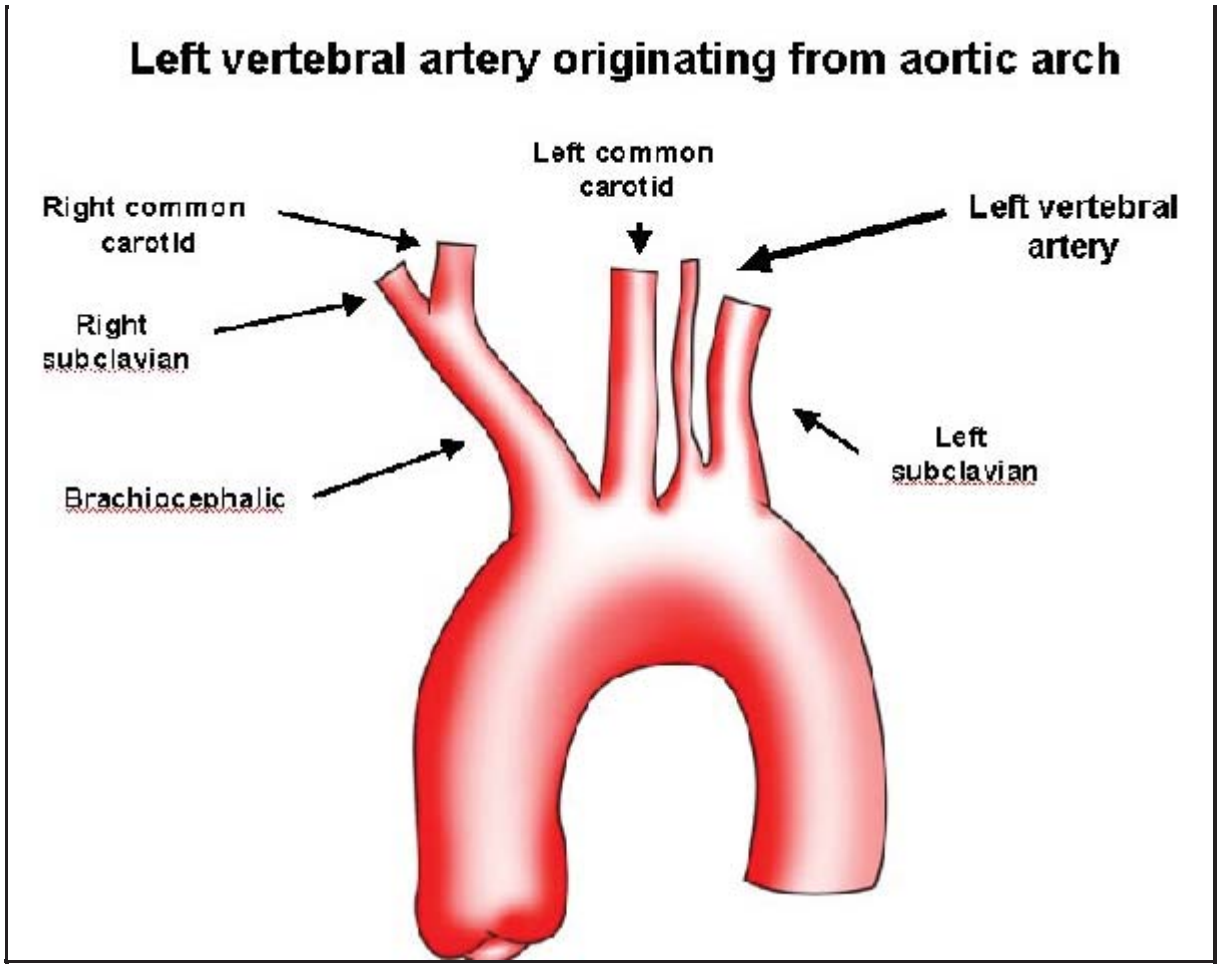
Figure 4



In this variant, there are four vessels arising directly from the aortic arch.

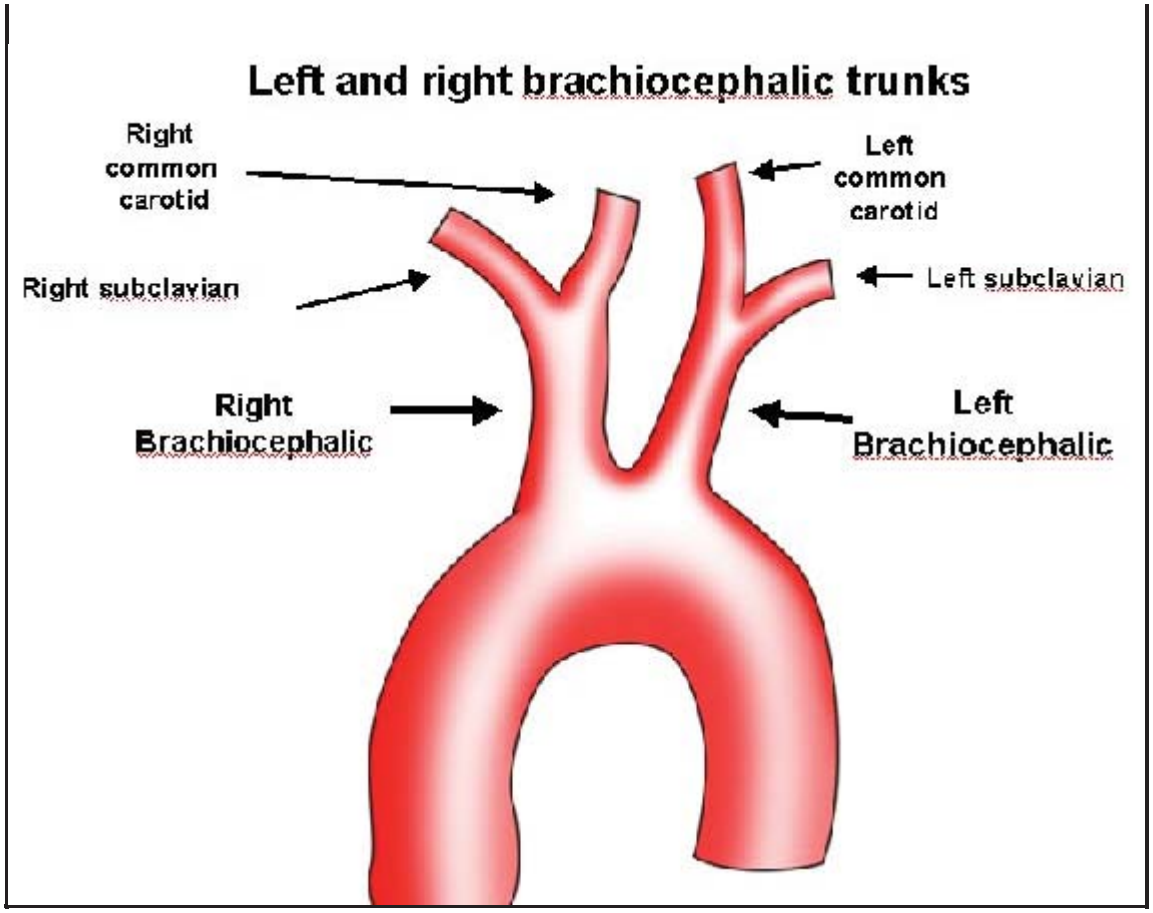
Normally the vertebral artery is the first branch of the subclavian artery. In 5% to 14% of people, the left vertebral artery originates from the arch of aorta between the left common carotid and left subclavian arteries (Figure 5).

Figure 5



Approximately 1% of people have both a right and left brachiocephalic trunk (Figure 6).

Figure 6



In this situation, there are two primary branches arising from the aortic arch.

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References:

Lamers LJ, Rowland DG, Seguin JH, Rosenberg EM, Reber KM. The effect of common origin of the carotid arteries in neurologic outcome after neonatal ECMO. *J Pediatr Surg* 2004;39:532-536

Moore KL, Dalley AF. *Clinically Oriented Anatomy.* 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 1999:143-148

Moore KL, Persaud TVN. *The Developing Human.* 6th ed. Philadelphia, Pa: WB Saunders; 1998:384-395

Weinber PM. Aortic arch anomalies. In: Allen HD, Clark EB, Gutgesell HP, Driscoll DJ, eds. *Moss and Adams' Heart Disease in Infants, Children, and Adolescents*. 6th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2001:707-735

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology, including genetics, of a neonate with an arterial vascular abnormality, such as anomalous origin of the subclavian artery or double aortic arch

Recognize the clinical features of a neonate with an arterial vascular abnormality, such as anomalous origin of the subclavian artery or double aortic arch

Recognize the laboratory features of a neonate with an arterial vascular abnormality, such as anomalous origin of the subclavian artery or double aortic

arch

Formulate a differential diagnosis for a neonate with an arterial vascular abnormality, such as anomalous origin of the subclavian artery or double aortic arch

Understand the total management plan (medical and/or surgical) and associated potential complications for such treatment of a neonate with an arterial vascular abnormality, such as anomalous origin of the subclavian artery or double aortic arch

PREVIOUS NEXT

August: Question 8

A male infant with a birthweight of 3.2 kg was delivered vaginally by a 32-year-old primigravida following an unremarkable term pregnancy. Intrapartum antibiotics were administered for suspected chorioamnionitis and group B *Streptococcus* colonization. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. At 2 hours of age, he developed progressively increasing respiratory distress requiring assisted ventilation. Physical examination revealed bounding femoral pulses, systolic murmur, and hepatomegaly. Chest radiograph was remarkable for cardiomegaly and pulmonary congestion. Echocardiogram revealed normal cardiac anatomy, severely dilated right-sided structures, accelerated flow within the inferior vena cava, and a large hepatic arteriovenous malformation (HAVM). An abdominal ultrasound showed multiple tubular anechoic and hypoechoic structures with Doppler and color flow findings consistent with a massive HAVM involving predominantly the left lobe of the liver with extension into the right lobe (Figures 1 to 3).

Figure 1 (Courtesy of C Becker, MD):

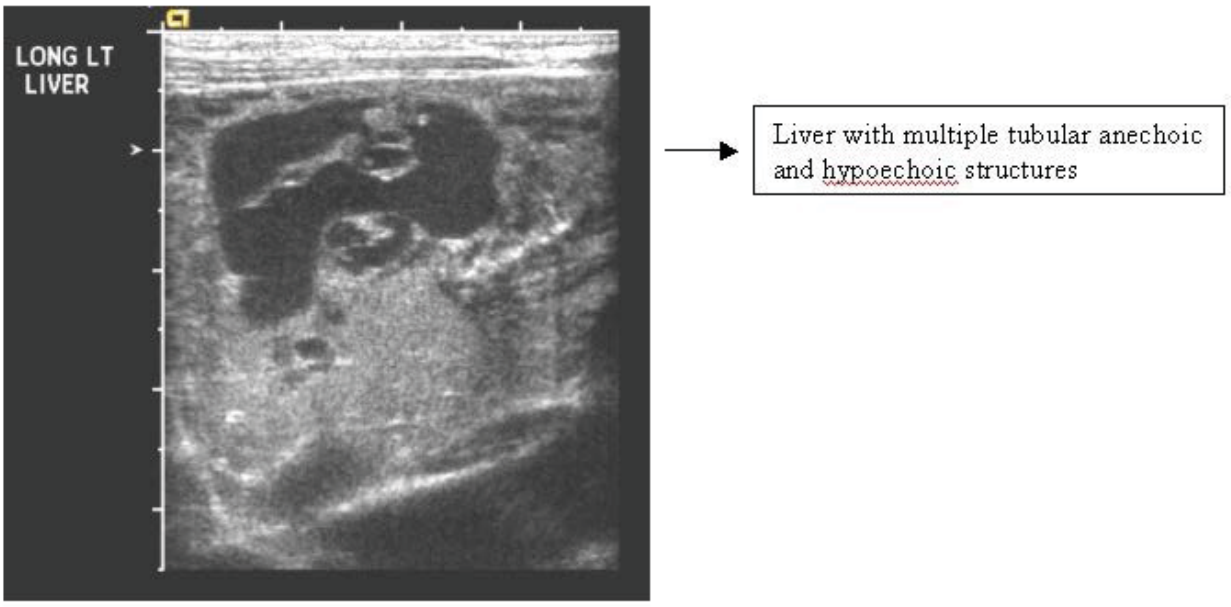
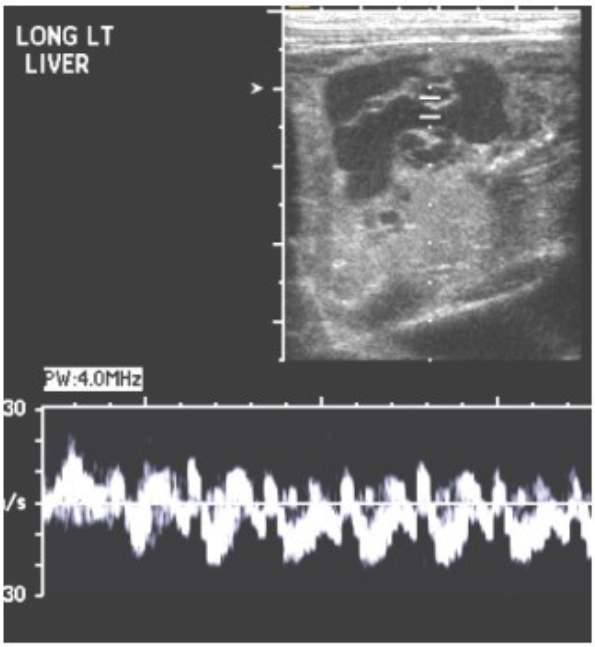
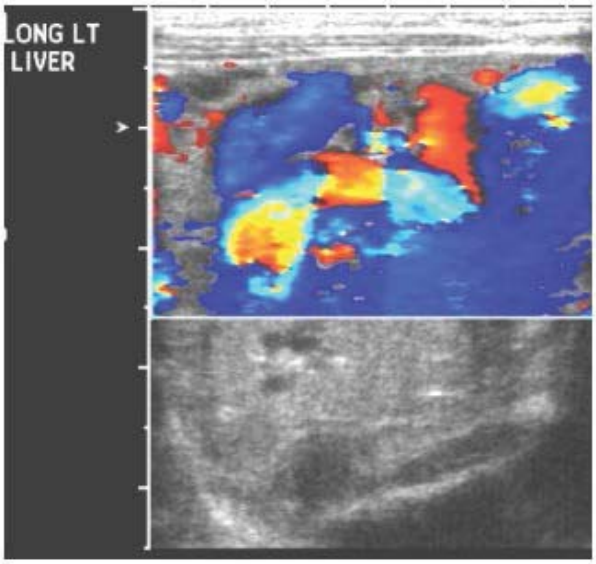


Figure 2 (Courtesy of C Becker, MD):



Doppler signal showing turbulent flow in a vein in the hepatic arteriovenous malformation.

Figure 3 (Courtesy of C Becker, MD):



Color flow showing tubular structures filled with rapidly flowing blood

Angiography showed a complex, extensive HAVM fed predominantly by an enlarged left hepatic artery and by a few abnormal branches from the right hepatic and cystic arteries.

Of the following, the MOST accurate statement about HAVM is that:

1	Cutaneous hemangiomas are important accompanying manifestations.
2	Hydrops fetalis is the most common presenting symptom of HAVM in newborns.
3	Most HAVMs undergo involution by 2 to 3 years.
4	Tests of liver function typically have normal or mildly deranged findings.
5	Treatment with corticosteroids is indicated only in symptomatic infants.

You selected 3, the correct answer is 4.

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Two fundamentally different types of benign hepatic vascular lesions are seen in infants and young children: the more common (90%) hepatic infantile hemangiomas (also known as hemangioendotheliomas) and the less common (10%) hepatic arteriovenous malformations (HAVM). The two lesions differ markedly in their clinical and radiologic manifestations, histopathologic features, and biological behavior.

Hepatic arteriovenous malformations are congenital abnormalities in the formation of blood vessels that shunt blood through direct arteriovenous connections without abnormal neoplastic tissue between the anomalous vessels. Unlike hemangiomas, they neither have growth potential nor are they capable of regression. These lesions are completely negative for the endothelial marker, GLUT1. Most cases become apparent at or shortly after birth (90%), although prenatal ultrasonographic diagnosis has been reported. No gender predilection is noted. Prompt surgical intervention is necessary in symptomatic patients. Abdominal mass or distention, congestive heart failure, cardiomegaly, and anemia are common signs; occasionally, severe edema/fetal hydrops and associated Kasabach-Merritt phenomenon also may occur. Liver function test results are usually normal. Ultrasound findings include a nest of tortuous enlarged vessels located usually in one lobe of the liver. Unenhanced computed tomography may demonstrate hypoattenuating areas within one lobe of the liver. After contrast administration, lesions enhance intensely and homogeneously in the arterial or early portal venous phase, with rapid washout of contrast material. The absence of delayed uptake of contrast material around the hypertrophic vessels supports a diagnosis of arteriovenous malformations.

Hepatic arteriovenous malformation does not regress spontaneously or respond to treatment with corticosteroids. Treatment involves medical management of CHF and definitive treatment of the underlying cause, ie, hepatic artery embolization or ligation, partial hepatic resection, or orthotopic liver transplantation. Surgical resection or ligation of the feeding artery is associated with significant risk in sick infants with extensive HAVM and multiple collateral vessels. Transcatheter embolization is most effective in patients with a single arteriovenous fistula. Embolization may improve outcomes in severely ill neonates with multiple collaterals. Orthotopic liver transplant may be the only recourse for those infants with HAVM and multiple collaterals who do not respond to transcatheter embolization and whose lesions are not amenable to surgical resection. Although rare, patients having HAVM have a 50% to 90% mortality risk, emphasizing the importance of a high index of suspicion for early diagnosis and definitive treatment.

Infantile hemangiomas are nonmalignant vascular tumors that exhibit hypercellularity and endothelial multiplication, resulting in a large cell mass that simultaneously involves the formation and dilation of feeding and draining vascular channels. The presence of low-resistance tumoral vessels and the association with large feeding arteries and draining veins explain the observation of arteriovenous shunting, even though hemangiomas are not arteriovenous malformations (AVMs) but neoplasms.

Hemangiomas may be clinically silent or may cause asymptomatic hepatomegaly in the first few weeks or months of life. Some infants may present with congestive heart failure (CHF), consumptive coagulopathy (Kasabach-Merritt phenomenon). Accompanying manifestations include hemangiomas of the skin and other organs (hemangiomatosis) and hypothyroidism. Laboratory studies are essentially normal except for mildly elevated serum transaminase levels. On ultrasonography, infantile hemangiomas may manifest as a localized mass or as multifocal diffuse masses with areas of both increased and decreased echogenicity relative to adjacent parenchyma, with or without calcifications. Histopathologically, they are characterized by closely packed capillary vessels with interspersed pericytes. The endothelium of the vascular channels is intensely and consistently GLUT1 immunoreactive. GLUT1 is an erythrocyte-type glucose transporter protein and an endothelial marker.

The natural history of infantile hepatic hemangioma consists of a growth period during the first 6 months, with progressive regression and involution over the next 2 to 3 years. They may be life threatening during the proliferative phase. Asymptomatic patients can be closely followed up without treatment. Standard treatment for symptomatic hemangiomas is administration of corticosteroids. If there is no clinical improvement, treatment with interferon a should be considered. Embolization or surgery should be reserved for patients in

whom CHF remains after a reasonable trial of medical therapy.

References:

Boon LM, Burrows PE, Paltiel HJ, et al. Hepatic vascular anomalies in infancy: a twenty-seven-year experience. *J Pediatr.* 1996;129:346-354

Gallego C, Miralles M, Marin C, Muyor P, Gonzalez G, Garcia-Hidalgo E. Congenital hepatic shunts. *Radiographics.* 2004;24:755-772

Mo JQ, Dimashkieh HH, Bove KE. GLUT1 endothelial reactivity distinguishes hepatic infantile hemangioma from congenital hepatic vascular malformation with associated capillary proliferation. *Hum Pathol.* 2004;35:200-209

Paley MR, Farrant P, Kane P, Heaton ND, Howard ER, Karani JB. Developmental intrahepatic shunts of childhood: radiological features and management. *Eur Radiol.* 1997;7:1377-1382

American Board of Pediatrics Content Specification(s):

Know the etiology, clinical and laboratory features, and treatments of abdominal masses in the neonate

Know the etiology and clinical manifestations of abdominal masses in the neonate

Know the laboratory and radiographic features, the differential diagnosis, and management of abdominal masses in the neonate

Understand the clinical features and evaluation of arteriovenous malformations

Understand the management, complications of management, and outcome of arteriovenous malformations

PREVIOUS NEXT

February: Question 9

A 26-year-old woman with four healthy children was transferred from a community hospital for suspected premature labor and possible chorioamnionitis. She was thought to be at 35 weeks' gestation and was treated with terbutaline, magnesium sulfate, and antibiotics. Fetal sonograph revealed multiple intracardiac tumors with left ventricular outflow obstruction. Tocolysis was temporarily successful, but a male infant was delivered vaginally the next morning. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively, and the infant was vigorous at birth, requiring no resuscitation.

Physical examination showed characteristics compatible with a 37-week normally grown infant. Heart rate was 129 beats per minute, and respiratory rate was 65 breaths per minute. Oxygen saturation was 96% in room air. Blood pressure was 47 mmHg (6.27 kPa) systolic and 26 mmHg (3.47 kPa) diastolic (mean = 33 mmHg [4.4kPa]). Neurological examination was normal, and there were no skin lesions. Cardiac examination showed three heart sounds (triple rhythm). There was a grade 3/6 high-pitched systolic murmur, heard best at the lower left sternal border, and a grade 2/6 lower-pitched systolic murmur at the upper left sternal border. Pulses were normal and full, and capillary refill time was 3 seconds. Echocardiography confirmed the multiple round tumors in the muscle of the ventricular septum and left ventricular wall with minimal outflow obstruction (Figure 1).

Of the following, the MOST likely cardiac diagnosis for this infant is multifocal:

1	fibroma
2	hemangioma
3	myxoma
4	rhabdomyoma
5	teratoma

You selected 4, the correct answer is 4.

Cardiac tumors are uncommon in childhood, occurring only in 0.08% to 0.14% of pregnancies. The apparent incidence has increased in the past several years, with many identified by fetal sonography screening. In the past, most cardiac tumors were either diagnosed at autopsy or were asymptomatic and not diagnosed at all. Most cardiac tumors found in the perinatal period are histologically benign, but they may cause serious problems-including death-depending on their effect on cardiac function. In an Armed Forces Institute of Pathology infant series, 45 cases were benign, and two malignant. Several of these tumors can be associated with

genetic disorders, such as tuberous sclerosis, familial myxoma syndrome, neurofibromatosis, the Gorlin-Goltz syndrome, and Beckwith-Wiedemann syndrome.

Of the benign cardiac tumors diagnosed in the fetus or neonate, the most common are rhabdomyomas, followed (in order of decreasing incidence) by teratomas, fibromas, hemangiomas, and mesotheliomas.

Rhabdomyomas of the heart comprise more than 60% of all cardiac tumors identified in the fetus or newborn. Clinical manifestations vary from asymptomatic to fatal. In between, there are rhythm disturbances, myocardial compromise, and degrees of intracardiac obstruction. Systolic cardiac murmurs along the right or left sternal borders can be the initial sign. Almost any arrhythmia in the fetus or newborn can be the first sign of this tumor (Figure 2).

Tuberous sclerosis is an autosomal dominant disorder, occurring in 1 in 6,000 to 10,000 births. Two-thirds of cases result from new mutations. The mutation in tuberous sclerosis is in the TSC1 or TSC2 gene, which code for tumor suppressors, hamartin and tuberin. The syndrome is typified by the triad of mental retardation, epilepsy, and facial angiofibromas. More than half of infants with tuberous sclerosis have cardiac rhabdomyomas at birth, and these initially may be the only sign of the syndrome. These cardiac tumors tend to regress spontaneously after 32 weeks' gestation and become undetectable by the first birthday. Skin lesions, such as hypopigmentation or "mountain ash" macules or even angiofibromas (adenoma sebaceum), might be present at birth or appear later. Cortical or subependymal hamartomas ("tubers") might be seen on brain imaging. Renal angiomyolipomas usually appear later in life.

Teratomas are the second most common cardiac tumors in this age group. They can originate from the pericardium or within the heart. Most occur in the pericardial space attached to a great artery.

Fibromas can produce left ventricular outflow obstruction, as seen in the vignette, but they are far less common. They most often are found in the intraventricular septum and can cause the same symptoms as rhabdomyomas.

Myxoma is the most common intracardiac tumor in adults but is extremely rare in infancy, as are vascular tumors of the heart.

References:

Choi JM, Jaffe R, Maidman J, Baxi LV. Multiple cardiac rhabdomyomas detected in utero. *Fetal Diagn Ther*. 2000;15:174-176

Department of Neurology, Children's Hospital, Boston. Multidisciplinary Tuberous Sclerosis Program: Research Update Web site. Available at: http://www.tsclinic.org/research_update.php. Accessed October 7, 2005

Isaacs H Jr. Fetal and neonatal cardiac tumors. *Pediatr Cardiol.* 2004;25:252-273

Lonergan GJ, Smirniotopoulos JG. Case 64: tuberous sclerosis. *Radiology.* 2003;229:385-388

Content Specification(s):

Understand the pathophysiology, including genetics, of an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor, and electrolyte imbalances

Understand the clinical features and diagnosis of neurocutaneous disorders, including neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, etc

PREVIOUS NEXT

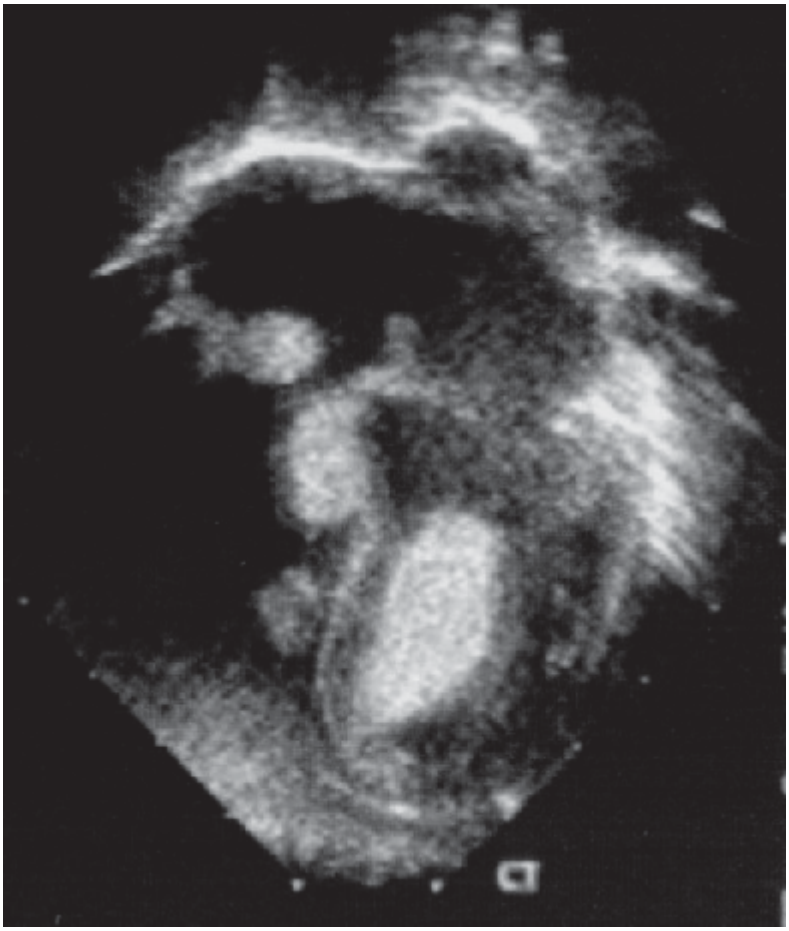
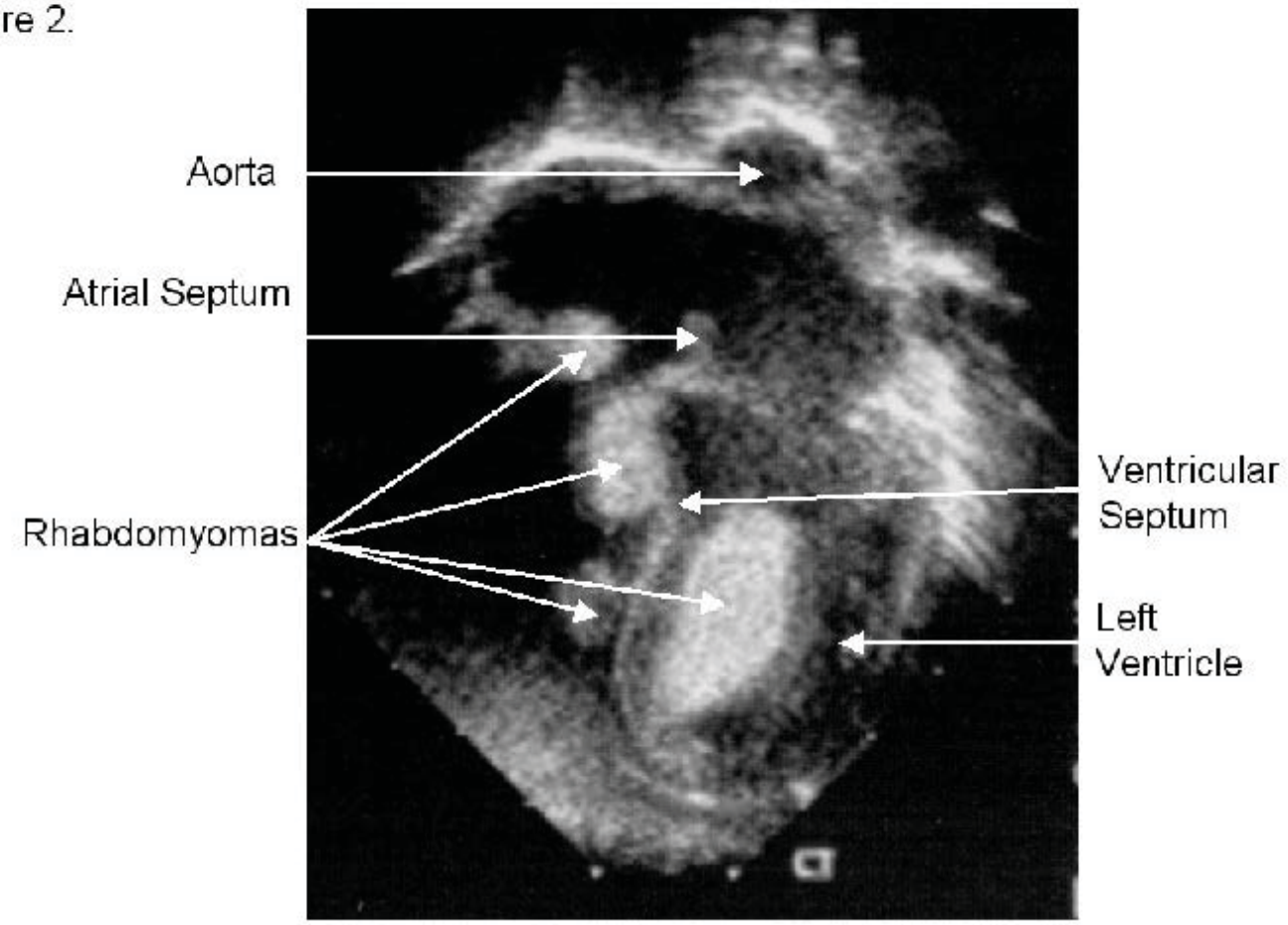


Figure 2.


Aorta
Atrial Septum
Rhabdomyomas
Ventricular Septum
Left Ventricle

January: Question 3

A 3-week-old child is admitted to the hospital for poor feeding and decreased urine output. Respiratory rate is 72 breaths/min, capillary refill time is 4 seconds, and the liver is felt 2 cm below the right costal margin. Arterial oxygen saturation is 90%. Echocardiogram shows a single functioning ventricle and pulmonary overcirculation.

Of the following, the treatment MOST likely to reduce pulmonary blood flow is:

1	induced alkalosis
2	inhaled nitric oxide
3	inhaled nitrogen
4	inhaled oxygen
5	lowered hematocrit

You selected 4, the correct answer is 3.

pulmonary blood flow

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Several cardiac lesions have the potential for manifesting, at different times, both left-sided and right-sided signs and symptoms. A single functioning ventricle is the clearest example of complete mixing of systemic and pulmonary venous blood. The systemic and venous circulations are in precarious balance, each side taking a portion of the output of the single ventricle.

Newborns with these mixed lesions can suffer initially from inadequate pulmonary blood flow (PBF), exhibiting arterial O_2 saturation <65%. After several weeks, pulmonary vascular resistance drops, and PBF can become excessive. Once PBF is more than twice systemic blood flow, signs of congestive heart failure are seen and can include tachypnea, decreased urine output, increased capillary refill time, systemic hypoperfusion, acidosis, and shock. Arterial O_2 saturation may approach 90% but with poor O_2 delivery to the tissues.

Cardiac lesions with this "single ventricle physiology" include double-outlet right ventricle, truncus arteriosus, complete common atrioventricular canal, tricuspid atresia with ventricular septal defect, and hypoplastic left heart syndrome.

Treatments that increase pulmonary vascular resistance will reduce PBF. Supplemental nitrogen to reduce inspired O_2 below 21% will cause pulmonary vasoconstriction and decrease PBF. This effect will increase systemic flow and give a greater O_2 delivery to the tissues, despite lower O_2 saturations. Nitrogen

administration is the preferred answer to the vignette.

Other strategies to reduce PBF include inducing hypoventilation with paralytic agents and mechanical ventilation to cause hypercarbia, acidosis, and pulmonary vasoconstriction. A high or low positive end expiratory pressure, resulting in a functional residual capacity (FRC) substantially higher or lower than normal, will reduce PBF by respectively hyperinflating or collapsing alveoli. Raising the hematocrit over 45% will increase blood viscosity and reduce PBF. The strategy chosen in specific clinical situations must be individualized.

Drugs given to change the systemic vascular resistance have unpredictable effects on pulmonary vascular resistance. Because the two resistances are in balance, a relatively greater effect on one than the other might cause unpredictable flow changes. Each case should be approached cautiously.

Several measures can be relied on to increase PBF in the face of the initial hypoxemia at birth. Hyperventilation and bicarbonate infusion will produce hypocarbia and alkalosis and will dilate the pulmonary vasculature and increase PBF. A normalized FRC and a low hematocrit will allow normal or increased PBF. Inhaled nitric oxide will dilate the pulmonary vascular bed and increase PBF without affecting the systemic vasculature. Oxygen is well known as a pulmonary vasodilator. These measures would not be appropriate for the child in the vignette, in whom a reduction in PBF is needed.

References:

Wernovsky G, Chang AC, Wessel DL. Intensive care. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:350-381

Wernovsky G, Gruber PJ. Common congenital heart disease: presentation, management, and outcomes. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:827-871

Content specification(s):

Understand the pathophysiology, including genetics, of a neonate with a mixed cardiac lesion

Recognize clinical features of a neonate with a mixed cardiac lesion

PREVIOUS NEXT

January: Question 4

An infant is delivered at 41 weeks' gestation after an uncomplicated pregnancy. He voided in the delivery room, breastfed, and roomed-in with his mother. Neonatology is consulted 12 hours after birth when the infant vomits during his first two attempts at feeding. A chest radiograph indicates dilation of the upper esophagus with an orogastric tube curled in the pouch. Review of the obstetrical history shows no suggestion of polyhydramnios on ultrasound examinations done at 18 weeks' and again at 40 weeks' gestation.

Of the following, the MOST likely explanation for failure to find increased amniotic fluid volume (polyhydramnios) in this case is:

1	decreased pulmonary secretion of fluid
2	diagnostic error
3	fetal oliguria
4	intramembranous fluid transfer
5	transmembranous fluid transfer

You selected 3, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The amniotic cavity forms early in gestation. At the time of implantation, the extracelomic cavity, which will become the amniotic cavity, already is present. As early embryogenesis proceeds, the amniotic cavity increases in volume relative to the embryo during the period of folding and flexion of the embryonic plate. During the subsequent fetal period, amniotic fluid (AF) volume increases parallel to fetal size.

AF water in the embryonic period comes from maternal plasma. During the early fetal period, AF is similar to fetal plasma, with easy transfer of fluid and solutes across fetal skin, amnion, placenta, and umbilical cord surfaces. Although fetal urination begins at 8 weeks' gestation and is followed by fetal swallowing, their influence on AF volume and content begin later, after midpregnancy.

Once the fetal skin is keratinized (20 to 25 weeks' gestation), AF volume and fetal size lose their linear relationship. AF volume reaches approximately 800 mL by 28 weeks' gestation and stays roughly the same until term, after which it decreases. After skin keratinization, AF dynamics result from the balance of two sources of production (fetal urine and fetal oral, nasal, tracheal, and pulmonary secretions) and three routes of removal (fetal swallowing, intramembranous transfer, and

transmembranous transfer).

AF production from fetal urine is approximately 300 mL/kg of fetal weight per day. Respiratory tract secretions add another 60 to 100 mL/kg of fetal weight per day, one-half of which is swallowed before entering the AF pool. The predominant route for AF removal is fetal swallowing, estimated to be 200 to 250 mL/kg fetal weight per day. Intramembranous transfer occurs when fluid from the AF cavity traverses the single-layered amnion to enter the fetal circulation in the vascularized chorion. Fluid transfer by this route can range from 200 to 500 mL per day. The transmembranous route allows transfer of fluid from the AF cavity across the membranes to enter the maternal circulation through the uterine lining. This pathway has a minimal effect on AF volume, estimated at 10 mL per day.

Infants who have intestinal obstruction may develop polyhydramnios, although only one-half of cases of esophageal atresia and one-third of cases of duodenal or jejunal blockage show this association. In these cases, the intramembranous pathway is the predominant route for AF removal. Animal studies suggest that a combination of passive diffusion and bulk transfer by a transcellular vesicular mechanism promotes transfer of AF and its dissolved solutes into the fetal circulation. The transcellular vesicular transfer is mediated by vascular endothelial growth factor, as suggested by ovine studies. Aquaporin proteins in fetal membranes are another potential regulator.

Decreased pulmonary secretion of fluid is unlikely in the case in this vignette because AF volumes were adequate on prenatal ultrasonographic studies and the child presents no respiratory symptoms suggesting pulmonary hypoplasia.

The absence of polyhydramnios should not exclude a diagnosis of esophageal obstruction. As noted above, polyhydramnios occurs in only one-half of cases of esophageal atresia, so its absence should not suggest a diagnostic error.

Fetal oliguria likely would be associated with reduced AF volume in utero, and passage of urine in the delivery room would be unlikely.

Although transmembranous AF removal occurs, its magnitude is insufficient to explain the significant AF clearance required for the AF volume to remain normal as noted in the vignette.

References:

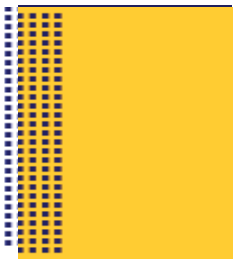
Underwood MA, Gilbert WM, Sherman MP. Amniotic fluid: not just fetal urine anymore. *J Perinatol.* 2005;25:341-348

Content Specification(s):

Know the mechanism of production and clearance of fetal lung fluid, its contribution to amniotic fluid, and its importance to fetal lung development

Know the indications for and complications of methods of direct assessment of the fetus, including chorionic villus sampling, amniotic fluid sampling, and fetal blood sampling

PREVIOUS NEXT



January: Question 9

A 3-week-old infant is seen in the office for poor feeding. She was born at home at term. Her heart rate is 180 beats/min and respiratory rate is 70 breaths/min. A murmur is heard. The liver is felt 4 cm below the right costal margin. You suspect congestive heart failure (CHF).

Of the following, the condition likely to present EARLIEST with CHF is:

1	atrial septal defect
2	common atrioventricular canal
3	patent ductus arteriosus
4	truncus arteriosus
5	ventricular septal defect

You selected 5, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Left-to-right shunt lesions become hemodynamically significant in the first six weeks after birth, when left-sided pressures supercede right-sided pressures, and pulmonary vascular resistance (PVR) drops, causing pulmonary overcirculation. Overcirculation causes pulmonary congestion and edema and respiratory symptoms, such as tachypnea and poor feeding. Overload of the right heart causes an enlarged liver and systemic venous congestion, with signs of tachycardia and sweating. Overcirculation of blood through the lungs comes at the expense of the systemic blood flow. Because of this compromise, there can be inadequate oxygen delivery to the tissues despite adequate oxygenation of the blood.

The left-to-right shunt can be through an atrial septal defect (Image 1), a ventricular septal defect (Image 2), a common atrioventricular canal (Image 3), a truncus arteriosus (Image 4), and a patent ductus arteriosus (Image 5). Among the conditions listed, the one likely to present earliest with CHF is truncus arteriosus (TA). Other conditions, such as aortopulmonary window or arteriovenous fistulae, also may present with early CHF.

In TA, the pulmonary arteries arise from a combined aorta and main pulmonary artery, the truncus. TA occurs in 1 in 16,000 live births. It is caused by the failure of septation of the conotruncus in the fifth through ninth weeks of development. It is associated with chromosomal microdeletion 22q11 more than one-third of the time, and with a ventricular septal defect (VSD) 98% of the time. Physical findings include bounding pulses caused by the frequently regurgitant truncal valve, a loud single second heart sound caused by the single valve, and a loud pansystolic

murmur from the truncal flow. The presentation with CHF earlier than the other left-to-right lesions is due to the systemic pressure in the truncus directing large flows directly into the pulmonary circulation, even before PVR decreases substantially. Untreated, the median survival is five weeks.

Atrial septal defect (ASD) occurs in 1 in 1,000 live births. It usually is caused by the failure of migration of the septum secundum over the fenestrations of the septum primum during the fifth and sixth weeks. Most cases are sporadic, although there can be familial transmission with Holt-Oram syndrome or with mutations on chromosome 5. Physical signs, if any, include a soft systolic murmur at the left second interspace with radiations to the lung fields, and a widely split second heart sound. The left-to-right flow is not as dependent on the pressure differences as on the relative atrial compliances; the right atrium is relatively stiff at birth and only slowly increases compliance. Symptoms of CHF rarely are seen, even if the ASD is untreated into adulthood.

Common atrioventricular canal (CAVC), also known as endocardial cushion defect, occurs in 1 in 5,000 live births. It is caused by incomplete closure of the atrial septum and the ventricular septum, and abnormal formation of the mitral and tricuspid valves, often forming one large atrioventricular valve. Approximately 70% of children with CAVC have Down syndrome. Murmurs heard include that of mitral insufficiency (holosystolic at the lower left sternal border with radiation to the axillae) and of increased pulmonary valve flow (systolic at the upper left sternal border). When PVR drops in the first six weeks after birth, the increased pulmonary artery flow causes pulmonary edema and CHF. The relative hypoplasia of the lungs in Down syndrome is thought to protect many of these children by limiting pulmonary flow.

Patent ductus arteriosus (PDA) persists in 1 in 2,000 term births. Unlike PDA in preterm infants, the ductus is structurally abnormal and will not close with prostaglandin synthetase inhibitor treatment. First-trimester rubella often results in persistent PDA. A genetic component is suggested in some families. Signs and symptoms correlate with the size of the communication. A small PDA may have no symptoms and a loud murmur. The murmur peaks in late systole and continues through the second heart sound into diastole. A moderate PDA may show slow development, over several months, of tachypnea, irritability, and poor feeding. The development is slow enough to allow compensatory left ventricular hypertrophy and a dynamic precordium. The murmur is harsh, machinery-like, and holosystolic. An infant with a large PDA is expected to tire easily and sweat excessively. Tachycardia and tachypnea are seen. A thrill is palpable, the precordium is hyperdynamic, and the pulse pressure is wide. The murmur may be inaudible due to the lower flow of ventricular failure.

VSD occurs in 1 in 280 live births. The failure of septation between the fourth and the eighth weeks may occur at various portions of the ventricular septum. The murmur is systolic over the left sternal border but may be holosystolic when large flows are involved. When PVR falls, small and medium defects limit the left-to-right shunt. A child with a VSD has a low probability of ever showing clinical symptoms. Closure occurs over the first year after birth in most children with a muscular or a perimembranous VSD. Inlet or outlet VSDs rarely close.

References:

Mair DD, Edwards WD, Julsrud PR, Seward JB, Danielson GK, Goldmuntz E. Truncus arteriosus. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in*

Infants, Children, and Adolescents. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:910-923

Moore P, Brook MM, Heymann MA. Patent ductus arteriosus. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:652-669

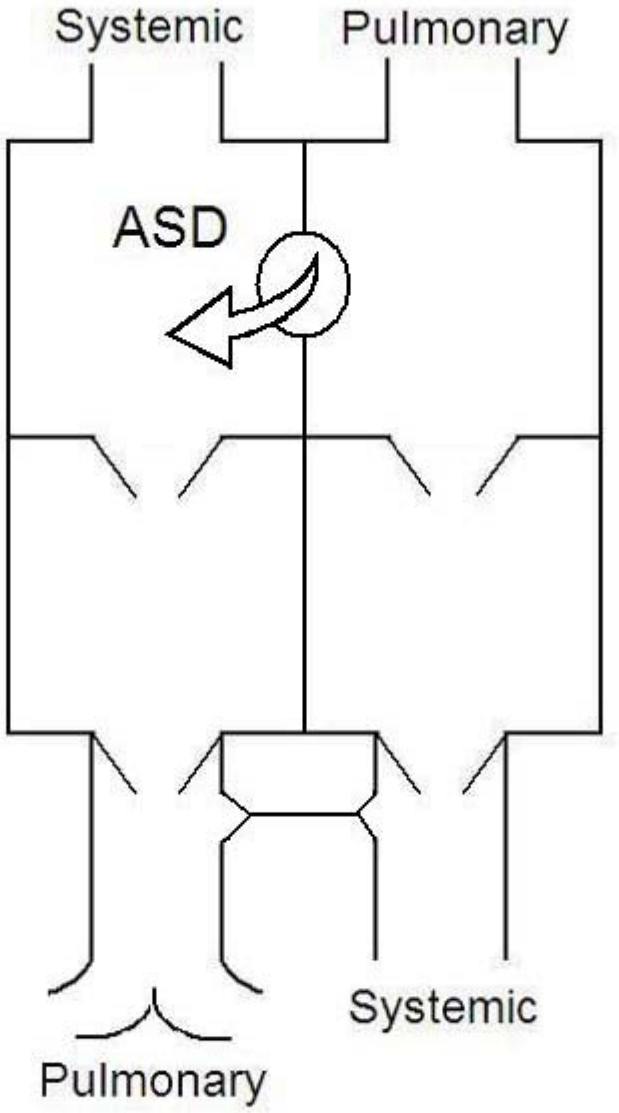
Wernovsky G, Gruber PJ, Common congenital heart disease: presentation, management, and outcomes. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:827-871

Content Specification(s):

Recognize the clinical features of a neonate with a left-to-right shunt lesion

Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion

PREVIOUS NEXT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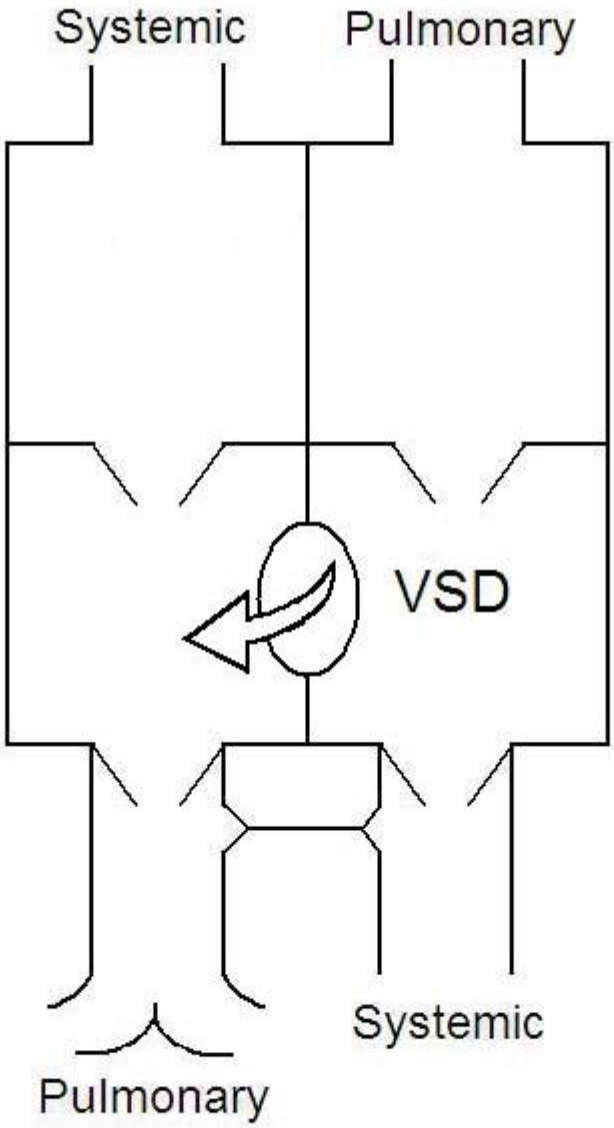
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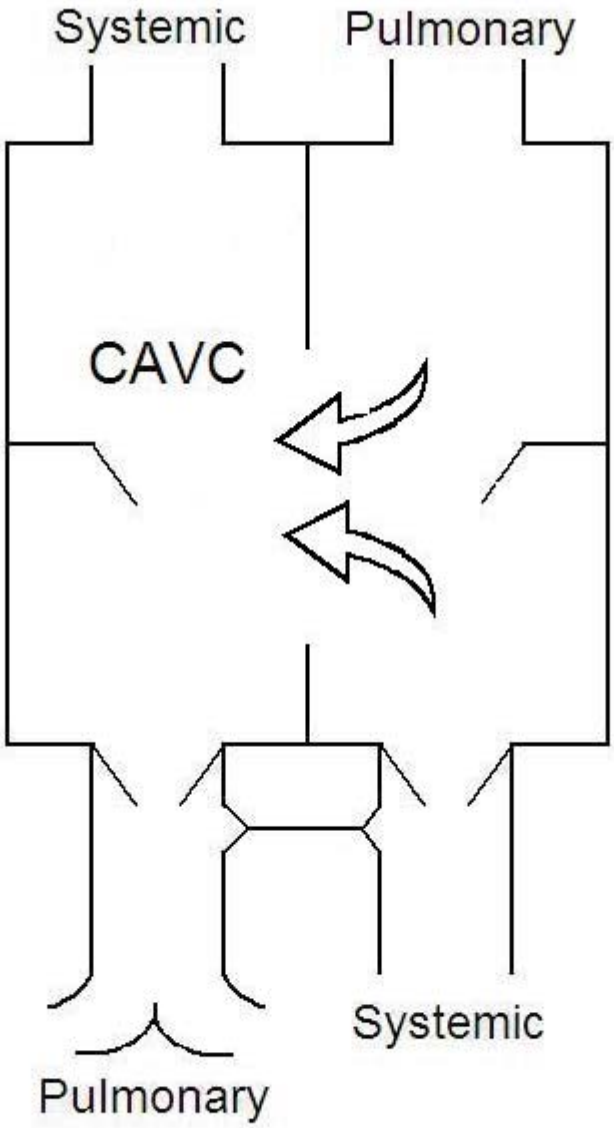
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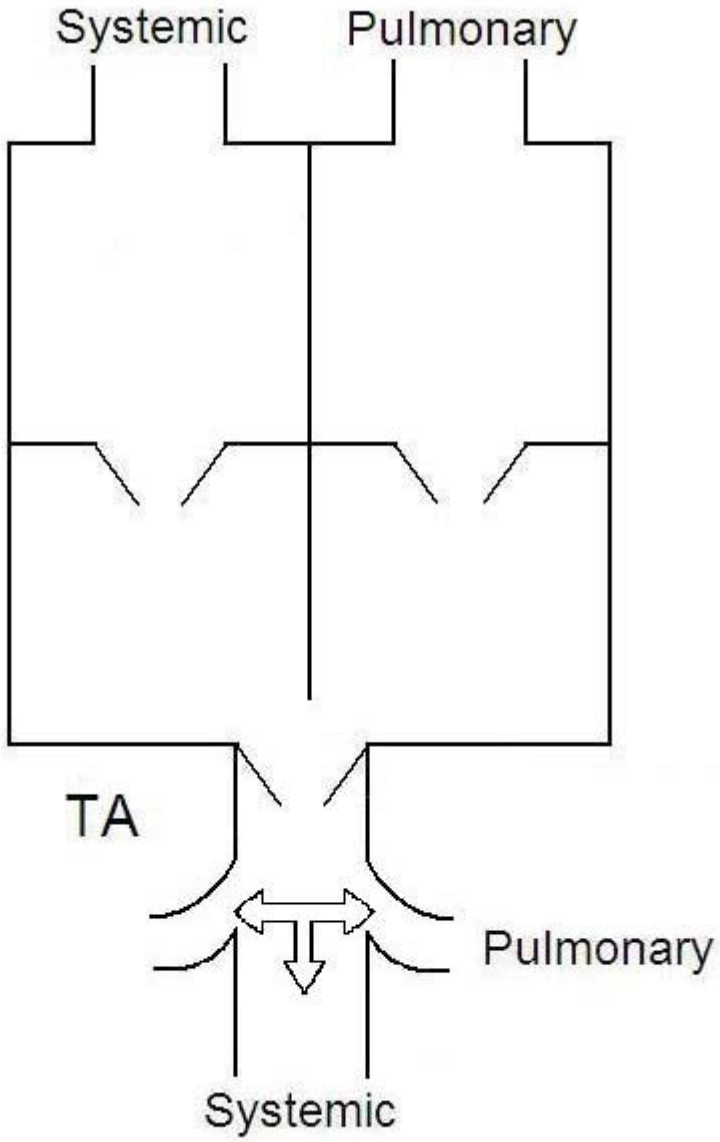
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TA
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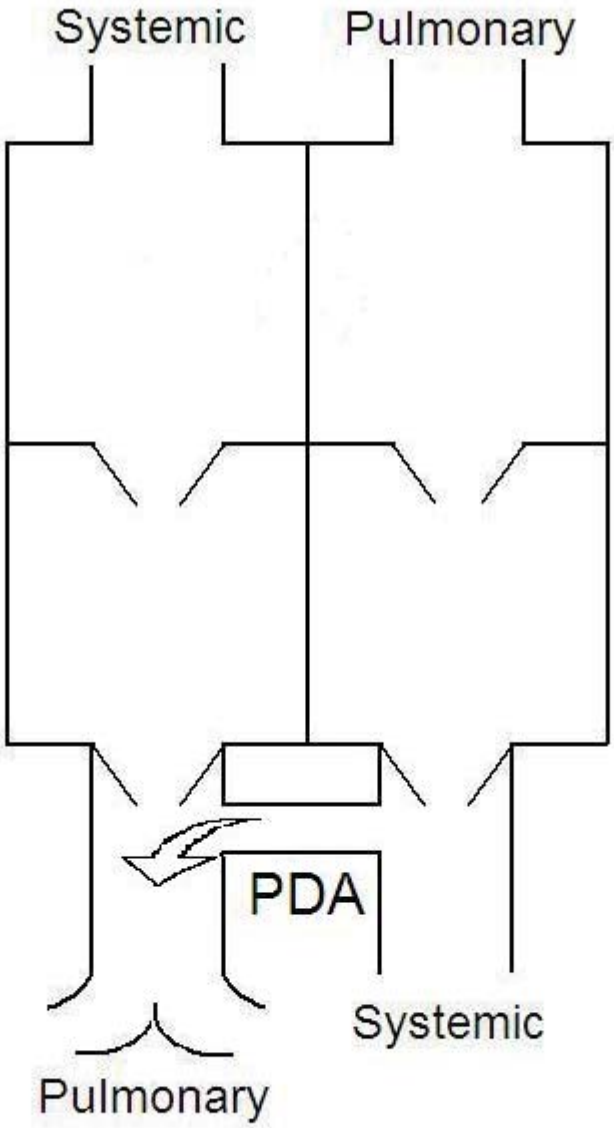
Systemic


Systemic
Pulmonary
PDA
Systemic
Pulmonary

January: Question 1

A female infant born at an estimated gestational age of 33 weeks has a sonorous seal-bark cry in the delivery room. After admission to the newborn intensive care unit, she develops excessive salivation requiring repeated suctioning. Physical examination reveals no dysmorphic features, mild respiratory distress, and normal cardiac examination. Abdominal examination reveals a flat abdomen with a three-vessel umbilical cord and no organomegaly. An orogastric tube is inserted to 9 cm at the infant's lower alveolar ridge. A prenatal ultrasonogram at the 20th week of gestation was significant for an absent fetal stomach bubble. The pregnancy was complicated by polyhydramnios.

Of the following, the MOST important study to complete before operative repair in this infant is:

1	chromosomal analysis
2	cranial ultrasonogram
3	echocardiogram
4	renal ultrasonogram
5	skeletal survey

You selected 3, the correct answer is 3.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in this vignette has the clinical features of an esophageal atresia (EA). The diagnosis of EA should be suspected if a prenatal ultrasonogram performed after the 18th week of gestation fails to identify the fetal stomach bubble. The combination of absent fetal stomach bubble and polyhydramnios has a positive predictive value of 56% for EA.

Newborns with EA may either present in the delivery room with a sonorous seal-bark cry because of associated tracheomalacia or present within the first few hours after birth with excessive oral secretions. Diagnosis of EA usually is confirmed by trying to pass an orogastric tube, which typically cannot be inserted beyond 10 to 11 cm from a term infant's lips (less in a preterm infant). Chest radiography confirms the position of the orogastric tube in the proximal esophageal pouch.

As many as 60% of patients with EA and tracheoesophageal fistula (TEF) have associated anomalies, including cardiac (25%), genitourinary (15%), skeletal (14%), and intestinal atresias (13%). The VACTERL association (vertebral defects, anorectal abnormalities, cardiac defects, TEF, renal abnormalities, limb defects) occurs in approximately 10% to 25% of cases.

Approximately 25% of infants with EA have associated cardiovascular anomalies.

The most common are ventricular septal defect and tetralogy of Fallot. All newborns with EA should undergo an echocardiogram before operative repair to determine the position of the aortic arch and identify any structural cardiac abnormalities. Most individuals have a left-sided aortic arch in which the ascending aorta crosses the left main stem bronchus and reaches its apex at the left side of the trachea (Image 1). A right-sided aortic arch occurs in approximately 2% to 3% of EA cases (Image 2). In a right-sided aortic arch, the ascending aorta crosses the right main stem bronchus and reaches its apex at the right side of the trachea. If a right-sided aortic arch is suspected by echocardiography, additional imaging (magnetic resonance or computerized tomography) should be performed for confirmation (Images 3 and 4). An infant with a right-sided aortic arch should undergo a left thoracotomy for repairing the EA and TEF, whereas an infant with a left-sided aortic arch should have a right thoracotomy.

Most patients with EA and TEF have normal chromosomes. Genetic abnormalities associated with EA include trisomy 21 and 18, and 13q deletion. Because the infant in this vignette has no dysmorphic features, chromosomal analysis is not necessary before operative repair.

Central nervous system abnormalities are rare in infants with EA. A preoperative cranial ultrasonogram is not needed in an infant with no dysmorphic features.

Approximately 15% of infants with EA have genitourinary anomalies. A renal ultrasonogram should be done to identify these anomalies, but it is not necessary to perform preoperatively.

Approximately 14% of infants with EA have vertebral/skeletal abnormalities. Many vertebral anomalies can be identified by chest radiography. A skeletal survey can be performed, but it is not necessary before operative repair.

References:

Blair G, Konkin D. Esophageal atresia with or without tracheoesophageal fistulae. eMedicine Web site. Available at: http://www.emedicine.com/ped/topic295.htm. Accessed July 18, 2005

Driver CP, Shankar KR, Jones MO, et al. Phenotypic presentation and outcome of esophageal atresia in the era of Spitz classification. *J Pediatr Surg.* 2001;36:1419-1421

Goldman AS, Kaplan S. Embryology. In: Polin RA, Fox WW, eds. *Fetal and Neonatal Physiology.* 2nd ed. Philadelphia, Pa: WB Saunders; 1998:31-33

Leibert PS. *Color Atlas of Pediatric Surgery.* 2nd ed. Philadelphia, Pa: W.B. Saunders; 1996:82-88

Merei JM, Huston JM. Embryogenesis of tracheoesophageal anomalies: a review. *Pediatr Surg Int.* 2002;18:319-326

Moore KL, Persaud TV. *The Developing Human*. 6th ed. Philadelphia, Pa: WB Saunders; 2000:261-262

Nakayama DK. Congenital abnormalities of the esophagus. In: O'Neill JA, Grosfeld JL, Fonkalsrud EW, Coran AG, Caldamone AA, eds. *Principles of Pediatric Surgery*. 2nd ed. St. Louis, Mo: Mosby; 2004:385-394

Spitz L. Esophageal atresia and tracheoesophageal malformations. In: Ashcraft KW, th

Holcomb G, Murphy JP, eds. *Pediatric Surgery.* 4 ed. Philadelphia, Pa: WB Saunders; 2005:352-366

Content Specification(s):

Know the morphogenesis of the GI tract and factors that lead to congenital malformations

Plan appropriate management for an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

Recognize the clinical features of VATER (*v*ertebral defects, *a*nal atresia, *t*racheoesophageal fistula with *e*sophageal atresia, and *r*adial and *r*enal anomalies) association

Know the various types of tracheoesophageal fistulae and esophageal atresias

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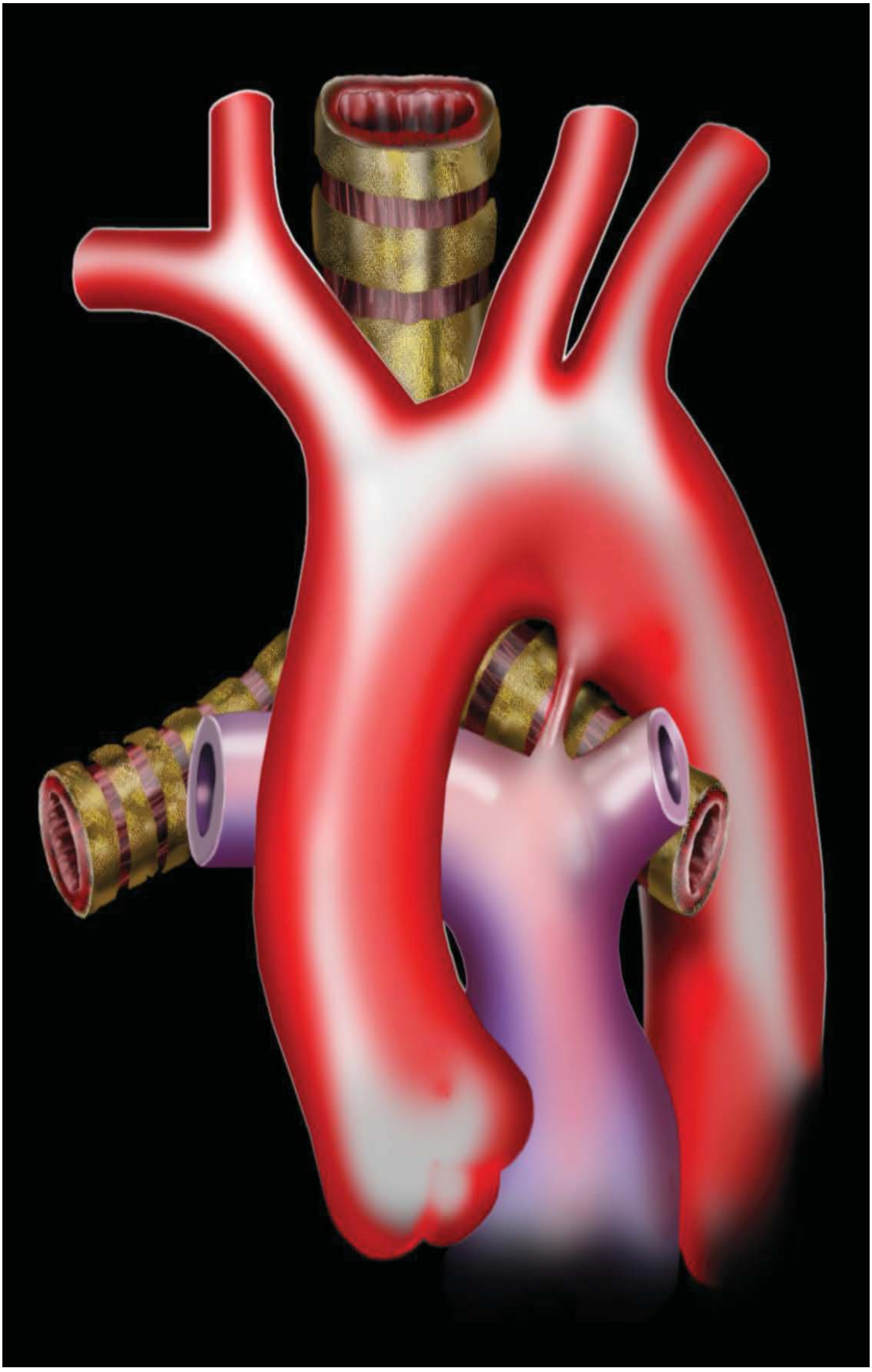

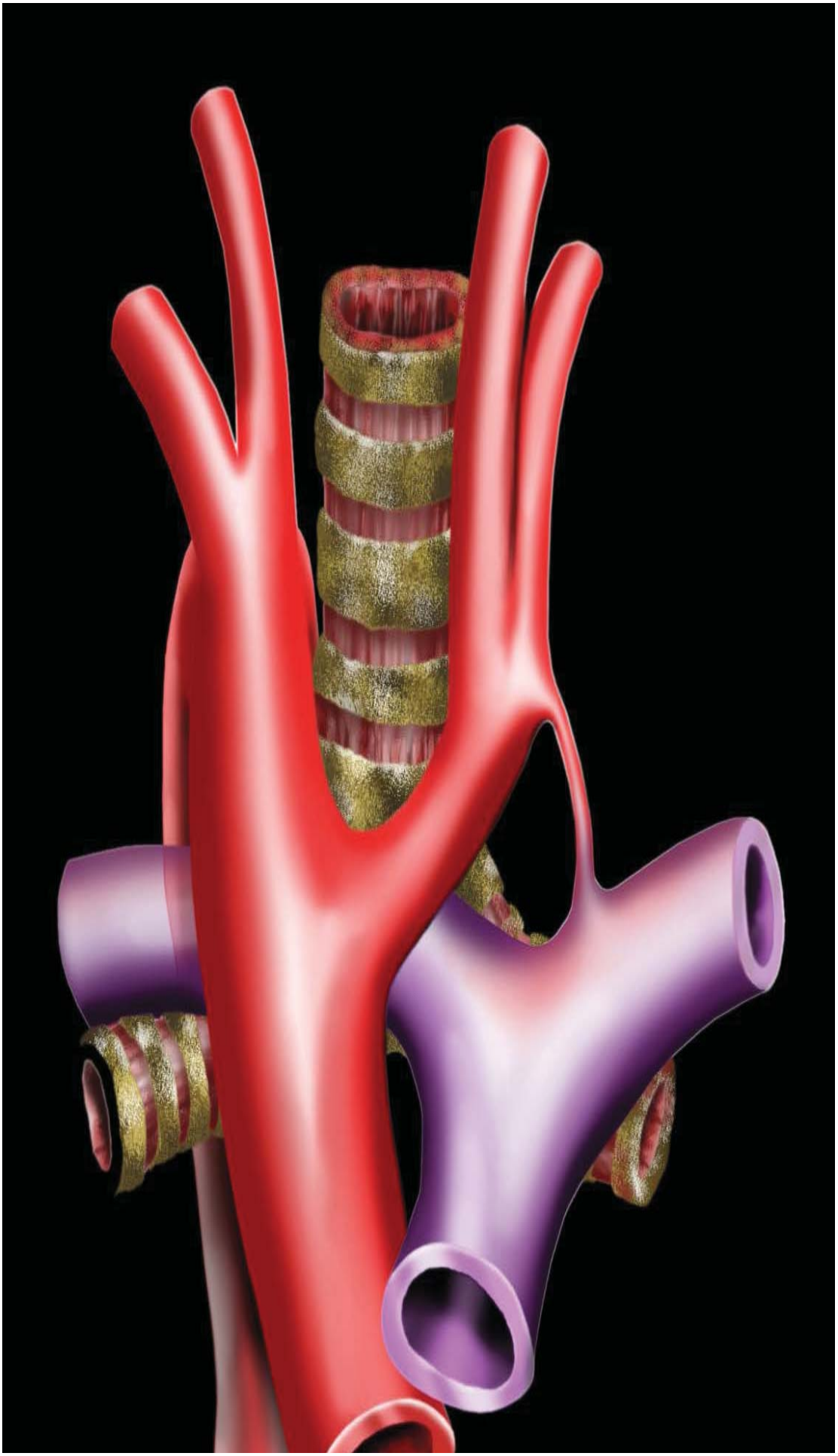

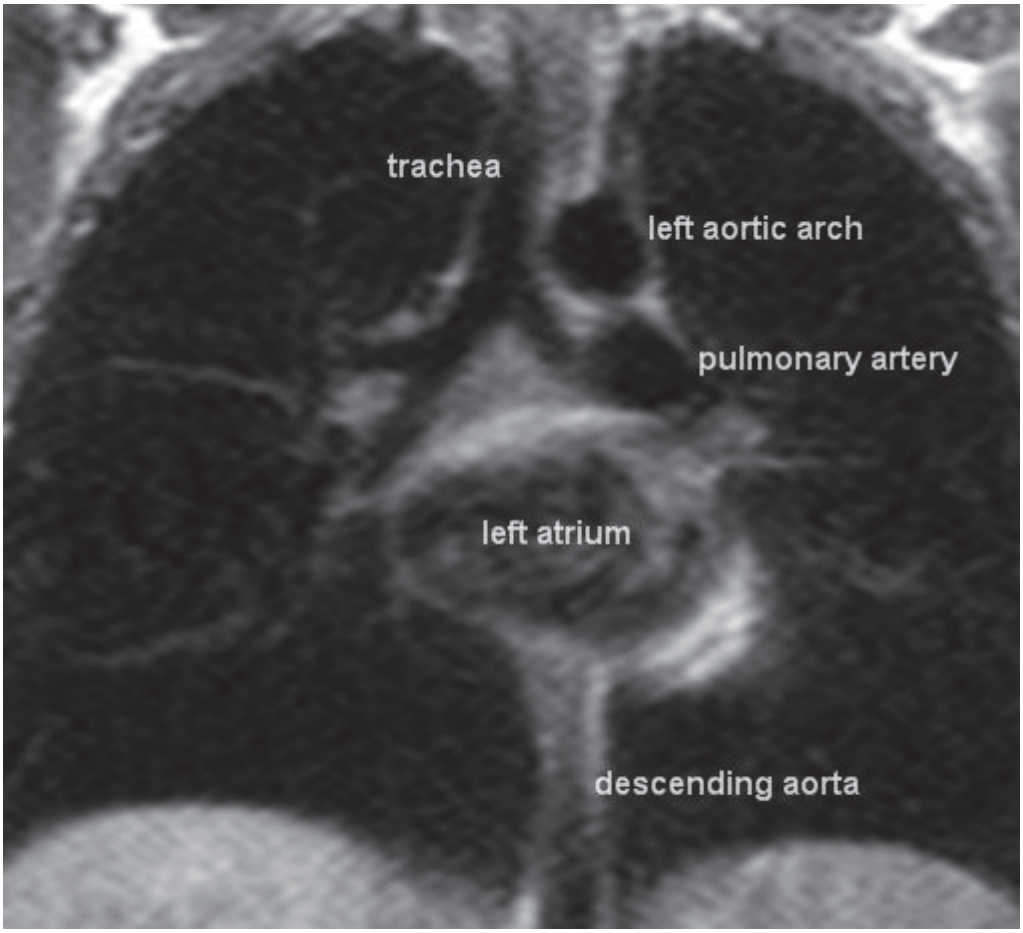
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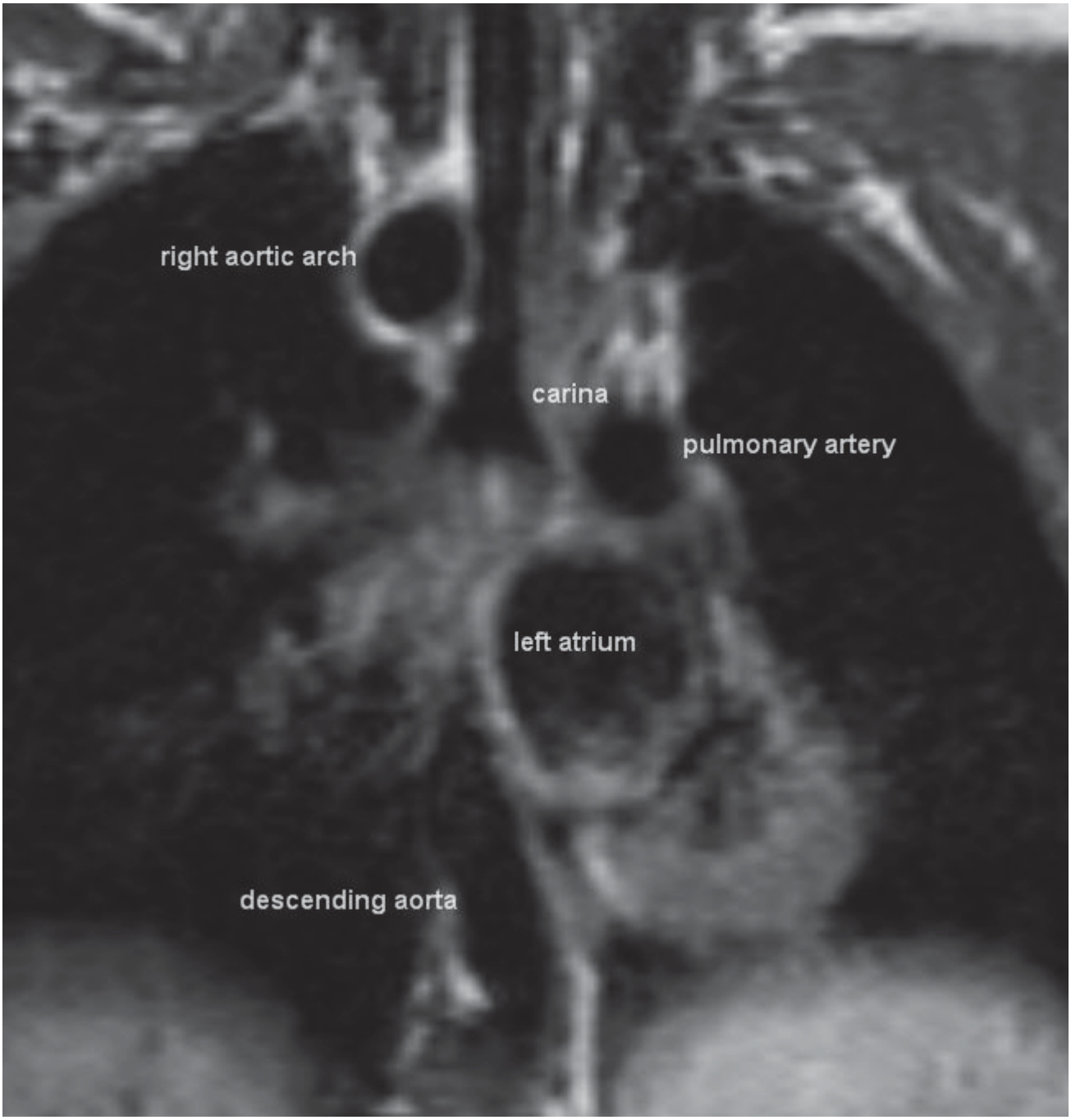
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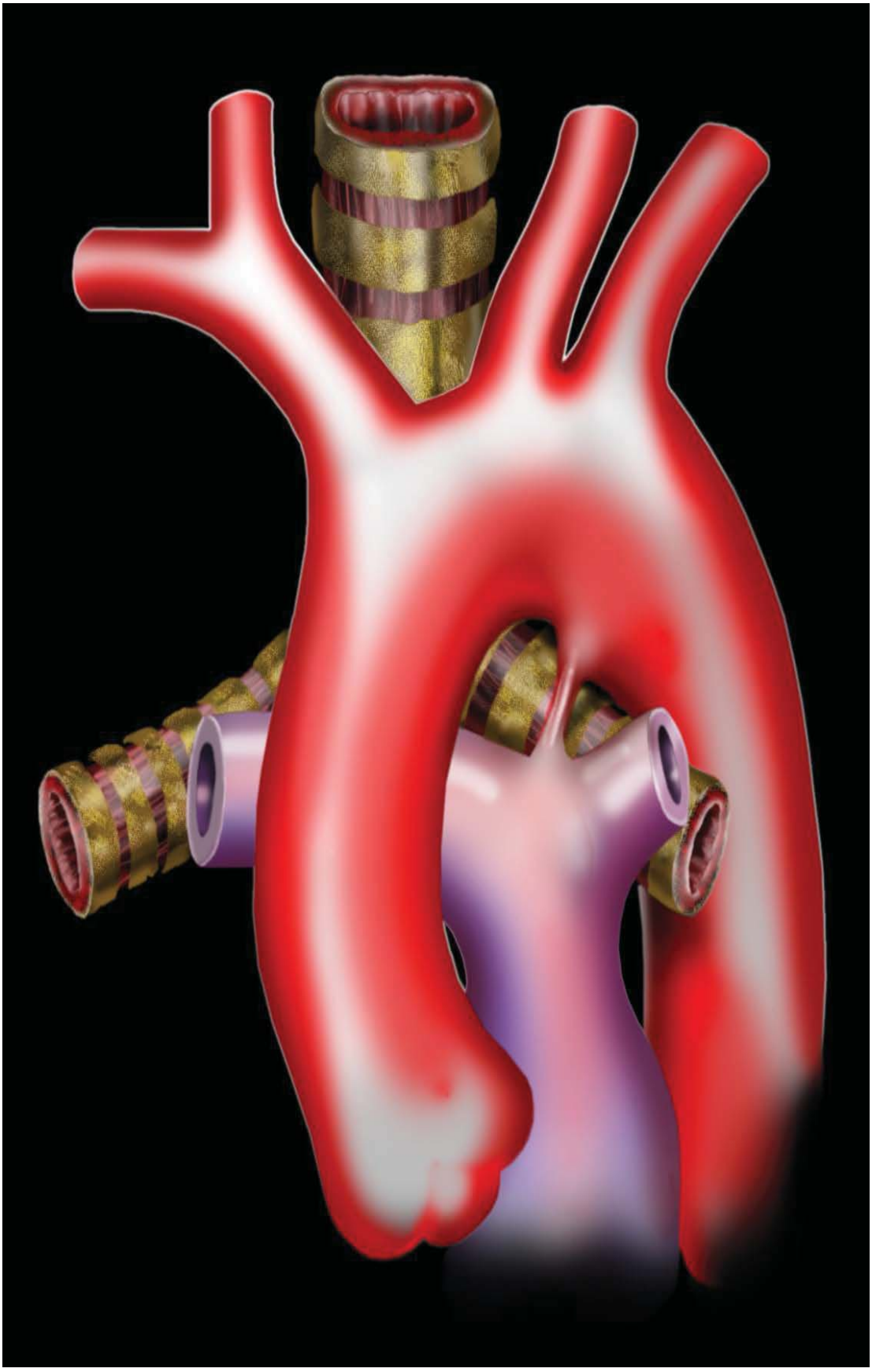

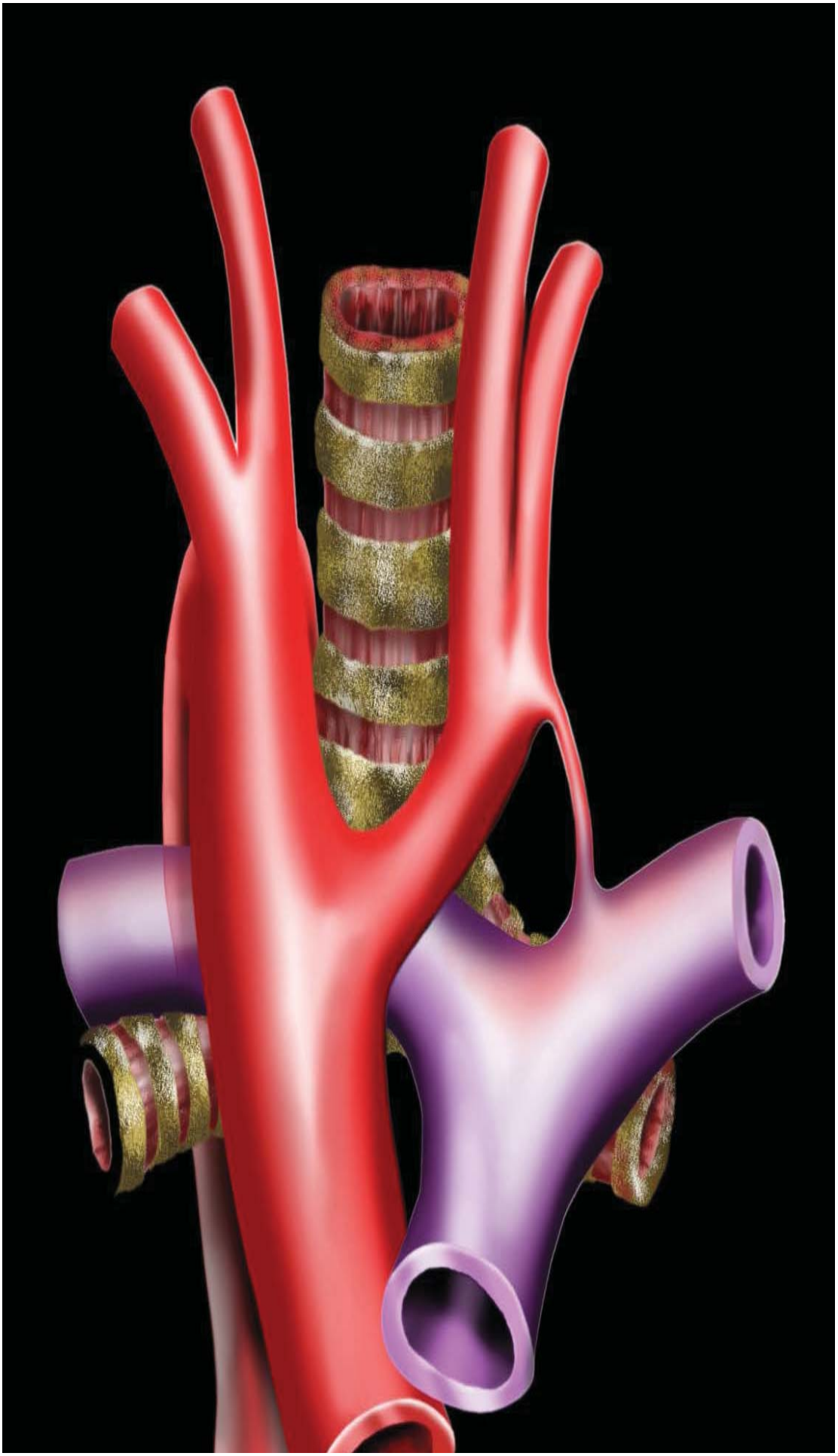

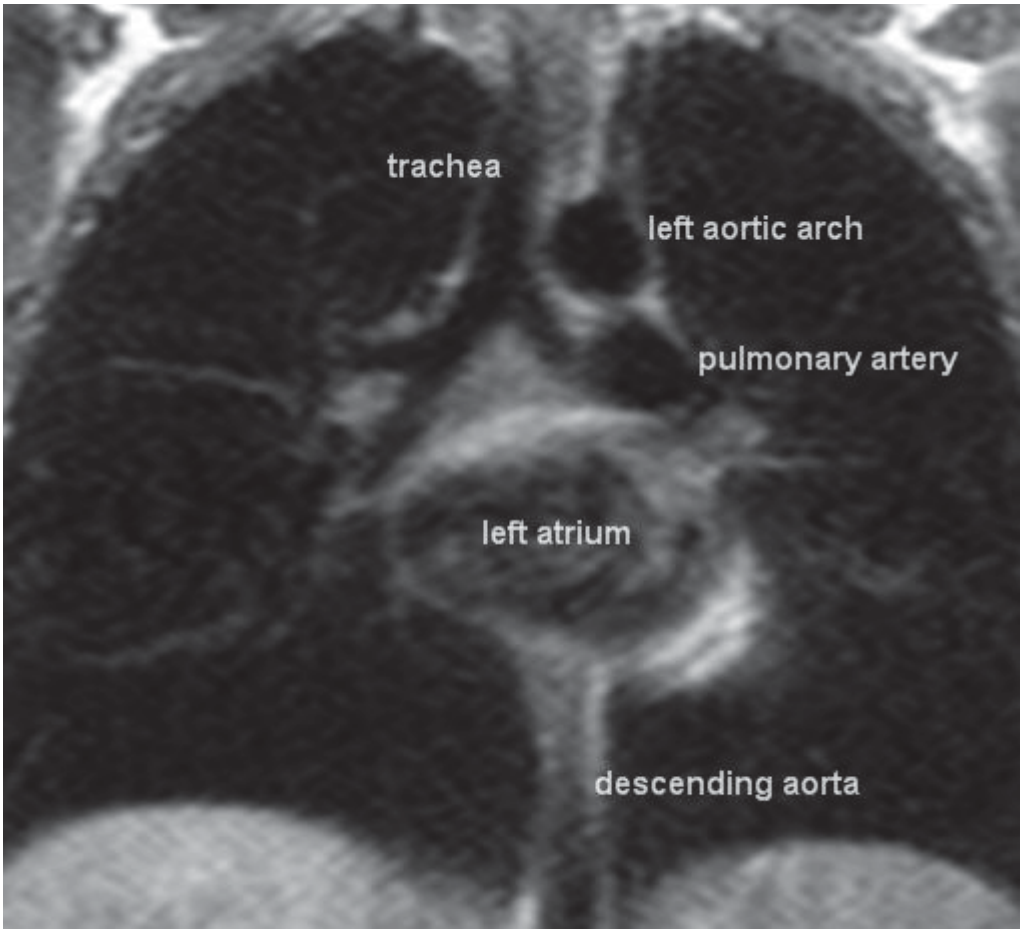
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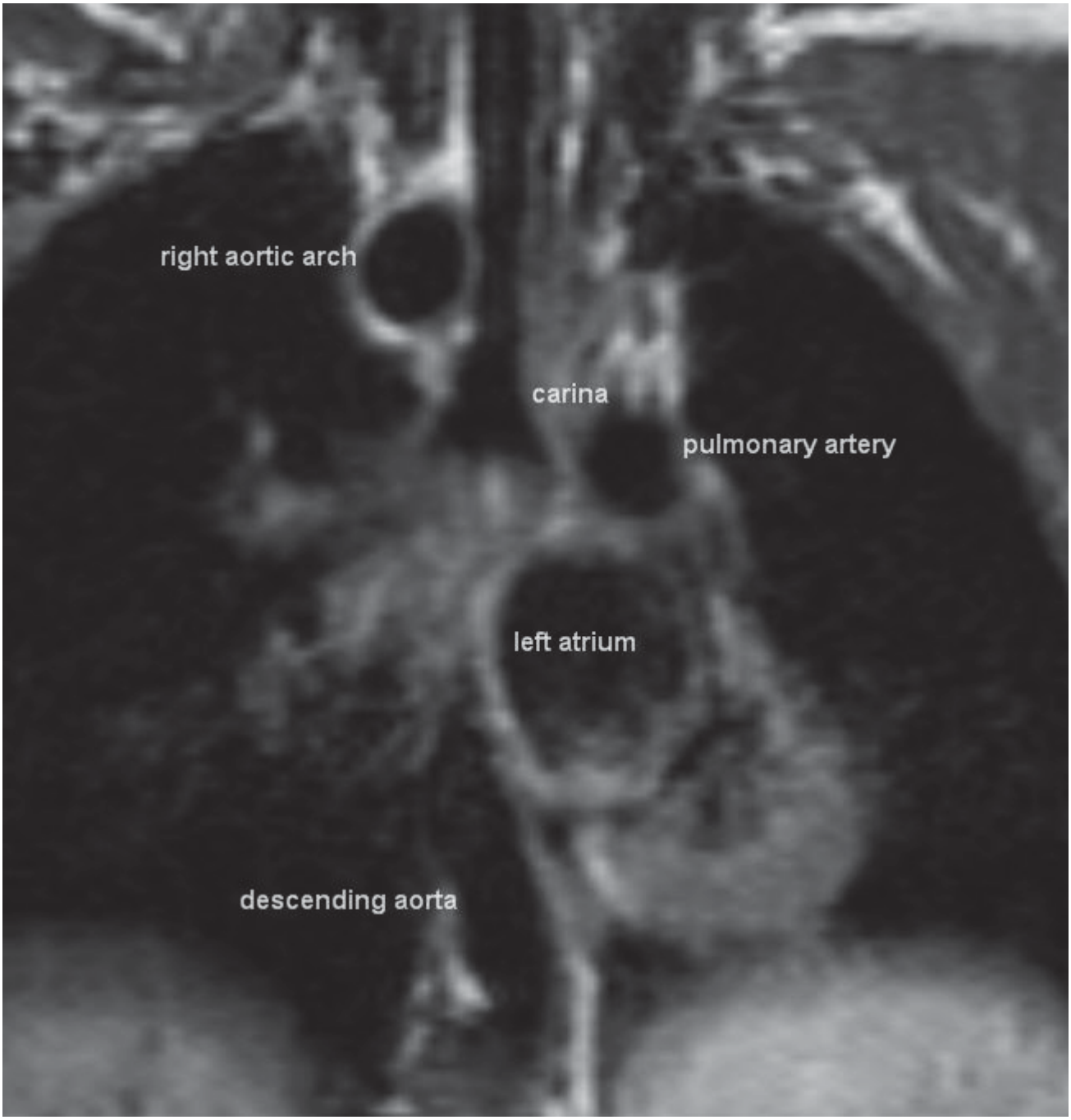
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pulmonary artery
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descending aorta

May: Question 5

A female infant weighing 3310 g at an estimated gestational age of 38 weeks is delivered by emergent cesarean section for severe fetal distress from placental abruption. Her Apgar scores are 2, 2, and 4 at 1, 5, and 10 minutes, respectively. Her cord blood pH is 6.78 with a base deficit of 19 mEq / L. She is resuscitated and given ventilatory assistance and intravenous fluids. Laboratory blood tests reveal markedly elevated liver enzymes, creatine kinase, and troponin, as well as mildly elevated creatinine. Echocardiography reveals no structural heart disease, but poor cardiac contractility. There is no clinical or hematologic evidence of sepsis.

The infant has arterial blood pressure measurements of: systolic 36 to 41 mmHg, diastolic 16 to 20 mmHg, and mean 24 to 27 mmHg. Plasma volume expanders and blood products have failed to improve the blood pressure. Vasopressor treatment is started.

Of the following, the vasopressor that MOST approximates the desirable hemodynamic profile of a pure beta-adrenergic receptor agonist (beta-agonist) is:

1	dobutamine
2	dopamine
3	epinephrine
4	levosimendan
5	milrinone

You selected 5, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in this vignette has evidence of shock with multiorgan involvement from perinatal asphyxia secondary to placental abruption. Hypotension associated with shock can be classified into three categories:

- **hypovolemic hypotension, characterized by depletion of blood volume from causes such as perinatal blood loss,**
- **cardiogenic hypotension, characterized by poor cardiac function from causes such as asphyxial cardiomyopathy, and**
- **distributive hypotension, characterized by decreased systemic vascular resistance from causes such as sepsis.**

The poor cardiac function on echocardiography and elevated blood troponin, together with the lack of response to plasma volume expansion, suggest

cardiogenic hypotension in the infant in this vignette. Vasopressor treatment with beta-agonists and/or phosphodiesterase (PDE) inhibitors is warranted under these conditions.

Beta-agonists enhance cardiac performance by inducing three specific effects. First, by enhancing fractional shortening of cardiac muscle with each contraction, the beta-agonists increase the stroke volume for any given end-diastolic volume (inotropic effect). Second, by regulating the membrane potential of cardiac pacemaker cells, the beta-agonists increase the heart rate in a dose-dependent manner (chronotropic effect). Because cardiac output is the product of stroke volume and heart rate, the net result of both inotropic and chronotropic effects is an increase in cardiac output. And third, by enhancing diastolic relaxation of the heart, the beta-agonists facilitate maintenance of adequate ventricular filling despite the reduction in diastolic filling time that occurs as heart rate increases (lusitropic effect). All of these beta-agonist effects are mediated by increased intracellular levels of cyclic AMP, which regulate the availability of calcium to the contractile proteins of the cardiac muscle.

Dobutamine, a synthetic sympathomimetic amine, is a vasopressor that most approximates the desirable hemodynamic profile of a pure beta-agonist. The commercially available formulation of dobutamine is a racemic mixture of enantiomers that have differential effects on adrenergic receptor subtypes. Both the (+) and (-) enantiomers stimulate $beta_1$-adrenergic receptors and, to a lesser extent, $beta_2$-adrenergic receptors. On the other hand, the effects of enantiomers on alpha-adrenergic receptors are variable. Whereas the (-) enantiomers act as alpha-adrenergic receptor agonists, the (+) enantiomers act as alpha-adrenergic receptor antagonists. The opposing hemodynamic effects of these enantiomers on the alpha-adrenergic receptor effectively negate each other.Thus, the predominant overall effect of dobutamine is that of an agonist of cardiac $beta_1$-adrenergic receptor and systemic $beta_2$-adrenergic receptor. The former accounts for the inotropic effect of dobutamine with a limited chronotropic effect. The latter accounts for the modest systemic vasodilatory effect of dobutamine with accompanying increase in coronary blood flow and myocardial oxygen delivery. On the basis of this constellation of clinical effects, dobutamine may be the vasopressor of choice for treating cardiogenic hypotension.

Dopamine, an endogenous sympathomimetic amine, is a precursor of norepinephrine and epinephrine. Dopamine activates cardiac $beta_1$-adrenergic receptors and exerts both inotropic and chronotropic effects. The effects of dopamine on systemic circulation are dose-dependent. At low doses (less than 5 µg/kg per minute), dopamine, through stimulation of dopaminergic receptors, has a vasodilatory effect in the periphery, particularly in the renal and mesenteric vascular beds. At midrange doses (5 to 10 µg/kg per minute), dopamine causes more widespread vasodilatation, although the preferential dilatation of renal and mesenteric vascular beds is lost. At high doses (more than 10 µg/kg per minute), dopamine predominantly activates alpha-adrenergic receptors and causes generalized systemic vasoconstriction with resultant increase in cardiac afterload. The latter makes dopamine the vasopressor of choice for treating distributive hypotension in which peripheral vasodilatation is the major contributing factor to circulatory failure. Conversely, by increasing the afterload, dopamine may burden the dysfunctional heart in cardiogenic hypotension.

Epinephrine, a nonselective adrenergic agonist, is released endogenously by the adrenal glands. Exogenously administered epinephrine stimulates $beta_1$, $beta_2$, $alpha_1$, and $alpha_2$ adrenergic receptors. Epinephrine is a potent stimulator of cardiac $beta_1$-adrenergic receptors with resultant inotropic, chronotropic, and lusitropic effects. The effects of epinephrine on systemic circulation are dose-dependent. At low doses, epinephrine predominantly stimulates peripheral $beta_2$-adrenergic receptors and causes systemic vasodilatation. At high doses, epinephrine predominantly stimulates $alpha_1$-adrenergic receptors and causes

generalized systemic vasoconstriction and tachycardia. These effects make epinephrine less desirable as a vasopressor for treating cardiogenic hypotension. The primary clinical application of epinephrine is in the setting of resuscitation from cardiac arrest, a setting in which rapid restoration of spontaneous circulatory function is the immediate treatment goal.

Milrinone is a PDE inhibitor, not a beta-agonist. PDE is an enzyme that hydrolyzes cyclic AMP and is found throughout the body. Milrinone inhibits a specific isoform of PDE, called PDE III, which has significant cardiovascular effects. The resultant increase in intracellular cyclic AMP raises the intracellular calcium concentration within the cardiac muscle cells, leading to its inotropic, chronotropic, and lusitropic effects. Milrinone also has important vasoactive effects in the peripheral circulation. These peripheral actions occur through cyclic AMP-mediated effects on intracellular calcium in vascular smooth muscle and result in decreased arterial and venous tone. In the systemic arterial circulation, vasodilatation decreases systemic vascular resistance and thus cardiac afterload. In the systemic venous circulation, an increase in venous capacitance decreases venous return to the heart and thus cardiac preload. These effects make milrinone desirable as a vasopressor for treating cardiogenic hypotension. Conversely, milrinone may worsen distributive hypotension in which peripheral vasodilatation is the major contributing factor to circulatory failure.

Levosimendan is a member of a novel class of calcium-sensitizing drugs with actions similar to PDE inhibitors. Levosimendan exerts its cardiovascular effects by enhancing sensitivity of troponin C to calcium within the cardiac muscle cells. This potentiating effect increases the actin-myosin interactions at any given concentration of intracellular calcium. The safety and efficacy of levosimendan and other calcium-sensitizing drugs has not been established in neonates.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Myers CW, Rocco TP. Pharmacology of cardiac contractility. In: Golan DE, Tashjian Jr AH, Armstrong EJ, et al, eds. *Principles of Pharmacology: The Pathophysiologic Basis for Drug Therapy.* Philadelphia, Pa: Lippincott, Williams & Wilkins; 2005:285-298

Noori S, Friedlich PS, Seri I. Pathophysiology of shock in the fetus and neonate. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and Neonatal Physiology*. 3rd ed. Philadelphia, Pa: Saunders; 2004:772-781

Young TE, Mangum B. *Neofax 2005.* 18th ed. Raleigh, NC: Acorn Publishing; 2005:108-109, 110-111, 116-117, 130-131

Content Specification(s):

Recognize the therapeutic indications for, and toxicity of, inotropic agents in treating cardiovascular distress

Understand the pathophysiology of an infant with cardiac manifestations produced by perinatal events, such as asphyxia or hypervolemia

Understand the mechanism of action of commonly used autonomic agonist and antagonist drugs

Understand the therapeutic indications for, and toxicity of, commonly used autonomic agonist and antagonist drugs

Recognize the therapeutic indications for, and toxicity of, vascular afterload-reducing drugs

PREVIOUS NEXT

March: Question 3

A term baby is delivered by elective cesarean section under spinal anesthesia to a 33-year-old woman at a community hospital. Maternal history is remarkable for the diagnosis four years ago of Systemic Lupus Erythematosus (SLE) with documented anti-Ro and anti-La antibodies. The baby has Apgar scores of 7 and 7 at 1 and 5 minutes, respectively. The infant is noted to have a resting heart rate of 55 to 67 beats per minute. He is otherwise comfortable. There is no respiratory distress or sign of congestive heart failure. The blood pressure is 74/49 mmHg. An echocardiogram reveals normal anatomy and cardiac function.

Of the following, the MOST appropriate next step in the management of this baby is:

1	isoproterenol drip
2	observation for signs of cardiac decompensation
3	pacemaker implantation
4	plasma exchange transfusion
5	systemic steroids

You selected 2, the correct answer is 2.

The infant in this vignette has neonatal lupus erythematosus (NLE), an uncommon autoimmune disease occurring in a small subset of infants whose mothers have anti-Ro and anti-La auto-antibodies. NLE is the most common cause of isolated complete congenital complete heart block, which usually has its onset during the second or third trimester of pregnancy. The initial finding may be first-, second-, or third-degree heart block, but ultimately almost all cases of heart block progress to the third degree. Once complete heart block (CHB) is established, it is permanent, as the atrioventricular (AV) nodal area is replaced by scar tissue. There is a clear association between SS-A/Ro or SS-B/La autoantibodies in the mother and the development of congenital complete AV block in the child. The antibodies are of the immunoglobulin (Ig) G class and can cross the placental barrier and enter fetal circulation. Timing of the antibody transfer is unknown, although onset has been reported as early as the 16th and 23rd weeks of gestation. Antibodies circulate for up to 3 months after birth. Litsey and associates demonstrated immunoglobulin G deposits only in the conduction system of a fetus with congenital complete AV block. In a study by Taylor et al, 35/35 mothers of babies with CHB had either Ro (SS-A) or La (SS-B) antibodies, compared to 0/5 mothers of babies with other types of heart block, 10/29 women with connective tissue disease whose babies did not have CHB, 4/445 normal pregnant women, and 2/109 healthy nonpregnant women. Of 15 babies with CHB, 10/10 younger than age 3 months possessed antibody. However, not all anti-Ro-positive mothers

had children with congenital complete AV block. Some other factor, such as human leukocyte antigen (HLA) type, in utero environment, or timing of antibody transfer to the fetus, may be necessary.

Symptoms of the newborn with a structurally normal heart and congenital complete AV block range from a total lack of symptoms to syncope, exercise intolerance, and congestive heart failure. Treatment falls into two main categories: treatment of patients thought to be at risk of sudden death and treatment of those with low cardiac output.

Neonates who are clinically asymptomatic do not require immediate treatment, but instead can be monitored clinically in an intensive care unit as long as the baseline heart rate is above the rate considered to place one at risk for sudden death (ie, 50 to 55 bpm), as seen in the child in the vignette. Any patient considered to be at risk of sudden death from congenital complete AV block should have a pacemaker implanted. In the asymptomatic infant, this would include an infant with a persistent ventricular rate less than 50 to 55 bpm. Treatment for the most part involves permanent pacing, because chronotropic drugs appear to have only modest success at best. However, if the patient is in extremis, chronotropic agents such as isoproterenol or atropine may be used while arrangements are being made for pacing. The use of external transcutaneous pacing may be appropriate in emergency situations.

The newborn infant with congestive heart failure requires intense medical support and treatment. These neonates may have significant anasarca, hepatomegaly, and lactic acidosis. Standard medical management often is combined with systemic corticosteroids. In one case, these therapies were supplemented by plasma exchange to lower circulating levels of maternal anti-Ro antibodies; however, the efficacy of plasma exchange needs to be substantiated.

References:

Arrhythmias. In: Gilette PC, Garson A, eds. *Clinical Pediatric Arrhythmias*. 2nd ed. Philadelphia, Pa: WB Saunders; 1999:66-70

Hamilton RM, Silverman ED, Gross GJ, Kirsh JA. Congenital Heart Block. In: Freedom RM, Yoo S, Mikailian H, Williams WG, eds. *The Natural and Modified History of Congenital Heart Disease*. New York, NY: Blackwell Publishing; 2004:562-568

Lee LA. Transient autoimmunity related to maternal autoantibodies: neonatal lupus. *Autoimmun Rev.* 2005;4(4):207-213

Content Specification(s):

Identify the effects of maternal immunologic diseases, including transplacental passage of immunoglobulins, and their management and treatment in the fetus

Know the effects on the fetus of maternal connective disorders and their treatment

Understand the physiologic consequences of a dysrhythmia in a newborn infant

Plan appropriate management of dysrhythmia in a newborn infant, including noninvasive and invasive management of electrophysiologic disturbances, and understand the potential adverse effects of approaches and drugs used

Understand the pathophysiology, natural history, and clinical features of conduction pathway abnormalities and other dysrhythmias

PREVIOUS NEXT

May: Question 3

A 1500-g infant is born at 33 weeks' gestation by cesarean section secondary to fetal decelerations. The pregnancy was complicated by a fetal tachyarrhythmia noted at 28 weeks' gestation that resolved spontaneously. A prenatal ultrasonogram demonstrated a hypertrophied heart and a small mass versus clot in the left ventricular outflow tract of the heart. After delivery, an echocardiogram demonstrated multiple rhabdomyomas in the walls of the left and right ventricles, the interventricular septum and in the left ventricular outflow tract.

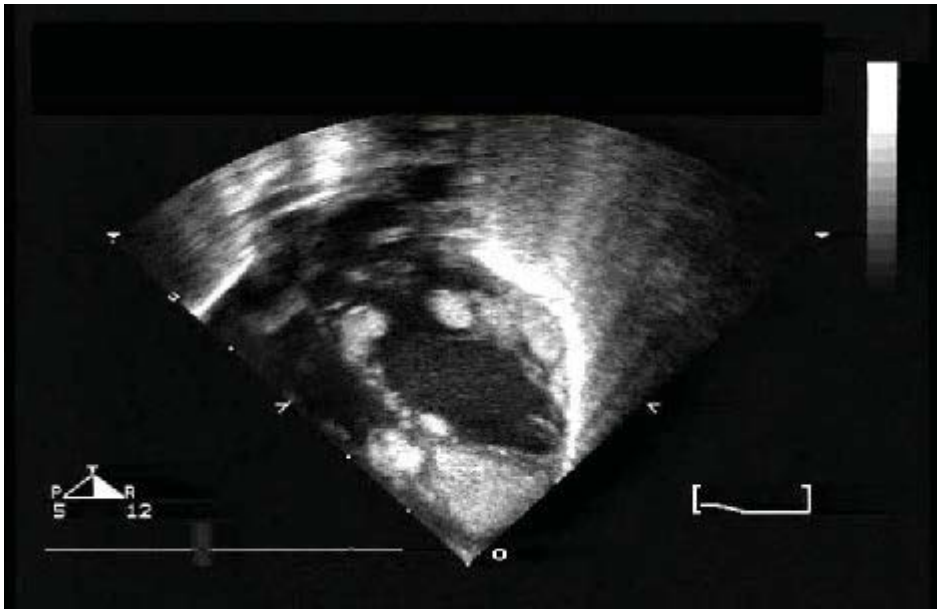


Figure. Echocardiogram demonstrating multiple rhabdomyomas
Courtesy of John Cotton, MD, University of North Carolina at Chapel Hill

Subsequently, the infant developed intermittent supraventricular tachycardia, requiring medical intervention.

Of the following, the MOST accurate statement regarding cardiac rhabdomyomas is:

1	Electrocardiographic findings may include a delta wave.
2	Lesions typically continue to enlarge postnatally.
3	Lesions typically require medical or surgical intervention.
4	Multiple lesions are pathognomonic for tuberous sclerosis complex.

5 Risk of fetal demise due to cardiac failure and hydrops is high.

You selected 4, the correct answer is 1.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in the vignette has tuberous sclerosis complex (TSC) and presented with cardiac rhabdomyomas (CRs) and supraventricular tachycardia (SVT). Primary cardiac tumors are rare, and rhabdomyomas predominate. Other primary cardiac tumors at this age include teratomas, myxomas, and fibromas. In addition, CRs are the most common cardiac tumor diagnosed in utero, usually midtrimester and as early as 22 weeks' gestation, and often with evaluation for a fetal dysrhythmia. Up to 80% of infants with CRs will have TSC, and among patients with TSC, up to 60% will manifest CRs (the earliest detectable hamartoma in TSC). CRs often are asymptomatic in utero and postnatally, and they may only be detected when signs or family history of TSC emerge, prompting a cardiac assessment. While even single CRs, in addition to other features, suggest a diagnosis of TSC, CRs no longer are sufficient to establish a diagnosis (Table).

Table. Revised Diagnostic Criteria for Tuberous Sclerosis Complex

Major Features

1. facial angiofibromas or forehead plaque
2. nontraumatic ungual or periungual fibroma
3. hypomelanotic macules (three or more)
4. shagreen patch (connective tissue nevus)
5. multiple retinal nodular hamartomas
6. cortical tuber*
7. subependymal nodule
8. subependymal giant cell astrocytoma
9. cardiac rhabdomyoma, single or multiple
10. lymphangiomyomatosis†
11. renal angiomyolipoma†

Minor Features

1. multiple randomly distributed pits in dental enamel
2. hamartomatous rectal polyps
3. bone cysts
4. cerebral white matter radial migration lines
5. gingival fibromas
6. nonrenal hamartoma
7. retinal achromic patch
8. "confetti" skin lesions
9. multiple renal cysts

Definite Tuberous Sclerosis Complex:
Either two major features or one major feature plus two minor features

Probable Tuberous Sclerosis Complex:
One major plus one minor feature

Possible Tuberous Sclerosis Complex:
Either one major feature or two or more minor features

*When cerebral cortical dysplasia and cerebral white matter migration tracts occur together, they should be counted as one rather than two features of tuberous sclerosis.
†When both lymphangiomyomatosis and renal angiomyolipomas are present, other features of tuberous sclerosis should be present before a definitive diagnosis is assigned.

From: Roach ES, et al. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol.* 1998;13:624-628

Infants with CRs may present with symptoms related to the size and anatomical location of the tumors. As in the vignette, multiple tumors usually occur and involve the left ventricle, right ventricle, interventricular septum, and atria. Large lesions may cause outflow tract obstruction or interfere with cardiac motility and predispose to cardiac failure. An association between TSC and supraventricular tachycardia, including the Wolff-Parkinson-White syndrome (WPW) exists, and nearly 50% of cases with CRs and TSC will have cardiac dysrhythmias. WPW occurs in 0.15% of the general population, 0.5% of children with cardiac disease, 1.5% of patients with TSC, but up to 13% of patients with CRs.

With WPW, an accessory atrioventricular conducting pathway exists, predisposing to atrioventricular reentry tachycardia. WPW is diagnosed during sinus rhythm from an electrocardiogram (ECG) demonstrating a shortened PR interval and a deformed QRS complex, widened in its initial portion by a slow-rising, slurred deflection called a delta wave. CRs contain some cells structurally identical to Purkinje cells, and it is postulated that rhabdomyomatous tissue traversing the atrioventricular junction acts as the accessory pathway, bypassing the atrioventricular node. Therefore, the infant in the vignette with TSC and SVT could have WPW, with overt pre-excitation (delta wave) visible on an ECG.

More than 80% of CRs will regress spontaneously, and some have been shown to disappear within weeks of delivery. These lesions have never been shown to enlarge postnatally. Although large obstructive lesions may require surgery and SVT may require medical management, CRs only occasionally present with symptoms necessitating intervention. In fact, even patients with WPW and TSC show resolution over time of overt pre-excitation and SVT. Similarly, the majority of cases of CRs have a benign perinatal course with a low risk of fetal demise (4% to 6%) due to cardiac failure and hydrops.

References:

Bader RS, Chitayat D, Kelly E, et al. Fetal rhabdomyoma: prenatal diagnosis, clinical outcomes, and incidence of associated tuberous sclerosis complex. *J Pediatr*. 2003;143:620-624

O'Callaghan FJK, Clarke AC, Joffe H, et al. Tuberous sclerosis complex and Wolff-Parkinson-White syndrome. *Arch Dis Child.* 1998;78:159-162

Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurology.* 1998;13:624-628

Webb DW, Thomas RD, Osborne JP. Cardiac rhabdomyomas and their association with tuberous sclerosis. *Arch Dis Child*. 1993;68:367-370

Content Specification(s):

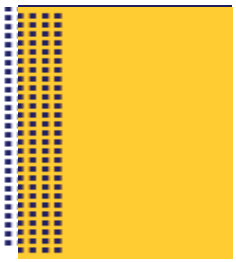
Recognize the clinical features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor and electrolyte imbalances.

Recognize the laboratory and radiographic features in an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor and electrolyte imbalances.

Formulate a differential diagnosis for a neonate with a condition affecting systemic myocardial performance, such as cardiomyopathy, myocarditis, tumor and electrolyte imbalances.

Understand the total management plan and associated potential complications of such management for an infant with a condition affecting myocardial performance, such as cardiomyopathy, myocarditis, tumor and electrolyte imbalances.

PREVIOUS NEXT



May: Question 1

A 26-day-old female infant suddenly collapses while her family is completing discharge preparations. She was treated for hypoplastic left heart syndrome with the first operative stage of the Norwood procedure. Her recovery was complicated by a brief episode of supraventricular tachycardia during the first postoperative day. Otherwise, she was breathing comfortably, eating well and gaining weight regularly on fortified breastmilk. Examination is remarkable for asystole, apnea, pallor, capillary refill time of 7 seconds, and unresponsiveness to vigorous stimulation. Resuscitation is initiated with bag-mask ventilation, followed by chest compressions, endotracheal intubation and endotracheal epinephrine administration; there is no return of respiratory efforts or spontaneous circulation. Breath sounds are equal, and chest excursion is equal. No gastric sounds are detected, and the abdomen is flat. The end tidal carbon dioxide detector does not change color. Attempts to place an intravenous line in the hand and foot are unsuccessful.

Of the following, the intervention that is your HIGHEST priority is:

1	endotracheal tube replacement
2	intraosseous needle placement
3	paracentesis
4	pericardiocentesis
5	thoracentesis

You selected 2, the correct answer is 2.

Resuscitation of neonates and young infants who are discovered with no pulse and no respiration is especially challenging. This event occurs most often in settings outside the hospital and usually is related to sudden infant death syndrome (70%) or respiratory disorders (12%); congenital heart disease accounts for only 2% of these cases. Sudden death of infants who apparently have recovered from surgery for congenital heart disease is rare. However, sudden cardiopulmonary collapse of infants with congenital heart disease is particularly difficult because of limited cardiac and respiratory reserve, as in the infant in the vignette.

Intravascular access for drug and fluid administration becomes a priority during the rare resuscitation unresponsive to positive pressure ventilation and chest compressions. The endotracheal route for medication administration often is established quickly but is limited due to slow or poor absorption and toxicity, a narrow list of resuscitation medications that are effective when given through an endotracheal tube, and inability to deliver infusions of fluids for volume expansion or continuous drip medications.

Intravascular sites for resuscitation medications and infusions include intravenous locations (peripheral, central) and intraosseous locations (anterior tibia, distal femur, medial and lateral malleoli). Peripheral venous access may be rapid to establish, although success is infrequent in the infant who has asystole, apnea, and undetectable blood pressure, as in the infant in the vignette. Intraosseous access is successful in approximately 80% of such neonates and infants and has the additional advantages of being rapid and simple to place. Placement of percutaneous and surgical central venous catheters generally is successful in approximately 75% to 80% of cases, although establishing venous access takes longer and is more technically difficult than the intraosseous route.

In the neonate experiencing cardiopulmonary collapse, intraosseous access is an alternative route to the intravascular space when intravenous access is not established quickly. Intraosseous access rarely has been necessary in neonates because the umbilical vein is easily cannulated during the first days after birth, there is the presence of intravenous access in infants who are ill, and the technical skills of neonatal nurses and pediatricians are usually available. It is rare but possible, however, that stable and growing infants with congenital heart disease, arrhythmias, sepsis, respiratory illnesses, metabolic disorders, neurologic diseases and sudden infant death syndrome may suffer a full arrest.

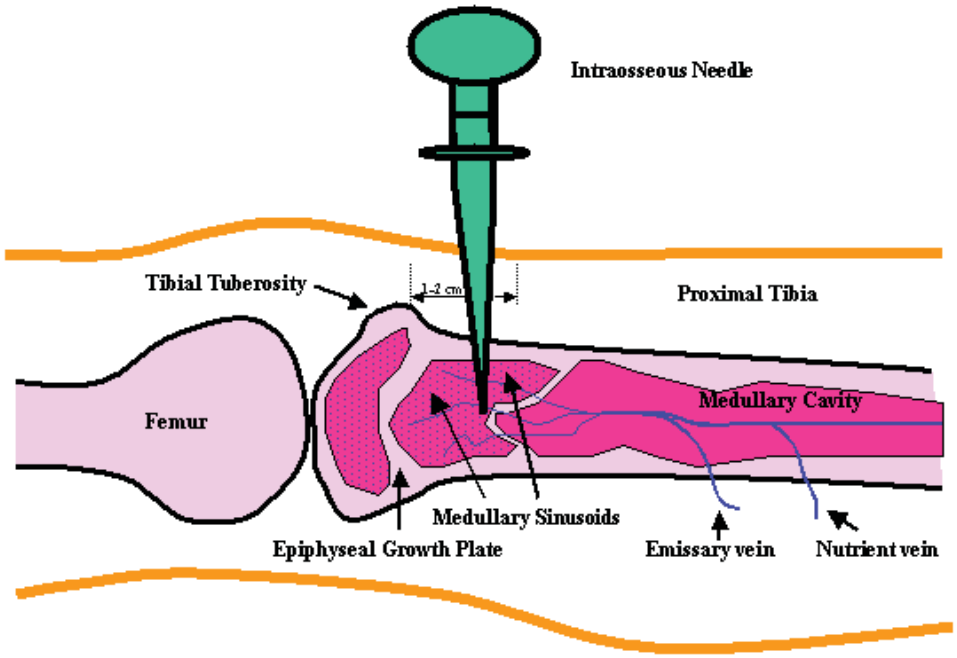
The body of literature focused on intraosseus access in neonates is limited to case reports and a single small case series. Therefore, information about the technique and complications is extrapolated from use in children and adults.

Infusions of blood and other fluids into the circulation by way of the bone marrow was described beginning in the 1940s as an alternative to infusion through the superior sagittal sinus in newborns and when intravenous access was impossible in older children and adults, as seen in widespread mutilations, burns, edema, poorly developed or obliterated veins, and states of shock. In 1947, Heinild and associates reported on 1,000 intraosseous infusions in infants and children younger than 4 years old.

Preterm infants weighing 1150 g, 1200 g, and 1750 g at birth were included in this case series. Intraosseous access was successful in 98% of patients, although 8% required change in site due to occlusion of the needle, hematoma or bent needle. Osteomyelitis only occurred in 1% of these children, and bone fractures were rare. Intraosseous vascular access fell out of favor from the 1950s through the 1970s with the advent of plastic intravascular cannulas that allowed easy and rapid access to the intravascular space. A renewed focus on intraosseous routes to provide rapid, easily performed vascular access occurred in the 1980s when interest in resuscitation at accident sites or on the battlefield developed.

Intraosseous needles with stylets are available commercially, although a spinal or butterfly needle may suffice. With butterfly needles, obstruction with bony spicules or clots may occur. The proximal tibia generally is preferred, due to ease of access. The needle is inserted with a back-and-forth twisting motion, with the tip directed away from the epiphysis (Figure).

Figure 1. Anatomy of the proximal tibia and vascular structures with intraosseous needle in situ



Entrance into the marrow is detected when a "give" is felt, the needle stands erect, and marrow can be drawn from the needle. Note that marrow return requires firm suction and may not occur during cardiopulmonary arrest. Medications and fluid infusions used during resuscitation can be given through the intraosseous route. Because of the possible depot effect of the bone marrow, infusion with a small bolus of saline after medication administration may be beneficial. Laboratory studies can be obtained and are similar to mixed venous samples; results are most reliable in the first minutes after placement and before infusion of fluids or medications, especially sodium bicarbonate. Intraosseous needles may be used for hours, if needed. The risk of complications is low. Osteomyelitis occurs in less than 1% of patients and is associated with hypertonic fluid or medication infusion. Subperiosteal or soft tissue extravasation, compartment syndrome, air or fat embolism, abnormal bone growth, medication or transfusion reactions, local tissue reactions, and abscess formation also are potential complications. Fractures are rare. Few contraindications exist for intraosseous access. However, bone disease associated with risk of fracture (such as osteogenesis imperfecta, severe osteopenia of prematurity), cellulitis, burn, or other overlying infection are reasons to avoid intraosseous needle insertion, if possible.

Replacement of the endotracheal tube in the infant in the vignette is a consideration, although physical findings suggest that the endotracheal tube is within the trachea. The absence of color change in the carbon dioxide detection device may occur when pulmonary perfusion is limited during low cardiac output states or if the device is contaminated by moisture. Careful clinical judgment is necessary in this circumstance, because an additional intubation procedure could delay other resuscitation interventions. Nevertheless, most resuscitations in neonates are of respiratory origin, and effective ventilation is the foremost priority.

Paracentesis is not suggested since the abdomen was flat, and there was no mention of ascites being present. Furthermore, ventilation appeared to be adequate; it was not impeded by abdominal distension.

Pericardial effusion after cardiac surgery may cause a variety of symptoms that usually evolve over hours to days (postpericardiotomy syndrome). Symptoms may include hypotension, tachycardia, malaise, and tachypnea. This syndrome does not usually present with asystole, apnea, and pulselessness. Pericardiocentesis is unlikely to be needed in the infant in the vignette-who was clinically thriving-although it is a consideration if there is no response to intraveascular medications.

The physical findings suggest adequate ventilation of the lungs in the infant in the vignette. Pneumothorax or pleural effusions requiring thoracentesis would not be anticipated as a cause for the cardiopulmonary collapse.

Reference(s):

Abe KK, Blum GT, Yamamoto LG. Intraosseous is faster and easier than umbilical venous catheterization in newborn emergency vascular access models. *Am J Emerg Med.* 2000;18:126-129

Alba M, Lopez R. Use of the intraosseous route in resuscitation in a neonate. *Inten Care Med.* 1994;20:529

Aziz HF, Martin JB. The pediatric disposable end-tidal carbon dioxide detector role in endotracheal intubation in newborns. *J Perinatol.* 1999;19:110-113

Bohn D. Intraosseous vascular access: From the archives to the ABC. *Crit Care Med.* 1999;27:1053-1054

Burnette DD, Fischer R. Intravascular access in pediatric cardiac arrest. *Am J Emerg Med.* 1988:6:577-59

Claudet I, Baunin C, Laporte-Turpin E, et al. Long-term effects on tibial growth after intraosseous infusion: a prospective, radiographic analysis. *Pediatr Emerg Care.* 2003;19:397-401

Ellemunter H, Simma B, Trawoger R, et al. Intraosseous lines in preterm and full-term neonates. *Arch Dis Child Fetal Neonatal Ed.* 1999;80:F74-75

Fiorito BA, Farrukh M, Doran TM, et al. Intraosseous access in the setting of pediatric critical transport. *Pediatr Crit Care Med.* 2005;6:50-53

Heinild S, Tyge S, Tudvad F. Bone marrow infusion in childhood. *J Pediatr.* 1947;400-412

International guidelines for neonatal resuscitation: an excerpt from the guideline 2000 for cardiopulmonary resuscitation and emergency cardiovascular care: international consensus on science. *Pediatr.* 2000;106:1-16. Available at: http://pediatrics.aappublications.org/cgi/content/full/106/3/e29

Kelsall AWR: Resuscitation with intraosseous lines in neonatal units. *Arch Dis Child.* 1993;68:324-325

LaRocco BG, Wang HE. Intraosseous infusion. *PreHosp Emerg Care.* 2003;7:280-285

Nasimi A, Gorin P, Berthier M, et al. Utilisation de la voie intraosseuse chez un premature. *Arch Pediatr.* 1998;5:414-417

Orlowski JP. Emergency alternatives to intravenous access. *Ped Crit Care.* 1994;41:1183-1199

Perlman JM, Risser R. Cardiopulmonary resuscitation in the delivery room. *Arch Pediatr Adolesc Med.* 1995;149:20-25

Ramet J, Clybouw C, Benatar A, et al. Successful use of an intraosseous infusion in an 800-grams preterm infant. *Euro J Emerg Med.* 1998;5:327-328

Rosetti VA, Thompson BM, Miller J, et al. Intraosseous infusion: an alternative route of pediatric intravascular access. *Ann of Emerg Med.* 1985;14:885-888

Spivey WH. Intraosseous infusions. *J Pediatr.* 1987;111:639-643

Smith MP, Kaji A, Young KD, Gausche-Hill M. Presentation and survival of prehospital apparent sudden infant death syndrome. *Prehosp Emerg Care.* 2005;9:181-185

Tocantins LM, O'Neill JF. Infusion of blood and other fluids into the circulation via the bone marrow. *Proc Soc Exp Biol Med.* 1940;45:782-783

Tocantins LM, O'Neill JF. Infusions of blood and other fluids into the general circulation via the bone marrow. *Surg Gyn and Obst.* 1941;73:281-287

Tsang TJ, Barnes ME, Hayes SN, et al. Clinical and echocardiography characteristics of significant pericardial effusions following cardiothoracic surgery and outcomes of echo-guided pericardiocentesis for management: Mayo Clinical Experience, 1979-1998. *Chest.* 1999;116:322-331

Zaritsky AL, Nadkarni UM, Hickey RW, et al. *PALS Provider Manual.* American Heart Association/American Academy of Pediatrics. 2002:156-158

Content Specification(s):

Understand the methods of administration of drugs used for neonatal resuscitation

Understand pharmacokinetics of drug use for neonatal resuscitation

PREVIOUS NEXT

October: Question 5

A term male infant is born with a large, soft, compressible mass involving the right axilla and the right side of his neck and face. During your discussion of congenital cystic hygromas with the medical students, you ask about the anatomy of the right lymphatic duct.

Of the following, the MOST likely site at which the right lymphatic duct drains lymph into the venous system is the junction of the:

1	right axillary and cephalic veins
2	right brachiocephalic vein and the superior vena cava
3	right internal jugular and external jugular veins
4	right internal jugular and subclavian veins
5	superior vena cava and right atrium

You selected 4, the correct answer is 4.

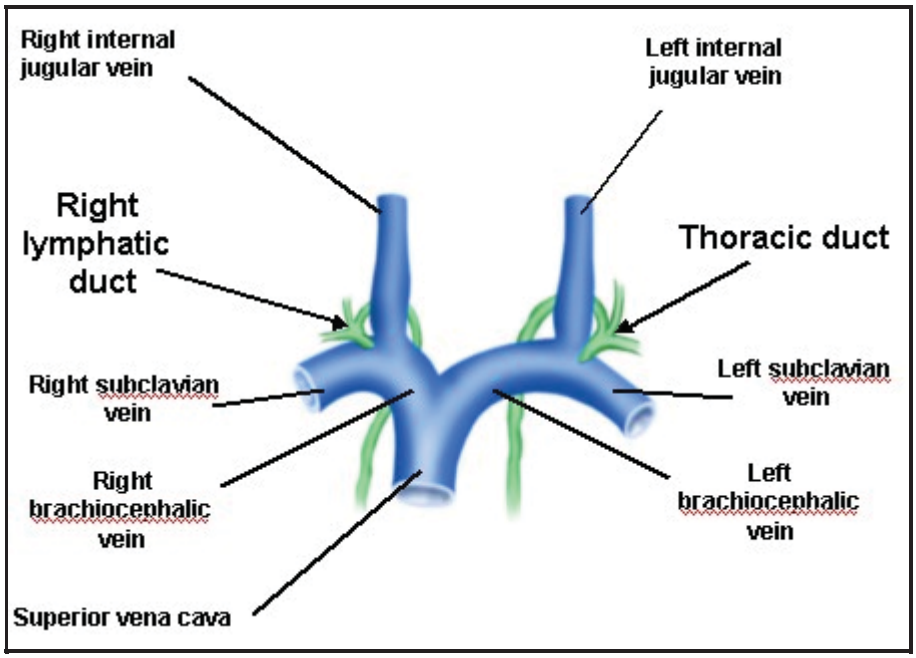
Cystic hygromas are benign multilocular lymphatic malformations that usually occur in the neck (75% of cases) and axilla (20% of cases). Cystic hygromas are most often localized to one side of the neck with approximately equal frequency between left and right. Most cystic hygromas are present at birth (65% of cases) and are frequently diagnosed prenatally by ultrasonography. Cystic hygromas are found with an increased frequency in individuals with chromosomal abnormalities such as trisomy 21, Turner syndrome, and trisomy 18. Airway obstruction is the most important immediate cause of morbidity and mortality. Other complications include infection (16% of cases) and hemorrhage (13% of cases).

The lymphatic system begins to develop in the embryo at the end of the sixth week in close association with the venous system. Six primary lymph sacs develop by the ninth week, and they later become interconnected by lymphatic vessels. The six primary lymphatic sacs include two jugular sacs, two iliac sacs, a retroperitoneal sac, and the cisterna chyli. The jugular lymph sacs form near the junctions of the subclavian veins and the anterior cardinal veins (which later become the internal jugular veins). Lymphatic vessels join the jugular lymph sacs and follow the major veins to the neck, head, and arms. A cystic hygroma that involves the head, neck, or axilla results from failure of connection of a jugular lymph sac with lymphatic vessels which gives rise to a mass of dilated lymphatic spaces.

The right lymphatic duct drains lymph from the right arm and the right side of the

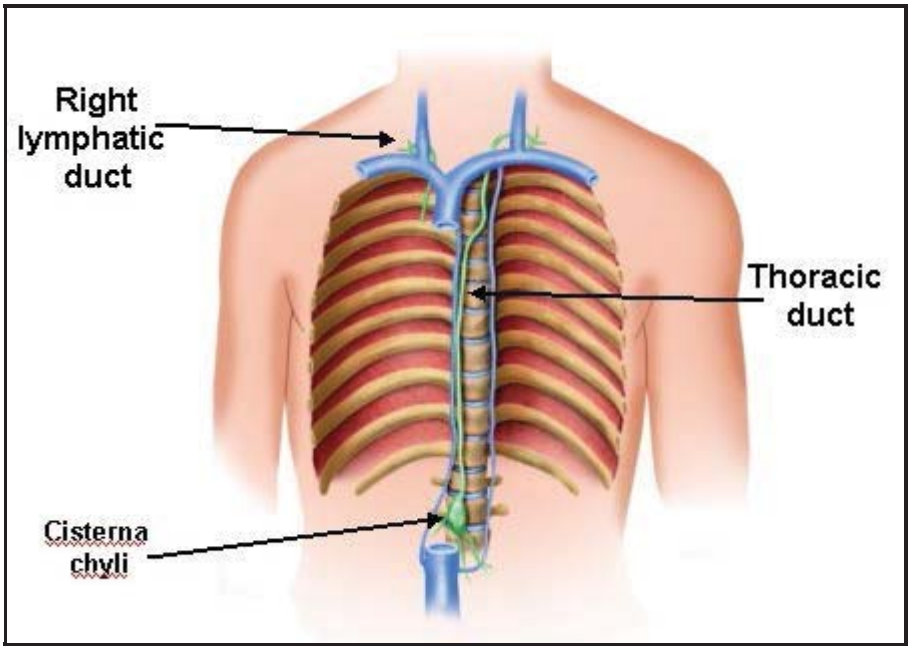
head, neck, and thorax. The right lymphatic duct drains into the bloodstream at the junction of the right internal jugular and right subclavian veins (Figure 1).

Figure 1



The thoracic duct drains lymph from the remainder of the body. The thoracic duct begins in the abdomen as an egg-shaped dilatation called the cisterna chyli which is located anterior to the second lumbar vertebra (Figure 2).

Figure 2



The thoracic duct ascends anterior to the vertebral bodies usually on the right side and enters the thorax through the aortic hiatus of the diaphragm. At the fourth or fifth thoracic vertebra, the thoracic duct crosses toward the left side and ascends behind the aortic arch. As the thoracic duct ascends into the neck, it forms an arch that rises above the clavicle. The thoracic duct drains lymph into the venous system at the junction of the left internal jugular vein and left subclavian vein (Figure 1).

Cystic hygromas tend to increase in size; surgical excision is the mainstay of treatment. Medical treatment with sclerosing agents is an alternative if the hygroma is extensive or crucial neurovascular structures are involved.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

References:

Miller MJ, Fanaraff AA, Martin RJ. Respiratory disorders in preterm and term infants. In: Fanaroff AA, Martin RJ, eds. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant*. 8th ed. St. Louis, Mo: Mosby; 2006:1143

Moore KL, Dalley AF. Thorax. In Moore KL, Dalley AF eds. *Clinically Oriented Anatomy*. 5th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2006:181-182

Moore KL, Persaud TVN. Development of the lymphatic system. In: Moore KL, Persaud TVN, eds. *The Developing Human: Clinically Oriented Embryology*. 6th ed. Philadelphia, Pa: WB Saunders; 1998:398-400

Neville H. Cystic hygroma. eMedicine Web site. Available at: http://www.emedicine.com/ped/topic536.htm. Accessed January 24, 2006

Smithers CJ, Fishman SJ. Vascular anomalies. In: Ashcraft KW, Holcomb GW, Murphy JP, eds. *Pediatric Surgery.* 4th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1044-1046

American Board of Pediatrics Content Specification(s):

Know the clinical manifestations and approaches to therapy of neck masses in the newborn infant

PREVIOUS NEXT

September: Question 5

A 7-day-old female infant born at 25 weeks' gestation with respiratory distress syndrome (RDS) is found to have a heart murmur, wide pulse pressure, and bounding pulses. She is more tachypneic than on the previous day, and her liver is palpated 3 cm below the right costal margin. Oxygen and mechanical ventilator requirements have increased. A chest radiograph shows enlargement of the cardiothymic silhouette and prominent interstitial markings. An echocardiogram confirms a large patent ductus arteriosus (PDA) and large right atrium; the heart is otherwise structurally normal.

Of the following, the MOST accurate statement about the ductus arteriosus (DA) in an extremely preterm infant with RDS is that:

1	Fluid restriction, diuretics, and digitalis effectively close patent ductus arterioses (PDAs) in most infants.
2	Ibuprofen and indomethacin are equally effective at closing PDAs.
3	Positive end-expiratory pressure increases left-to-right shunt through the PDA.
4	Spontaneous closure of the ductus arteriosus (DA) occurs within 3 days of birth.
5	Surgical closure is the preferred treatment.

You selected 1, the correct answer is 2.

The ductus arteriosus (DA) is derived from the sixth branchial arch. During fetal life, it serves as a conduit to divert blood from the high-resistance pulmonary circulation to the descending aorta and low-resistance placenta. The DA functionally closes in nearly all term infants within 3 days after birth. The DA closes in about 80% of healthy preterm infants without respiratory distress syndrome (RDS) within 3 days (Table).

Table. Factors that Promote Ductal Closure

Increase in PaO_2
Decrease in blood pressure within the ductal arteriosus (DA; due to postnatal fall in pulmonary vascular resistance)
Decrease in concentration of prostaglandin (PG) E_2 in blood (due to loss of placental PG production and increase in pulmonary PG metabolism)
Reduction in number of DA PGE_2 receptors

However, spontaneous DA closure only occurs in about 23% of extremely preterm infants with RDS within 3 days of birth. The combination of failure of ductal closure and presence of clinical symptoms of a patent DA (PDA) may be associated with risk of neonatal morbidity and lead to recommendations for pharmacologic closure or surgical ligation of the PDA.

Pharmacologic closure of the symptomatic PDA has been successful using the cyclooxygenase inhibitors indomethacin and ibuprofen. A meta-analysis that included 566 patients found these medications to be equally effective (relative risk [RR], 1.02; 95% confidence interval [CI], 0.94, 1.10; *P*=.7). The impact of ibuprofen on renal function, however, was less with a lower rise in creatinine (weighted mean difference [WMD], 0.44; 95% CI, 0.25, 0.63; *P*<.001) and lower decrease in urine output (WMD, 0.74; 95% CI, 0.55, 0.94, *P*<.001). Ibuprofen was associated with a greater risk of infants requiring oxygen supplementation 28 days after birth (RR, 1.37; 95% CI, 1.01, 1.86, *P*=.04). The risks of developing intraventricular hemorrhage, periventricular leukomalacia, surgical intervention, DA reopening, and other complications of prematurity were not different.

Prevention trials have demonstrated that the DA closes with both indomethacin and ibuprofen. However, in 60% of the control populations (including both healthy infants and those with RDS), the DA closed spontaneously within 3 days of birth. The benefit of exposing 60% of preterm infants to a pharmacologic intervention has raised doubts about use of cyclooxygenase inhibitors to "prevent" symptomatic PDA. Two large randomized trials found that indomethacin reduced the risk of developing severe intraventricular hemorrhage and PDA. Ibuprofen reduces the incidence of PDA but does not reduce the risk of intraventricular hemorrhage. In populations with a high risk of severe intraventricular hemorrhage (such as extremely preterm infants), the benefit of indomethacin prophylaxis needs to be weighed against risks.

Fluid restriction and diuretics may be useful in closing the DA in extremely preterm infants with RDS, although more definitive therapy usually is required. Fluid restriction and diuretics also reduce caloric and protein intake and may lead to electrolyte imbalances. Myocardial activity typically is increased with a clinically significant PDA; digitalis likely would not provide benefit. Continuous positive airway pressure has been found helpful in reducing the left to right shunt that occurs with PDA, which, although similar to fluid restriction, diuretics, and digitalis, is more a temporizing measure until more definitive closure occurs.

Surgical ligation of the PDA is a definitive, but higher risk, intervention than pharmacologic therapy as long as there are no contraindications to the use of cyclooxygenase inhibitors (such as renal failure and gastrointestinal bleeding). Risks associated with surgical closure include respiratory compromise, fluctuations in blood pressure, intracranial hemorrhage, infection, chylothorax, recurrent laryngeal nerve paralysis, inadvertent ligation of the pulmonary artery or aorta, and death.

References:

Clyman RI. Patent ductus arteriosus in the premature infant. In: Taeusch HW, Ballard RA, Gleason CA, eds. *Avery's Disease of the Newborn.* 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005;816-826

Dani C, Bertini G, Pezzati M, et al. Prophylactic ibuprofen for the prevention of

intraventricular hemorrhage among preterm infants: a multicenter, randomized study. *Pediatrics.* 2005;115:1529-1535

Hammerman C, Kaplan M. Commentary on prophylactic ibuprofen in premature infants. *J Pediatrics.* 2005;146:709-710

Thomas RL, Parker GC, Overmeire BV, Aranda JV. A meta-analysis of ibuprofen versus indomethacin for closure of patent ductus arteriosus. *Eur J Pediatr.* 2005;164:135-140

American Board of Pediatrics Content Specification(s):

Understand the total management plan (medical or surgical) and associated potential complications of such management for a preterm neonate with a ductus arteriosus

PREVIOUS NEXT

January: Question 10

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11 November 07

12 December 07

You are asked to evaluate a newborn with a heart murmur. An echocardiogram reveals that the infant has normal cardiac anatomy with a persistent left superior vena cava (LSVC).

Of the following, the MOST likely structure into which a LSVC drains directly is the:

1	coronary sinus
2	left atrium
3	left brachiocephalic vein
4	right atrium
5	right superior vena cava

You selected 3, the correct answer is 1.

Do you want to add anything to your Learning Plan?
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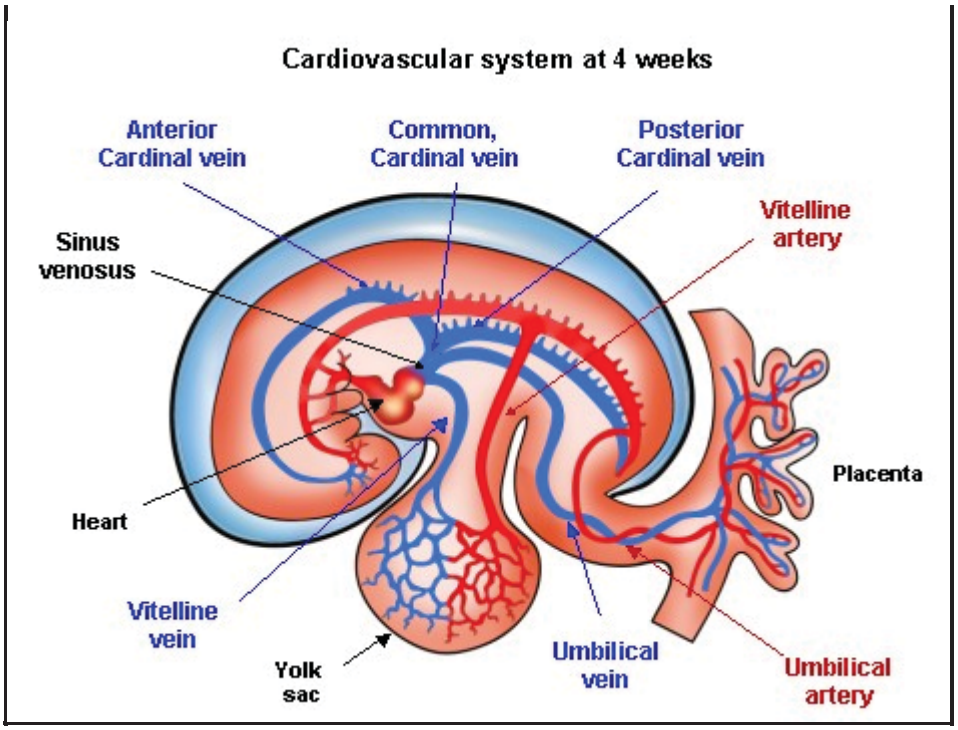
The embryologic development of the heart and great vessels is a complex process. The primordial heart and vascular system first appear in week 3 of embryonic development, and the heart begins to beat at 22 to 23 days. The vascular system develops in a bilateral symmetric fashion and undergoes a sequence of obliterations, remodeling, and anastomoses. Obliterations tend to occur on the left side of the embryonic venous system and the right side of the arterial system. Obliterations of embryonic left-sided venous structures results in venous drainage being channeled to the right atrium. Vascular malformations can arise at many stages of development. Failure of obliteration of left-sided venous structures results in a persistent left superior vena cava (LSVC).

Three major sets of paired veins drain into the tubular heart of a 4-week embryo (Figure 1).

Figure 1:Cardiovascular system at 4 weeks.

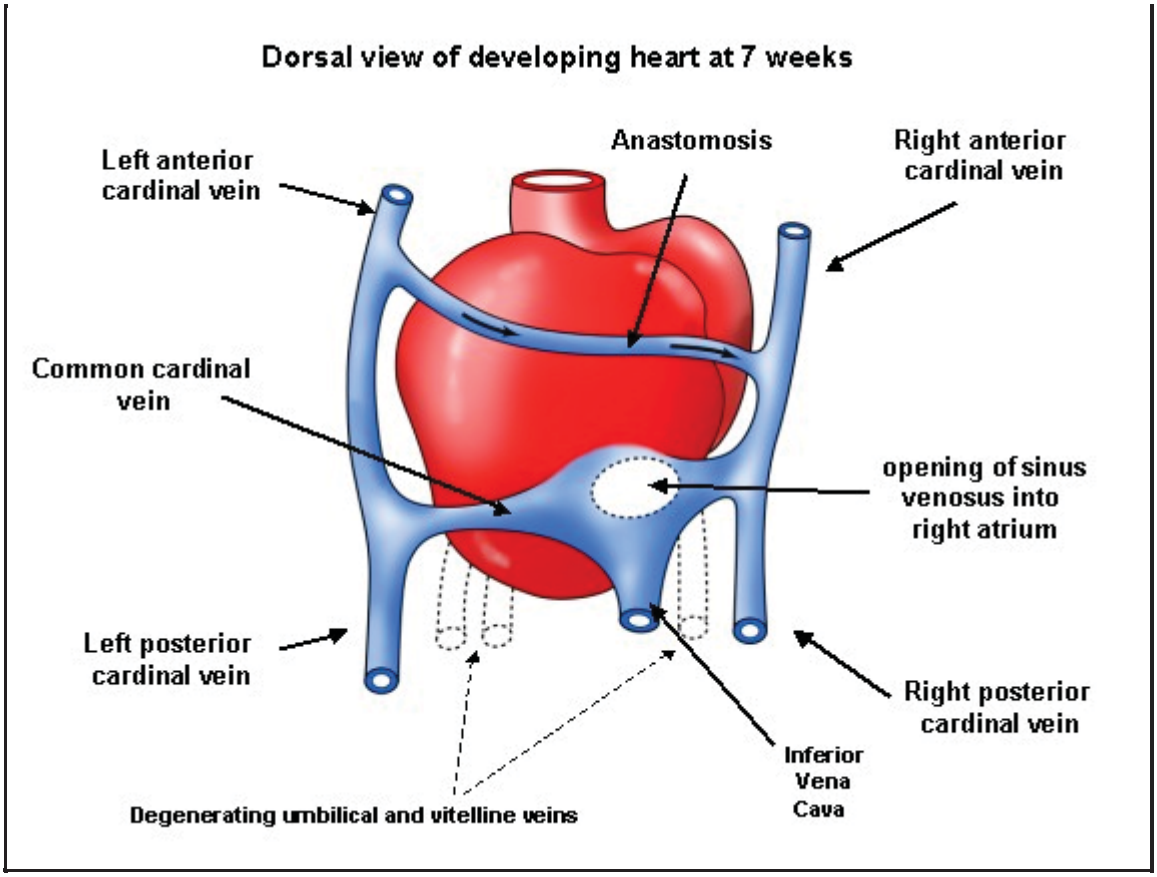


The left and right umbilical veins carry oxygenated blood from the primordial placenta; the left and right vitelline veins return poorly oxygenated blood from the yolk sac; and the left and right cardinal veins return poorly oxygenated blood from the body of the embryo.

The left and right cardinal veins, the main venous drainage system of the embryo, are further subdivided into anterior cardinal veins that drain the cephalic part of the embryo, and posterior cardinal veins that drain the caudal part of the embryo. The left and right anterior and posterior cardinal veins join as the common cardinal veins and drain into the sinus venosus (coronary sinus) which in turn drains into the primordial atrium.

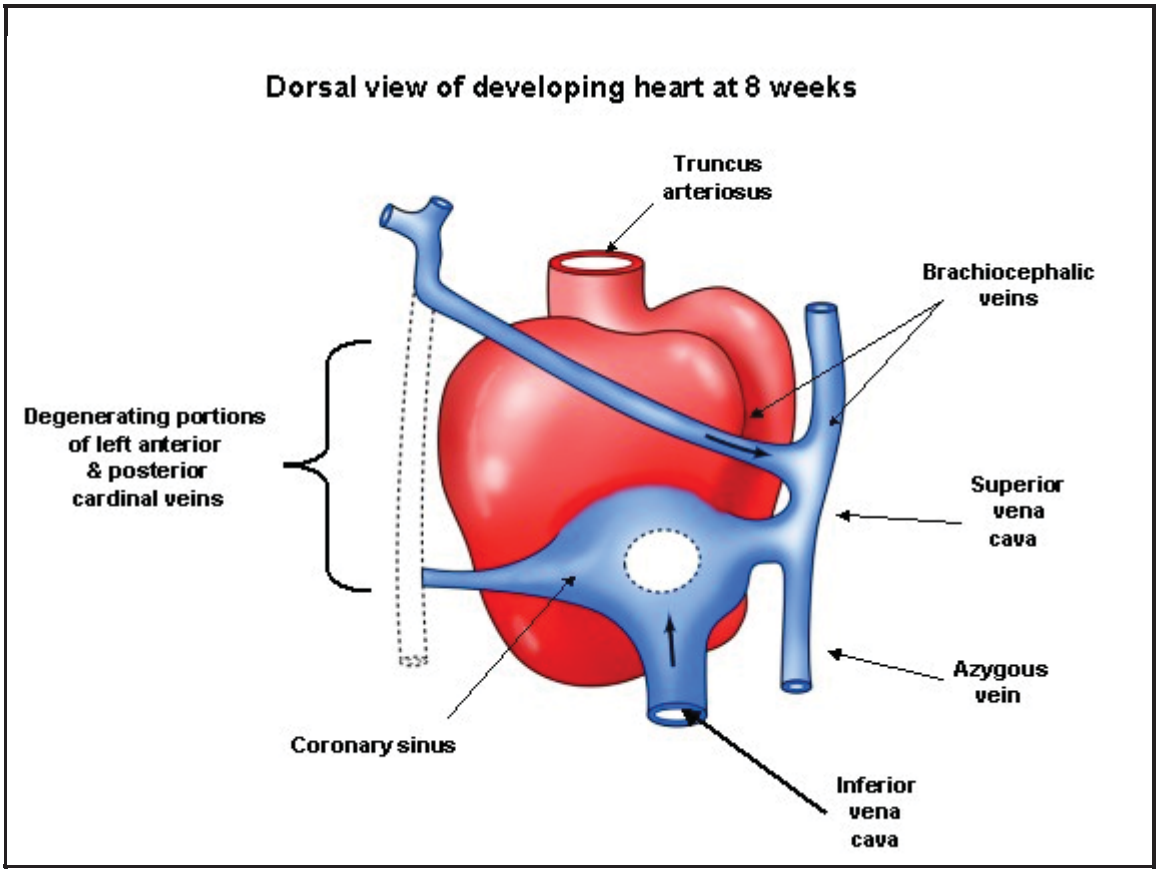
At week 7 of gestation, the left and right anterior cardinal veins are connected by an oblique anastomosis that shunts blood from left to right (Figure 2).

Figure 2:Dorsal view of developing heart at 7 weeks.



At week 8 of gestation, the caudal portion of the left anterior cardinal vein degenerates (Figure 3).

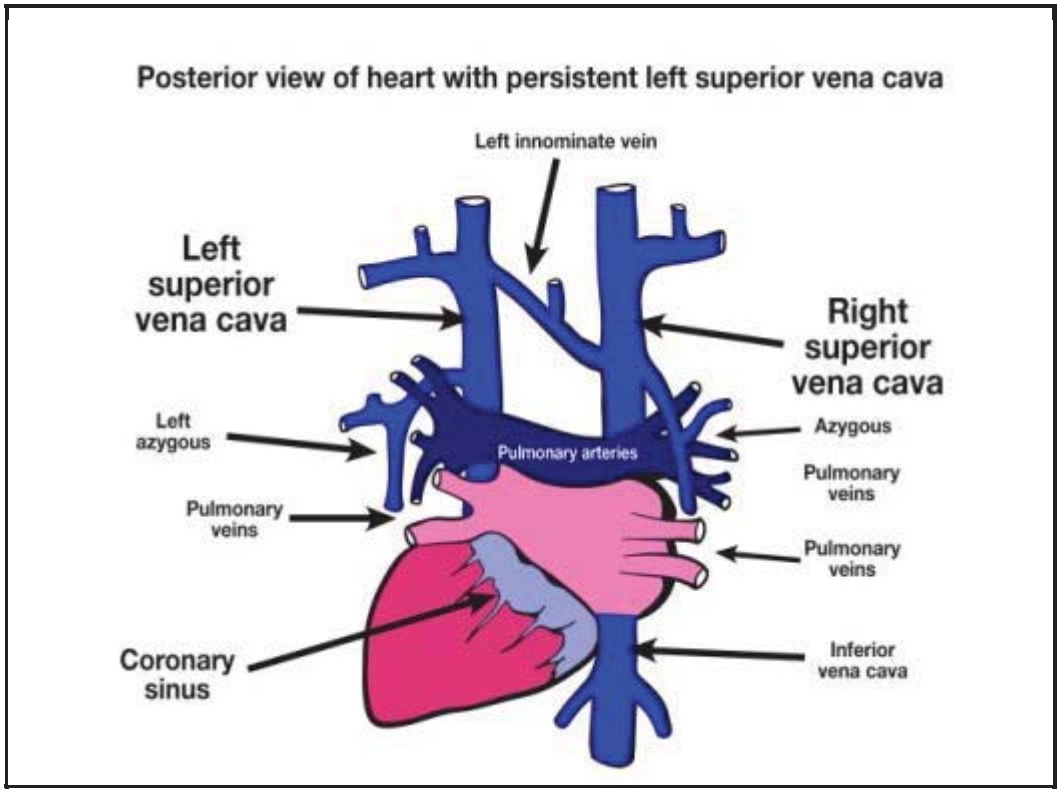
Figure 3: Dorsal view of developing heart at 8 weeks.



The cephalic portion of the left anterior cardinal vein and the oblique anastomotic shunt become the left brachiocephalic vein. The right anterior cardinal vein and right common cardinal vein become the superior vena cava. Failure of obliteration of the caudal portion of the left anterior cardinal vein results in a persistent LSVC.

A persistent LSVC is the most common malformation of systemic venous drainage. A persistent LSVC is present in 0.4% of the population and 10% of patients with congenital heart disease. The LSVC starts at the junction of the left internal jugular and left subclavian vein, passes lateral to the aortic arch, and receives blood from the left superior intercostal vein and hemiazygous system. In approximately 90% of cases, the LSVC drains into the coronary sinus which in turn drains into the right atrium (Figure 4).

Figure 4: Posterior view of heart with persistent left superior vena cava.



Although drainage of a LSVC into the coronary sinus causes dilation of the coronary sinus, it is usually asymptomatic. The adverse events that have been reported include cardiac arrhythmias due to stretching of the atrioventricular node, and obstruction of left ventricular flow because of partial occlusion of the mitral valve.

Echocardiographic findings of a LSVC include dilation of the coronary sinus that may protrude into the left atrium and be mistaken for a left atrial mass. A LSVC may be suspected on a chest radiograph if there is a prominent vertical border along the superior mediastinum lateral to the aortic knob. The diagnosis of a LSVC can be confirmed by contrast echocardiography, computerized tomography, or magnetic resonance imaging (Figure 5-Magnetic resonance image angiography demonstrating persistent left superior vena cava.)

Approximately 10% of LSVCs drain into the left atrium. Drainage of a LSVC into the left atrium produces a small right to left shunt. However, most patients with drainage of a LSVC into the left atrium have associated atrial septal defects or heterotaxy syndromes.

Drainage of LSVC into the left brachiocephalic vein, right atrium, and right superior vena cava rarely occur.

Do you want to add anything to your Learning Plan?
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References:

Cherian SB, Ramesh BR, Madhyastha S. Persistent left superior vena cava. *Clin Anat.* 2005:1-5. [Epub ahead of print.]

Larsen WJ. Development of the vasculature. In Larsen WJ ed. *Human Embryology.* 3rd ed Philadelphia, Pa: Churchill Livingstone; 2001:195-234

Moore KL, Persaud TVN. The cardiovascular system. In Moore KL, Persaud TVN, eds. *Before We Are Born: Essentials of Embryology and Birth Defects.* 6th ed. Philadelphia, Pa: Saunders; 2003

American Board of Pediatrics Content Specification(s):

Know normal and abnormal embryologic development of the heart and great arteries and the factors affecting these

PREVIOUS NEXT

The analysis of pleural fluid is helpful in the diagnosis of congenital chylothorax. The fluid, in the absence of enteral feeding, typically is amber colored, is rich in lymphocytes (differential count >70%), and may not show an elevated triglyceride concentration. With enteral feeding, especially using milk rich in long-chain triglycerides, the pleural fluid becomes milky in appearance, remains rich in lymphocytes, and shows an elevated triglyceride concentration (>110 mg/dL [1.2 mmol/L]). The evolution of pleural effusion in the infant in this vignette, its manifestation at birth before any postnatal interventions, and the pleural fluid analysis are compatible with the diagnosis of congenital chylothorax.

Pleural effusion resulting from heart failure often is bilateral and accompanied by hydrops. Hydrops fetalis may be associated with congenital structural heart malformations and abnormalities of cardiac rhythm. The structural malformations typically include hypoplastic left heart syndrome and endocardial cushion defect. Among the rhythm abnormalities, tachyarrhythmias, including supraventricular tachycardia and atrial flutter, are more common than bradyarrhythmias such as heart block. The severity and unilateral localization of the pleural effusion as well as the absence of generalized edema make heart failure an unlikely cause of pleural effusion in the infant in this vignette.

Extravasation of fluid into the pleural space can result from injury to the thoracic duct, or obstruction of the subclavian vein or superior vena cava. Surgical procedures, such as correction of coarctation of aorta, ligation of patent ductus arteriosus, and repair of congenital diaphragmatic hernia, may cause inadvertent injury to the thoracic duct. The thrombosis of the subclavian vein or superior vena cava and resultant increase in central venous pressure may cause extravasation of fluid into the pleural space. The thrombosis often is a complication of long-term use of indwelling catheters for administration of parenteral nutrition. The absence of any of these interventions makes iatrogenic extravasation an unlikely cause of pleural effusion in the infant in this vignette.

Pneumonia resulting from perinatally acquired bacterial infection involving organisms such as group B *Streptococcus* may be associated with pleural effusion. Typically, the effusion is bilateral, less voluminous than that described in this vignette, and characterized by neutrophilic preponderance. Rarely, in extreme cases of late-onset bacterial sepsis, the pneumonia may be complicated by a localized collection of pus as in lung abscess or empyema. The nature of the pleural fluid and the absence of features suggestive of sepsis make intrauterine infection an unlikely cause of pleural effusion in the infant in this vignette.

Mediastinal malignancies, such as lymphoma, sarcoma, or neuroblastoma, are rare causes of pleural effusion in neonates. The effusion in such cases may result from obstruction and rupture of the lymphatics induced by the tumor, or from invasion of the lymphatics by the tumor.

Do you want to add anything to your Learning Plan?
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References:

Beghetti M, La Scala G, Belli D, Bugmann P, Kalangos A, LeCoultre C. Etiology and management of pediatric chylothorax. *J Pediatr.* 2000;136:653-658

Devine PC, Malone FD. Noncardiac thoracic anomalies. *Clin Perinatol.* 2000:27:865-899

Dubin PJ, King IN, Gallagher PG. Congenital chylothorax. *Curr Opin Pediatr.*

2000;12:505-509

Wasmuth-Pietzuch A, Hansmann M, Bartmann P, Heep A. Congenital chylothorax: lymphopenia and high risk of neonatal infections. *Acta Paediatr.* 2004;93:220-224

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology and recognize the clinical, radiographic, and laboratory manifestations of hydrothorax/chylothorax

PREVIOUS NEXT

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11 November 07
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January: Question 2

A term male infant with primary persistent pulmonary hypertension of the newborn (PPHN) requires substantial support with fraction of inspired oxygen (Fio_2) of 1.0, high-frequency oscillatory ventilation, dopamine, and inhaled nitric oxide. The mean airway pressure (MAP) on the ventilator is 24 cm H_2O and the partial pressure of arterial oxygen (Pao_2; right radial) is 60 torr. The oxygenation index calculated from these values is 40 (MAP × Fio_2 × 100/Pao_2). After discussion with the infant's parents, venovenous extracorporeal membrane oxygenation (VV ECMO) using a double lumen catheter is initiated.

Of the following, the MOST accurate statement about the expected physiologic effects of VV ECMO is that:

1	Cardiac output is reduced because blood flow to the coronary circulation is decreased.
2	Oxygen consumption is reduced because venous oxygen content is increased.
3	Oxygen extraction increases because systemic arterial oxygen content is increased.
4	Pulmonary blood flow increases because the oxygen content of blood perfusing the pulmonary circulation is increased.
5	Systemic oxygen delivery increases because arterial oxygen saturation is maximized (>98%).

You selected 3, the correct answer is 4.

Do you want to add anything to your Learning Plan?
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Persistent pulmonary hypertension of the newborn (PPHN) affects 1 to 2 per 1,000 live births. Most infants with PPHN are born after 34 weeks' gestation, and have an underlying cardiorespiratory disorder such as meconium aspiration syndrome, sepsis, transient tachypnea, pneumothorax, congenital diaphragmatic hernia, and some congenital heart lesions (eg, transposition of the great vessels, total anomalous pulmonary venous return). Primary PPHN affects about 10% of infants with this illness.

The essential pathophysiology of PPHN involves persistent or recurrent elevation in pulmonary vascular resistance after birth, often associated with hypoxic respiratory failure (Figures 1 and 2).

Figure 1: Normal newborn.

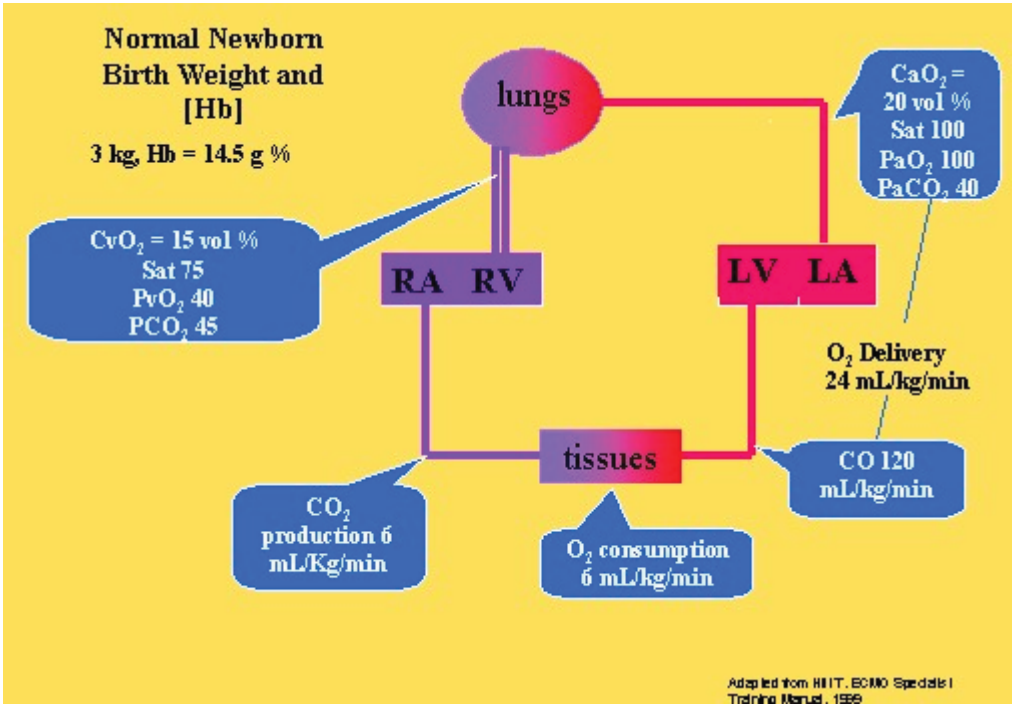
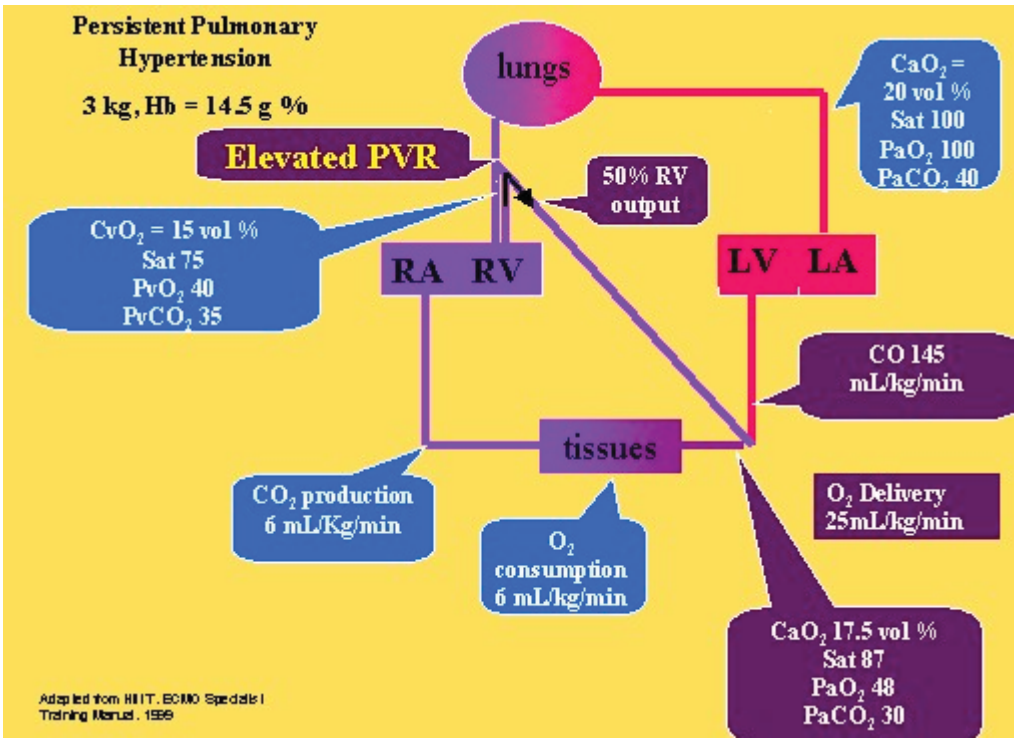


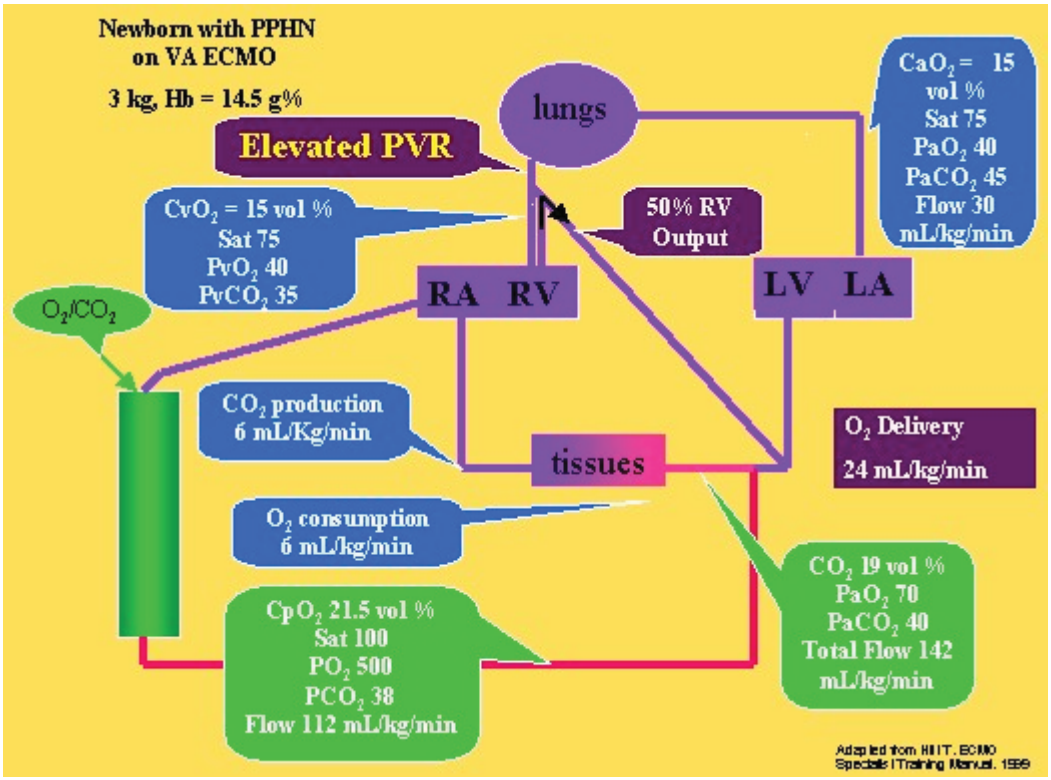
Figure 2: Newborn and persistent pulmonary hypertension (PPHN).



Venous blood is shunted from the right-sided circulation to the left-sided circulation through the ductus arteriosus, foramen ovale, and across poorly functioning diseased lung segments. These right-to-left shunts lead to systemic hypoxemia and cyanosis. Improvements in care have increased survival of such infants. Physiology-targeted management strategies, high-frequency ventilation, surfactant, and inhaled nitric oxide have proven beneficial in clinical series and randomized clinical trials. Extracorporeal membrane oxygenation (ECMO), usually initiated as a rescue intervention when all other treatments have failed to reverse the clinical spiral of PPHN, was also proven beneficial in a multicenter, randomized, controlled clinical trial.

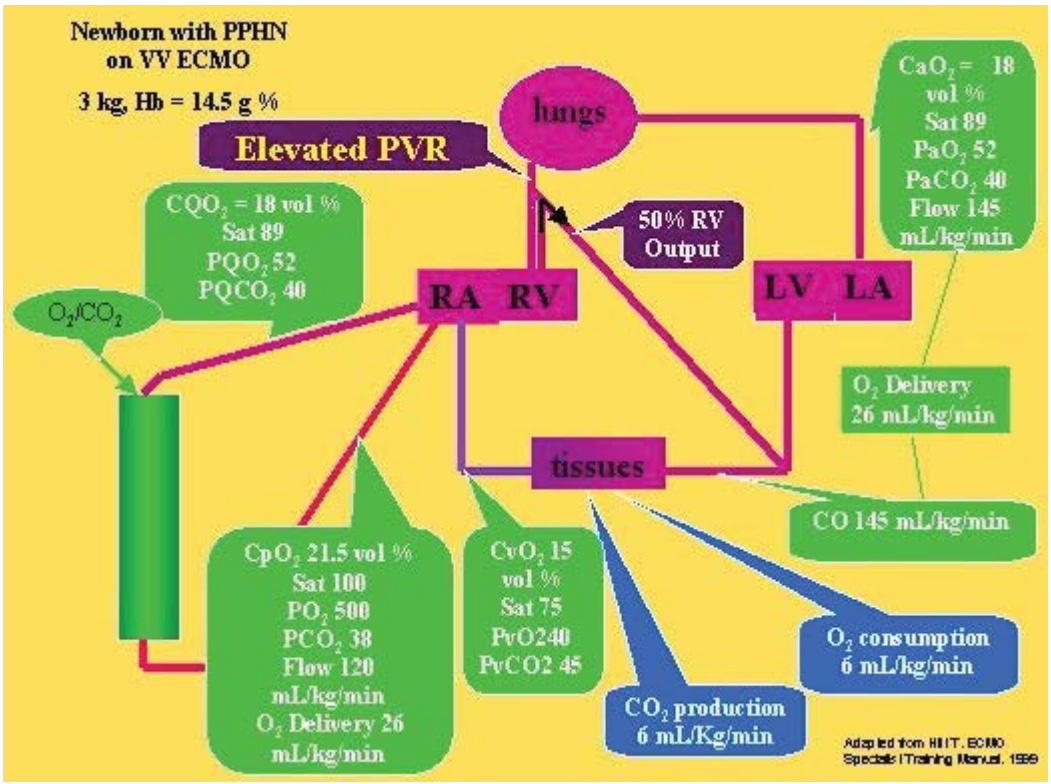
Extracorporeal membrane oxygenation is most often applied to newborns with respiratory failure through catheters placed in both the right internal jugular vein and right carotid artery (venoarterial ECMO or VA ECMO, Figure 3)

Figure 3: Newborn and persistent pulmonary hypertension (PPHN) and venoarterial extracorporeal membrane oxygenation (ECMO).



or through a single double-lumen catheter in the right internal jugular vein (venovenous ECMO or VV ECMO, Figure 4).

Figure 4: Newborn and persistent pulmonary hypertension (PPHN) and venovenous extracorporeal membrane oxygenation (ECMO).



As seen in the infant in the vignette, VV ECMO provides well-oxygenated blood to the pulmonary circulation. Improved pulmonary arterial oxygenation is a potent vasodilator that reduces pulmonary vascular resistance and increases pulmonary blood flow. The mechanism for the oxygen effect is complex, involving vasodilatation and alleviation of hypoxic vasoconstriction. Increased oxygen tension improves blood flow, which induces shear-stress-related vasodilatation, reduces myogenic tone, and increases endogenous production of a number of different endothelial- and nonendothelial-derived vasodilators, especially nitric oxide and prostacyclin.

Venovenous ECMO indirectly improves cardiac function. With increased pulmonary blood flow, pulmonary venous return to the left atrium increases, thereby providing more adequate preload for the left ventricle. Importantly, blood that flows to the coronary ostia and circulation is derived from the left ventricle in both VV ECMO and VA ECMO. During VV ECMO, pulmonary venous blood is highly saturated with oxygen. In contrast, VA ECMO diverts blood from the right atrium and returns it to the aortic arch, essentially bypassing the heart completely at total ECMO support. Blood from the right atrium is venous in origin and the volume of blood flow through the pulmonary circulation to the left atrium and left ventricle is reduced. Thus, during complete VA ECMO support, there is a reduction in cardiac output and oxygen tension that may compromise cardiac function. The higher risk of cardiac stun during VA ECMO compared with VV ECMO is indirect evidence for reduced oxygen delivery to the coronary circulation during VA ECMO. Of note, during VA ECMO the extracorporeal support is most often partial, and oxygen delivery to the coronary circulation is adequate.

Oxygen consumption is calculated by multiplying the cardiac output (CO) by the difference between the oxygen content of the arterial (Cao_2) and venous circulations (Cvo_2):

$$O_2 \text{ Consumption} = CO \times (Cao_2 - Cvo_2)$$

$$O_2 \text{ Content} = \{(Hb) \times 1.34 \text{ mL } O_2/\text{g Hb} \times So_2\} + 0.003 \times Po_2$$

During VV ECMO, O_2 consumption is maintained as long as adequate oxygen delivery is present; it is not reduced. Oxygen delivery (DO) equals the CO

multiplied by the oxygen content (Cao_2).

$$O_2 \text{ Delivery} = CO \times Cao_2$$

As stated before, cardiac output likely increases during VV ECMO. The increase in CO usually compensates for any drop in arterial oxygen content that occurs due to lower arterial oxygen saturation (80% to 95%, see O_2 content equation above), which is sometimes seen after the transition to VV ECMO.

Venovenous ECMO and VA ECMO are both intended to provide improved oxygen delivery by increasing arterial oxygen content and cardiac output. Improved oxygen delivery is expected to reverse the compensatory responses of blood flow redistribution and increased oxygen extraction that occur when tissues sense inadequate oxygen delivery. Oxygen extraction should be reduced, and mixed venous oxygen saturation is anticipated to normalize. If oxygen consumption is increased due to seizures, jitteriness, or septic shock, however, additional oxygen delivery may be necessary. Oxygen delivery can be increased with improved cardiac output and/or higher arterial oxygen content (higher arterial oxygen saturation or hemoglobin). If this increase in oxygen delivery cannot be achieved with maximal ECMO flow, blood flow redistribution to essential organs (brain, heart, adrenal glands) and increased oxygen extraction (O_2 extraction) may be required by the tissues of the body (indicated by a decrease in mixed venous oxygen saturation and venous oxygen content).

$$O_2 \text{ Extraction} = (Cao_2 - Cvo_2)/Cao_2$$

Venovenous ECMO improves oxygen delivery by increasing venous oxygen content, increasing cardiac output and, in many instances, increasing arterial oxygen saturation (Sao_2) and content. However, Sao_2 values of 80% to 95% are expected even during full VV ECMO flow (>120-150 mL/kg per minute) because it is the venous admixture in the right atrium that perfuses the systemic circulation (Figure 4). Thus, increased systemic oxygen delivery is not usually due to maximum Sao_2 values (>98%). If endogenous pulmonary function contributes to oxygen exchange, Sao_2 may be greater than 95%. Of note, the relatively lower Sao_2 values achieved with VV ECMO compared with VA ECMO are often accepted in exchange for a reduction in the pulmonary parenchymal and vascular injury associated with high concentrations of oxygen and positive pressure ventilation.

References:

Dakshinamurti S. Pathophysiologic mechanisms of persistent pulmonary hypertension of the newborn. *Pediatr Pulmonol.* 2005;39:492-503

Fortenberry JD, Pettignano R, Dykes F. Principles and practice of venovenous ECMO. In: Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *Extracorporeal Cardiopulmonary Support in Critical Care.* 3rd ed. Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:85-105

Ghanayem NS, Gordon JB. Modulation of pulmonary vasomotor tone in the fetus and neonate. *Respir Res.* 2002;2:139-144

Hilt T, Graves D, Zwischenberger JB. ECMO physiology. In: Van Meurs K, ed. *ECMO Specialist Training Manual.* 2nd ed. Ann Arbor, Mich: Extracorporeal Life Support Organization; 1999:19-40

Kinsella JP, Abman SH. Recent developments in the pathophysiology and

treatment of PPHN. *J Pediatr.* 1995;126:853-864

Wojciak-Stothard B, Haworth SG. Perinatal changes in pulmonary vascular endothelial function. *Pharmacol Ther.* 2006;109:78-91

American Board of Pediatrics Content Specification(s):

Understand the various factors affecting oxygen uptake, transport, and delivery, including the blood and circulation

Know the management of persistent pulmonary hypertension

Understand the indications for and techniques of extracorporeal membrane oxygenation (ECMO)

PREVIOUS NEXT

February: Question 1

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11 November 07

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You are asked to evaluate a 2,900-g female infant born at 41 weeks' gestation with multiple anomalies (Figures 1-4). Additional findings on physical examination include diminished femoral pulses.

Figure 1

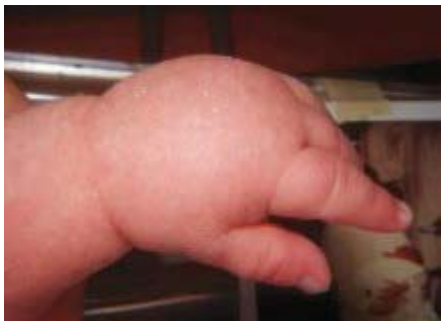


Figure 2

Figure 3

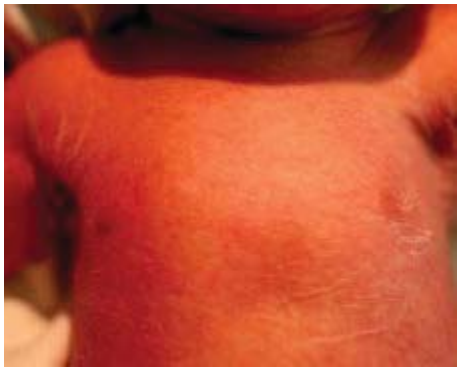
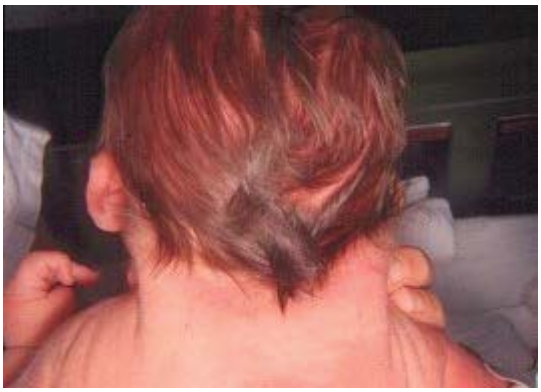


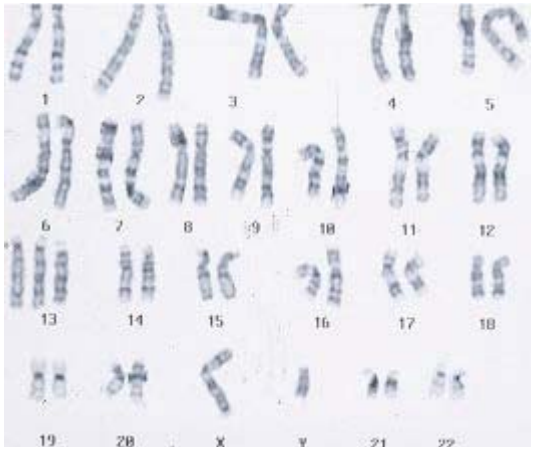
Figure 4



Of the following, the MOST likely karyotype of this infant is shown in:

Figure 5

Figure 6



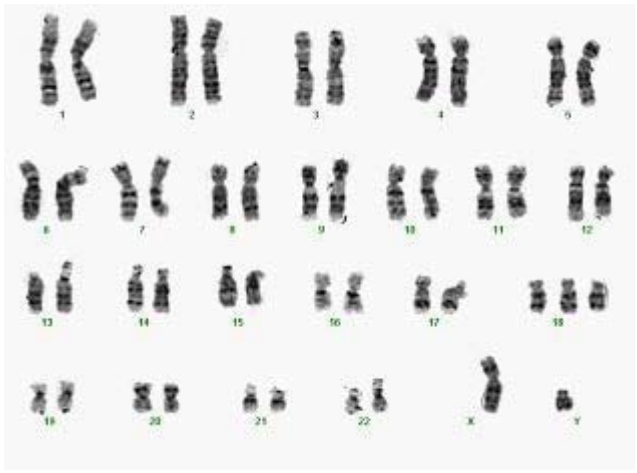
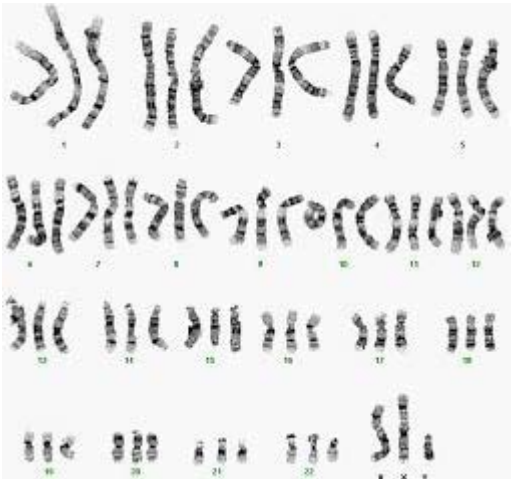


Figure 7

Figure 8

Figure 9



1	Figure 5
2	Figure 6
3	Figure 7
4	Figure 8
5	Figure 9

You selected 4, the correct answer is 4.

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Making the diagnosis of a syndrome in an infant with multiple birth defects requires recognition of overall patterns of anomalies. The diagnosis of a syndrome is rarely possible upon identification of a single birth defect. Even unusual defects such as rocker bottom feet and a short sternum may be present in several different syndromes. Moreover, individuals with the same syndrome have variance in the expression of anomalies. Most clinical features are found in less than 80% of individuals with any given syndrome. Obtaining a karyotype is of central importance in confirming the clinical diagnosis of an infant with multiple anomalies.

The infant described in this vignette has the pattern of anomalies consistent with Turner syndrome. The karyotype of Turner syndrome is 45X (Figure 8). The clinical features of Turner syndrome include congenital lymphedema with puffiness over the dorsum of the hands (Figure 1) and feet (Figure 2), broad chest with wide-spaced nipples (Figure 3), prominent auricles, and webbed posterior neck (Figure 4). Infants with Turner syndrome are usually small for gestational age with a mean birthweight of 2,900 g. Cardiac defects are common in Turner syndrome. The infant described in this vignette has diminished femoral pulses, suggesting a coarctation of the aorta. Bicuspid aortic valve or coarctation of the aorta occurs in approximately 40% of patients with Turner syndrome.

The karyotype in Figure 5 is trisomy 13. The clinical features described in the infant in this vignette would be unusual for trisomy 13. Approximately 60% to 80% of patients with trisomy 13 have a cleft lip and cleft palate frequently midline. Localized scalp defects in the parieto-occipital area, abnormal helices with low-set ears, holoprosencephaly, polydactyly, colobomata of irides, and

retinal dysplasia occur in more than 50% of patients. Congenital heart disease occurs in 80% with ventricular septal defect (VSD) as the most common abnormality.

The karyotype in Figure 6 is trisomy 18. The clinical features described in the infant in this vignette would be unusual for trisomy 18. At birth, infants with trisomy 18 are feeble, with a weak cry and frequently require resuscitation. The clinical features of trisomy 18 include a prominent occiput with low-set malformed ears, skin redundancy, mild hirsutism of the forehead, prominent cutis marmorata, clenched hands with tendency for overlapping fingers, hypoplastic nails, rocker bottom feet, syndactyly of second and third toes, short sternum with reduced numbers of ossification centers, and limited hip abduction. Congenital heart disease occurs in more than 50% with VSD as the most common abnormality.

The karyotype in Figure 7 is trisomy 21. The clinical features described in the infant in this vignette would be unusual for trisomy 21.The clinical features of trisomy 21 include brachycephaly with flat occiput, flat facies with tendency to keep mouth open and tongue protruding, small nose with low nasal bridge, inner epicanthal folds and upward slant of eyes, and a single palmar crease. Congenital heart disease occurs in 40% with endocardial cushion defect as the most common abnormality.

The karyotype in Figure 9 is triploidy. Triploidy is a complete extra set of chromosomes (69) in the nucleus of each cell. The clinical features of triploidy include dysplastic calvaria with a large posterior fontanel, a large bulbous nose, and hypertelorism. The clinical features described in the infant in this vignette would be unusual for triploidy.

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References:

Gilbert-Barness E. Chromosomal abnormalities. In: Gilbert-Barness E, ed. *Potter's Pathology of the Fetus and Infant.* St. Louis, Mo: Mosby; 1997:388-432

Jones KL. Dysmorphology: approach and classification. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:1-6

Jones KL. Trisomy 13 syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:18-21

Jones KL. Trisomy 18 syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:13-17

Jones KL. Trisomy 21 syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:7-12

Jones KL. Triploidy syndrome and diploid/triploid mixoploidy syndrome In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:28-31

Jones KL. 45X syndrome. In: Jones KL, ed. *Smith's Recognizable Patterns of Malformation.* 6th ed. Philadelphia, Pa: WB Saunders; 2005:76-81

American Board of Pediatrics Content Specification(s):

Recognize the physical findings and chromosomal pattern in trisomy 13

Identify the physical characteristics and chromosomal pattern in trisomy 18

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Recognize the physical characteristics and chromosomal pattern of sex chromosome aneuplody

Know fetal and placental manifestations of triploidy

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11 November 07

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July: Question 4

Three days after birth, a 26-week-gestation, 719-g preterm infant shows increase in oxygen demand and ventilator settings. Physical examination discloses a systolic murmur in the left infraclavicular region, prominent cardiac impulse to palpation, and presence of palmar pulses. Your suspicion of patent ductus arteriosus is confirmed on echocardiography. By coincidence, you had recently discovered a patent ductus arteriosus on examining a term infant, leading you to consider the effect of the ductus arteriosus among term and preterm infants.

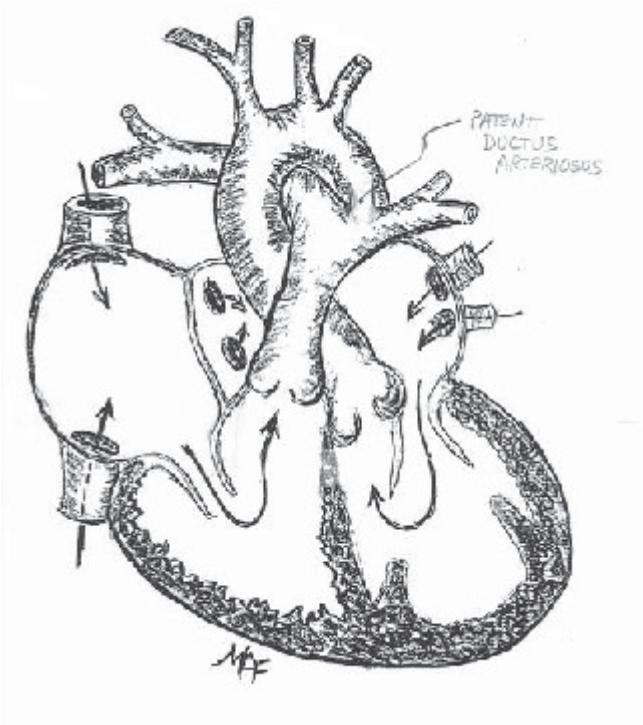
Compared with term infants with patent ductus arteriosus, preterm infants are MOST likely to have:

1	enhanced effect of oxygen on ductal remodeling
2	greater susceptibility for pulmonary edema
3	higher risk for associated structural cardiac defects
4	less responsiveness to pharmacologic closure with indomethacin
5	more positive family histories for ductal patency

You selected 3, the correct answer is 2.

The ductus arteriosus (DA) connects the aorta just distal to the left subclavian artery to the junction of the main and left pulmonary arteries (Figure 1).

Figure 1



In fetal life, the DA, derived embryologically from the sixth aortic arch, functions to bypass blood flow from the pulmonary circulation to the systemic circulation, and carries about 50% of the combined cardiac output. Flow through the DA in fetal life is enhanced by at least four factors:

- **ductal dilation mediated by low oxygen tension of the blood traversing the DA**
- **ductal dilation mediated by prostaglandins, some of placental origin**
- **high pulmonary vascular resistance secondary to pulmonary vascular constriction**
- **low systemic vascular resistance due to high placental blood flow**

At birth, transitional effects influence all four of these factors in the following manner:

- **blood oxygen tension rises as the lungs expand, leading to constriction of the DA**
- **vasodilatory prostaglandins are no longer supplied by the placenta and undergo increased metabolism in the lung, leading to constriction of the DA**
- **lung expansion combined with higher blood oxygen content relaxes pulmonary vasculature, promoting flow from the pulmonary arteries into the lungs**
- **removal of the placenta from the systemic circuit increases systemic peripheral resistance**

The combination of these events causes the flow in the DA to reverse, exposing the DA to blood with higher oxygen content and lower concentrations of vasodilatory prostaglandins, which causes constriction of the DA. This constriction results in functional closure beginning within 10 to 15 hours after delivery with resultant hemodynamic closure in 50% of term infants by 24 hours after birth, in 90% by 48 hours, and in virtually all by 72 hours.

Functional closure is followed by a series of anatomic changes resulting in structural closure. Paradoxically, oxygen-mediated constriction of the DA results in a zone of tissue hypoxia in the ductal media, the signal for irreversible anatomic closure. Hypoxia-induced growth factors, including

vascular endothelial growth factor and transforming growth factor-beta, initiate ductal remodeling. With greater degrees of prematurity, the thinner ductal wall is more permeable to oxygen. Unless ductal flow is interrupted in the preterm infant, medial hypoxia will not develop and the necessary cell death and remodeling will not occur, enhancing the opportunity for reopening.

The vasodilatory prostaglandins, PGE2 and PGI2, along with a nitric oxide-like vasodilator, produced by the DA, promote ductal patency. The vasodilator effect of the prostaglandins declines with gestational age and with postnatal age. This decline makes prostaglandin synthetase inhibitors less effective with advancing postnatal and gestational age. Early studies in animals have demonstrated a synergistic effect between indomethacin (prostaglandin synthetase inhibitor) and a nitric oxide inhibitor in effecting ductal constriction. Antenatal corticosteroids are associated with a reduced incidence of ductal patency, presumed to be the result of the corticosteroid-induced reduction in sensitivity of ductal tissue to PGE2. On the other hand, among fetuses exposed to indomethacin in utero, 60% will have ductal constriction in utero, which may induce hypoxic damage to the vasoconstrictory musculature of the DA and inhibit constriction after birth.

Among preterm infants, closure of the DA may be delayed and the DA becomes more susceptible to reopening. Most healthy preterm infants of more than 30 weeks' gestation have a closed DA by 4 days of age. As gestational age decreases, and especially if the infant's course is complicated by respiratory distress syndrome, the incidence of patent ductus arteriosus (PDA) increases. Up to 70% of infants delivered at less than 28 weeks' gestation receive treatment for PDA.

The preterm infant will develop symptoms of PDA sooner than term infants. Pulmonary vascular resistance decreases more rapidly among preterm infants because of their immature pulmonary arteries, resulting in a larger left-to-right shunt occurring earlier after birth. The increase in pulmonary blood flow, low plasma oncotic pressure, and increased capillary permeability of the premature lung lead to increases in pulmonary interstitial and alveolar fluids with resultant increased clinical demands for oxygen and ventilatory assistance with continuous positive airway pressure or assisted ventilation. Chest radiography may show haziness of the lung fields, fluid in fissures, and cardiomegaly. The low systemic diastolic pressure may result in shifts in distribution of the systemic circulation, resulting in gastrointestinal disturbance from feeding intolerance, necrotizing entercolitis, or diminished renal function. The clinical presentation is often first noted as an increase in oxygen or ventilatory settings, increasing apnea, or feeding intolerance. The PDA may be silent, so it must be considered in the diagnostic evaluation for deterioration of respiratory status, gastrointestinal difficulties, blood pressure and fluid balance, or other nonspecific concerns. When typical cardiac findings are noted, the diagnosis can be confirmed by echocardiography, or echocardiography can help in finding the occult PDA.

Among term infants patent ductus arteriosus

- occurs less frequently than among preterm infants
- is more likely to result from a primary structural abnormality of the DA
- has an incidence of 1 in 2,500 to 1 in 5,000 live births
- is twice as prevalent among males as in females
- may be associated with other cardiac structural abnormalities

Because the structure of the DA is more often abnormal in term infants, strategies

directed toward the normal physiologic mechanisms of DA closure such as indomethacin are less likely to be successful. Clinical presentation of significant PDA among term infants tends to be later, at 3 to 6 weeks after birth, with heart failure as the predominant feature. Family history may be positive, with occurrence among siblings ranging from 2% to 4%.

The optimal management strategy for PDA is controversial, less so for term PDA than for preterm PDA. In the term infant, PDA is unlikely to close spontaneously. Incidentally discovered PDA can be treated on a nonemergent basis. In the interim, prophylaxis against bacterial endocarditis is indicated. Children presenting with heart failure should be medically stabilized, followed by closure of the DA. Closure may be accomplished surgically or with catheter-based techniques.

Preterm infants with documented PDA and clinical deterioration generally are candidates for treatment to close the DA, using a combination of intensive general and respiratory care combined with prostaglandin inhibition or surgery if medical treatment is not indicated. Indomethacin is the most commonly used drug to date, but recent studies show similar effectiveness using ibuprofen-lysine. Debate exists regarding the optimal management strategy. Prophylactic treatment (initiated within 15 hours of birth) leads to a higher rate of closure initially and yields reduced incidence of symptomatic PDA and need for surgical treatment. However, it affords no benefits over waiting for symptoms to develop before treatment in reducing pulmonary morbidity or necrotizing enterocolitis. Similar rates of reopening are found using both strategies, because reopening is more greatly influenced by the presence of any degree of residual flow after treatment. If residual PDA flow is noted on posttreatment Doppler study, 90% will reopen. In preterm patients with normal overall progress who are discovered to have a PDA, a potential for spontaneous closure exists. The optimal treatment strategy in such patients remains fodder for debate.

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References:

Aranda JV, Thomas R. Intravenous ibuprofen for preterm newborns. *NeoReviews.* 2005;6:e516-e523

Doyle T, Kananaugh-McHugh A, Graham TP. Overview of patent ductus arteriosus. UpToDate.com Web site. Accessed January 26, 2007, at: www.uptodate.com (subscription required)

Kajino H, Goldbarg S, Roman C, et al. Vasa vasorum hypoperfusion is responsible for medial hypoxia and anatomic remodeling in the newborn lamb ductus arteriosus. *Pediatr Res.* 2002;51(2):228-235.

Mancini MC. Patent ductus arteriosus: surgical perspective. emedicine.com Web site. Accessed January 26, 2007, at: www.emedicine.com/ped/topic2834.htm

Narayanan-Sankar M, Clyman RI. Pharmacologic closure of patent ductus arteriosus in the neonate. *NeoReviews.* August 2003;4:e215-e221. Accessed March 15, 2007, at: http://neoreviews.aappublications.org/cgi/content/full/4/8/e215 (subscription required)

Neish SR. Patent ductus arteriosus. emedicine.com Web site. Accessed January 26, 2007, at: www.emedicine.com/ped/topic1747.htm

Pegoli W. Pericardium and great vessels. In: Oldham KT, Colombani PM, Foglia RP, Skinner MA, eds. *Principles and Practice of Pediatric Surgery.* Philadelphia, Pa:

Lippincott Williams & Wilkins; 2005:1007-1022

Welty SE. Patent ductus arteriosus in premature infants. UpToDate.com Web site. Accessed January 26, 2007, at: www.uptodate.com (subscription required)

American Board of Pediatrics Content Specification(s):

Understand the physiology of the ductus arteriosus

Understand the pathophysiology of a preterm neonate with a ductus arteriosus

Recognize the clinical features of a preterm neonate with a ductus arteriosus

Recognize the laboratory and radiographic features of a preterm neonate with a ductus arteriosus

Formulate a differential diagnosis of a preterm neonate with a ductus arteriosus

Understand the total management plan (medical and/or surgical) and associated potential complications of such management for a preterm neonate with a ductus arteriosus

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October: Question 3

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11 November 07

12 December 07

You admit a newborn infant with bradycardia. Fetal ultrasonography at 20 weeks' gestation had detected fetal sinus bradycardia. The fetus had a structurally normal heart with isolated first-degree heart block that had been diagnosed on echocardiography and resolved with maternal dexamethasone therapy. The mother had presented in advanced labor at 39 weeks, at which time the fetal heart rate was 60 beats per minute. With the exception of the bradycardia, the newborn infant is vigorous. The postnatal electrocardiogram demonstrates complete heart block.

Of the following, the MOST predictable event or finding in this case is:

1	death during infancy
2	maternal anti-Ro/SSA and/or anti La/SSB antibodies
3	maternal symptomatic lupus erythematosus
4	neonatal cutaneous manifestations
5	subsequent sibling(s) with complete heart block

You selected 2, the correct answer is 2.

Sustained fetal bradyarrhythmias are uncommon and are caused by sinus bradycardia, atrial bigeminy, or varying degrees of atrioventricular (AV) block. Complete AV block is the most common sustained fetal bradycardia. The degree of AV block can be diagnosed by measuring the electrical PR interval using noninvasive fetal cardiography or by estimating the AV interval using Doppler echocardiography. Fetal AV block (incomplete or complete) may be associated with complex cardiac malformations involving the AV junction. If the fetal heart is structurally normal, AV block is almost always associated with high titers of maternal anti-Ro/SSA and/or anti-La/SSB antibodies. Autoantibodies are present in more than 85% of women who have fetuses with varying degrees of AV block.

Although the presence of maternal anti-Ro/SSA and anti-La/SSB antibodies is highly likely in fetuses and infants with AV block, pregnant women who have these antibodies have about a 2% risk of delivering an infant with AV conduction abnormalities. The antibodies alone are insufficient to cause AV nodal injury and it is likely that fetal factors also contribute, suggesting a "two-hit" disease process. In the first step, maternal autoantibodies bind fetal cardiomyocytes, dysregulate calcium metabolism, and produce apoptosis in affected cells. Subsequently, tissue damage can lead to an inflammatory response in genetically predisposed fetuses, progressing to fibrosis and AV node calcification. Pregnant women with these autoantibodies and a previous infant with complete heart block have only a 10% to 25% chance of having another fetus with this conduction abnormality, providing additional support for this two-hit hypothesis. Even though maternal antibodies are cleared postnatally, the AV

injury in infants may progress, suggesting that infant factors are also involved.

Although the precise pathogenic mechanism is unknown, there are a few therapeutic options for fetal heart block. Isolated incomplete AV block may be treated and reversed to normal rhythm in utero with maternal fluorinated steroids (dexamethasone or betamethasone). However, while some studies found improvements in the fetal arrhythmias with such therapies, the results have not been consistent. Once complete heart block has developed, intrauterine steroid therapy is usually ineffective at reversing the abnormal rhythm because antibody-mediated nodal damage is irreversible. Fluorinated steroid therapy in utero may be considered for complete heart block to mitigate or prevent myocardial inflammation and/or improve cardiac output. The fetus that is exposed to intrauterine dexamethasone must be monitored closely for severe intrauterine growth restriction and adrenal insufficiency or hypoplasia. Treatment with beta-mimetic agents has generally been less successful than glucocorticoid exposure.

Despite intrauterine therapy, some fetuses experience progression to complete heart block, as in the vignette. Fetuses with complete heart block have an increased mortality of 15% to 30% with most deaths occurring in utero or during the first year after birth. Fetuses and infants at greatest risk include those with hydrops fetalis, lower ventricular rates (<50 beats/minute), and premature birth. Two-thirds of the surviving infants develop severe congestive heart failure and require pacemaker placement.

Only 1% of infants who acquire anti-Ro/SSA and anti-La/SSB antibodies through transplacental passive transfer develop neonatal lupus erythematosus. Diagnosis of this rare disease can be confirmed by measuring titers of these antibodies, as well as anti-U_1-ribonucleoprotein (U_1-RNP) antibody. While some mothers of affected infants have a diagnosis of systemic lupus erythematosus or SjÖgren syndrome, a considerable proportion of women (40%) are asymptomatic at the time of neonatal diagnosis. If these asymptomatic women develop clinical signs of lupus erythematosus later in life, it is usually a mild form.

Although AV abnormalities are found in 15% to 30% of infants with neonatal lupus, dermatologic findings are more common, and occur in 90% of such infants. Cutaneous lesions appear as nonscarring erythematous annular plaques located on the scalp or periorbital region. These plaques typically appear within the first 2 months after birth and resolve within 4 to 6 months, corresponding with the disappearance of maternal antibodies from the neonatal circulation. When infants display these skin manifestations, management includes sun avoidance, sunscreen, and low-potency corticosteroids. Dermatologic lesions and cardiac abnormalities are seen simultaneously in about 10% of infants with neonatal lupus. Transient hepatitis, thrombocytopenia, hemolytic anemia, and neutropenia also can be present in infants with neonatal lupus. For infants without cardiac manifestations, overall prognosis is good. Approximately 10% of infants with neonatal lupus may develop a systemic rheumatic and/or autoimmune disease later in life.

References:

Breur JM, Visser GH, Kruize AA, Stoutenbeek P, Meijboom EJ. Treatment of fetal heart block with maternal steroid therapy. *Ultrasound Obstet Gynecol*. 2004;24:467-472

Buyon JP, Clancy RM. Neonatal lupus syndromes. *Curr Opin Rheum.* 2003;14:535-541

Costedoat-Chalumeau N, Amoura Z, Villain E, Cohen L, Piette J-C. Anti-SSA/Ro antibodies and the heart: more than complete congenital heart block? a review of electrocardiographic and myocardial abnormalities and of treatment options. *Arthritis Res Ther*. 2005;7:69-73

Jaeggi ET, Nii M. Fetal brady- and tachyarrhythmias: new and accepted diagnostic and treatment methods. *Semin Fetal Neonatal Med*. 2005;10:504-514

Jayaprasad N, Johnson F, Venugopal K. Congenital complete heart block and maternal

connective tissue disease. *Int J Cardiol.* 2006;20:153-158

Kleinman CS, Nehgme RA. Cardiac arrhythmias in the human fetus. *Pediatr Cardiol*. 2004; 25:234-251

McKinlay JR, Cooke LM, Cunningham BB, Gibbs NF. Neonatal lupus erythematosus. *J Am Board Fam Pract*. 2001;14:68-70

Wahren-Herlenius M, Sonesson SE. Specificity and effector mechanisms of autoantibodies in congenital heart block. *Curr Opin Immunol*. 2006:18:690-696

American Board of Pediatrics Content Specification(s):

Identify the effects of maternal immunologic disease with transplacental passage of immunoglobulins and its treatment on the fetus

Know how to diagnose and manage neonatal lupus erythematosus

Recognize the cardiac manifestations of maternal diseases and of common perinatal syndromes in the newborn infant

Understand the pathophysiologic consequences and plan appropriate management of a dysrhythmia in a fetus, including management of electrophysiologic disturbances

Know the effects on the fetus of maternal connective tissue disorders and their treatment

Understand the potential adverse effects of approaches used in the management of fetal arrhythmias

Understand the pathophysiology, natural history, and clinical features of conduction pathway abnormalities and other dysrhythmias

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11 November 07

12 December 07

December: Question 1

A newborn male infant presents with central cyanosis that is unresponsive to oxygen therapy in the delivery room. He was born via scheduled cesarean section at 40 weeks' gestation to a gravida 3, para 2 mother with an uncomplicated prenatal history. On admission to the neonatal intensive care unit, his postductal oxygen saturation is 72% in 100% oxygen delivered via oxyhood. He demonstrates no respiratory distress, no cardiac murmur is heard, and his chest radiograph appears normal. With a diagnostic consideration of persistent pulmonary hypertension of the newborn, treatment with inhaled nitric oxide is proposed. The possibility of congenital heart disease comes up.

Of the following, what is the congenital heart disease MOST likely to be worsened by initiation of inhaled nitric oxide?

1	Hypoplastic left heart syndrome
2 ✗	Tetralogy of Fallot
3	Transposition of the great arteries
4	Tricuspid atresia
5	Truncus arteriosus

You selected 2, the correct answer is 1.

The use of inhaled nitric oxide (iNO) is contraindicated in congenital heart disease that is dependent on right-to-left shunting across the ductus arteriosus (eg, critical aortic stenosis, interrupted aortic arch, and hypoplastic left heart syndrome). In addition, iNO may worsen pulmonary edema in infants who have obstructed total anomalous pulmonary venous return because of the fixed venous obstruction. Before beginning iNO, echocardiography can obtain the combined benefits of defining the cardiac anatomy and documenting pulmonary hypertension.

Hypoplastic left heart syndrome (HLHS) consists of a number of conditions involving underdevelopment of the left side of the heart, most commonly, aortic atresia, severe mitral stenosis, and marked hypoplasia of the left ventricle. Right-to-left shunting via the ductus arteriosus provides retrograde perfusion of the ascending and transverse portions of the aorta so that the subclavian, carotid, and coronary arteries are supplied. Generally, HLHS presents after the patent ductus arteriosus (PDA) closes sometime during the first week after birth.

If the atrial septal defect is highly restrictive or if total pulmonary resistance is high and pulmonary blood flow is diminished, HLHS can present at birth with severe hypoxemia (Figure. NOTE: If you have a problem playing the file, you may need to update your QuickTime

software [go to http://www.apple.com/quicktime/download/, and click on "Free Download."]) As is possible in the child in this vignette, iNO would decrease pulmonary vascular resistance, facilitate flow to the lungs, and result in decrease in blood flow to the systemic circulation.

The following conditions do not present with dependency on pulmonary artery–to-aorta shunting across the ductus arteriosus. Thus iNO therapy will not worsen the infant's clinical condition.

Tetralogy of Fallot comprises a tetrad of defects, including an overriding aorta, right ventricular hypertrophy, subpulmonary stenosis, and malalignment of the ventricular septal defect (VSD). The clinical presentation depends on the degree of pulmonary stenosis. More severe stenosis leads to greater reduction of pulmonary blood flow and increased cyanosis.

Transposition of the great arteries (TGA) involves placement of the great vessels across the plane of the interventricular septum so that the aorta arises from the right ventricle and the pulmonary artery from the left ventricle. The most common form of TGA is the dextro type, in which the origin of the aorta is anterior and to the right of the origin of the pulmonary artery. This creates two parallel circulations, with systemic venous blood returning to the right atrium being sent to the systemic circulation via the right ventricle, and pulmonary venous blood returning to the left atrium being pumped via the left ventricle back to the pulmonary circulation. Oxygen saturation is typically lower in the right hand (preductal) than in the lower body (postductal). The affected infant's survival depends on mixing of these circulations at the atrial level via a patent foramen ovale, at the ventricular level (approximately one-third of patients also have a VSD), or by connection of the great vessels through a PDA.

In tricuspid atresia, there is no communication between the right atrium and right ventricle. Numerous anatomic variations involve the presence or absence of a VSD, pulmonary stenosis, or TGA. However, the common physiologic consequence is a total and obligatory right-to-left atrial shunt.

Truncus arteriosus is a condition in which a single great vessel arises from the heart and the aorta, and pulmonary and coronary arteries originate from the ascending portion of the vessel. There is always an associated VSD. The various subtypes of truncus arteriosus relate to the branching pattern of the pulmonary arteries. Hypoxemia results because the aorta contains combined output from the left and right ventricles, but may be mild if pulmonary vascular resistance is low and pulmonary blood is excessive. In that case, cyanosis may not be visible.

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References:

Angus DC, Linde-Swirble WT, Clermont G, Griffin MF, Clark RH. Epidemiology of neonatal respiratory failure in the United States. *Am J Resp Crit Care Med.* 2001;164:1154-1160

Artman M, Mahony L, Teitel DF. *Neonatal Cardiology.* New York, NY: McGraw-Hill; 2002:73-100

Roberts JD Jr, Fineman JR, Morin FC 3rd, et al. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure: the Neonatal Inhaled Nitric Oxide Study Group. *N Engl J Med.* 1997;336:597-604

Steinhorn RH. Pulmonary hypertension, persistent-newborn. emedicine.com Web site. Accessed May 1, 2007, at: www.emedicine.com/ped/topic2530.htm

Steinhorn RH, Farrow KN. Pulmonary hypertension in the neonate. *NeoReviews*. 2007;8(1):e14

American Board of Pediatrics Content Specification(s):
Recognize the clinical features of a cyanotic neonate

Formulate a differential diagnosis of a cyanotic neonate

Plan appropriate management for a cyanotic neonate and understand the potential adverse effects of specific therapeutic approaches used

Understand the pathophysiology (including genetics) of a neonate with a left-to-right shunt lesion

Plan appropriate management for a neonate with a left-sided cardiac obstructive lesion and understand the potential adverse effects of specific therapeutic approaches used

Recognize the clinical features of persistent pulmonary hypertension

Recognize the laboratory, radiographic, and pathologic features of persistent pulmonary hypertension

Know the management of persistent pulmonary hypertension

Understand the risks of administration of inhaled nitric oxide

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January: Question 2

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11 November 08

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A male infant was delivered at 39 weeks' gestation by a 27-year-old primigravida after an uneventful pregnancy. His Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. The infant stayed in the regular nursery for 5 additional days because of poor feeding.

At 5 months of age, the infant is referred to your clinic because of a heart murmur and trouble gaining weight, associated with colic and reflux symptoms. The infant weighs 5.8 kg (5th percentile) and has an occipitofrontal circumference of 41.5 cm (10th percentile). He is receiving thickened feedings and omeprazole treatment. The infant has facial features dissimilar to those of his parents (Figure).

Figure

Cardiovascular examination shows a pulse rate of 120 beats per minute; respiratory rate of 36 breaths per minute; and blood pressures of 85/55 and 82/50 mm Hg in the right and left arms, respectively. A loud, harsh systolic crescendo-decrescendo murmur is heard best at the base of the heart with radiation to the neck and apex. No ejection click is present. A second soft blowing systolic murmur heard best in the axilla radiates to the back. No diastolic murmur is heard. Oxygen saturation in room air is 98%. The primary echocardiographic finding is shown in the video (NOTE: If you have a problem playing the file, you may need to update your QuickTime software. Go to http://www.apple.com/quicktime/download/, and click on "Free Download.").

Of the following, the laboratory test MOST likely to aid in the diagnosis of this infant's syndrome is:

1	fluorescence in situ hybridization (FISH) probe for 7q11 deletion

2	FISH probe for 20p12 deletion
3	FISH probe for 22q11 deletion
4	routine chromosome analysis
5	sequencing of the *PTPN11* gene

You selected 1, the correct answer is 1.

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The infant in this vignette has echocardiographic evidence of supravalvular aortic stenosis and clinical features of Williams syndrome. Such infants should undergo fluorescence in situ hybridization (FISH) study to detect a microdeletion at the 7q11 region.

Specific congenital heart defects are often associated with genetic syndromes (Table). The combination of minor or major anomalies with cardiac malformations often can suggest underlying conditions for which specific confirmatory tests exist.

Table

Table. Some Genetic Syndromes Associated With Specific Cardiac Malformations*

Cardiac Malformation	Most Specific Associated Genetic Syndrome	Test	Other Conditions That Can Have Same Cardiac Malformation
Atrial septal defect	Holt-Oram	Research only (*TBX5* gene mutations)	Turner syndrome; trisomy 21
	Kabuki	None	Noonan syndrome
Atrioventricular canal	Trisomy 21 (Down)	Routine chromosome study	Situs ambiguous 22q11 deletion
Coarctation of the aorta	Turner	Routine chromosome study	Kabuki syndrome
Conotruncal defects; interrupted aortic arch; truncus arteriosus; tetralogy of Fallot; perimembranous ventricular septal defect	22q11 deletion (DiGeorge/velocardiofacial syndromes)	Fluorescence in situ hybridization (FISH) to detect microdeletion of the 22q11 region	
	Dextrocardia and situs inversus (Kartagener)	Ciliary biopsy	
	Situs ambiguous	Research	
Hypoplastic left heart	Turner	Routine chromosome study	
	Jacobsen (11q-)	Routine chromosome study	
Peripheral pulmonary artery stenosis	Alagille	FISH (clinical) to detect microdeletion of the 20p12 region	Williams syndrome, Turner syndrome
		JAG1 gene mutation analysis (research)	
	Noonan	Sequence *PTPN11* gene	
Supravalvular aortic stenosis	Williams	FISH with 7q11 region probe	
Ventricular septal defect	Trisomy 21	Routine chromosome study	Kabuki syndrome, Holt-Oram syndrome
	22q11 deletion	FISH with 22q11 region probe	Trisomy 13; trisomy 18

*** Adapted from Beck and Hudgins (2003).**

Aortic stenosis occurs in 1 in 3,000 newborn infants, and may be subvalvular, valvar, or supravalvular. In the supravalvular form of this condition, as demonstrated in the echocardiogram from the infant in this vignette, a fibromembranous narrowing (arrows in video) is seen above the aortic valve. The aortic obstruction can lead to left ventricular hypertophy or aortic insufficiency.

Fluorescence in situ hybridization involves the use of a unique DNA sequence to "probe" for the complementary sequence in patients' chromosomes. The gene-specific DNA probe is labeled with a fluorochrome tag that can be visualized with a fluorescence microscope. During FISH, double-stranded DNA, as present in metaphase chromosomes or interphase nuclei on a cytogenetic slide, is denatured into a single-strand of DNA. The DNA bound to the slide is then renatured in the presence of excess copies of a single-stranded fluorochrome-labeled DNA base pair probe. The probe anneals or "hybridizes" to the site of the complementary DNA sequence on the chromosome. The probe signal can then be imaged on the chromosome or nucleus using a fluorescent microscope. The advantages of a FISH probe include the ability to rapidly analyze a large number of cells with high sensitivity and specificity and to analyze uncultured nondividing cells. However, FISH probes require knowledge of the loci involved in a disorder and the appropriate probes that will detect the aberration. This technique is generally used either to complement classic chromosome methods or as a substitute for the identification of chromosomes that are in metaphase or interphase, and should not be used as a screening tool.

Microdeletions such as seen in Williams syndrome were previously unknown because the chromosomal deletions and rearrangements were usually not visible on routine chromosome preparations. These syndromes are usually characterized by specific minor anomalies and major malformations. At times it is difficult to examine newborns for these minor anomalies because of the presence of edema, dressings, and extraneous instrumentation. FISH has facilitated the diagnosis of these syndromes in the absence of all of the usual diagnostic findings.

Williams syndrome occurs in about 1 in 20,000 births. It is a multisystem disorder that includes a characteristic facies described as "elfin," cardiovascular defects, and specific neurobehavioral traits. Neonates with Williams syndrome can have mild microcephaly and facial features that include medial eyebrow flare, a depressed nasal bridge, periorbital fullness, blue stellate irises, short palpebral fissures, short anteverted nares, a long philtrum, and a large mouth with a prominent lower lip. The cardiovascular disease results from an elastin arteriopathy that may affect any artery. The most common cardiac defect is supravalvular aortic stenosis occurring in 35% to 73% of cases. Other defects may include peripheral pulmonary stenosis, pulmonic valvular stenosis, atrial septal defect, and ventricular septal defect. The infant in the vignette had both supravalvular stenosis and peripheral pulmonary stenosis. Early onset of hypertension, likely caused by renal artery stenosis, is evident in 40% of patients with Williams syndrome by the age of 34 years. Neurobehavioral characteristics of patients with Williams syndrome include mild to moderate retardation but an overfriendly and outgoing personality often can mask mental deficiency.

Connective tissue abnormalities are common in infants with Williams syndrome who are usually hypotonic and have hyperextensible joints. Motor milestones are delayed, but infants usually begin walking by age 24 months. Many patients with Williams syndrome have feeding difficulties, including recurrent vomiting, gastroesophogeal reflux, colic, and diarrhea, which may hinder weight gain during the first year after birth. Approximately 10% of neonates with Williams syndrome have hypercalcemia, the cause of which is unknown.

Williams syndrome is one of the contiguous gene syndromes in which haploinsufficiency of multiple genes at the 7q11.23 locus contributes to the phenotypic features. At least 19 genes, apart from *ELN*, are included in the commonly deleted region. Hemizygosity at the elastin locus (*ELN*) on chromosome 7 occurs in 95% of patients with Williams syndrome. The *ELN* gene deletion results in the loss of elastin function and is likely responsible for the cardiovascular aspects of the disorder. Recent evidence suggests that elastin not only functions as a structural protein, but also acts as a signaling molecule and regulates the proliferation of smooth muscle

cells. The reduced deposition of elastin in arterial walls of patients with Williams syndrome and supravalvular aortic stenosis leads to increased proliferation of vascular smooth muscle cells and narrowing of the vessel lumen. The *LIMK1* gene, which lies telomeric to the *ELN* gene, has been implicated in the cognitive deficit of this syndrome because it is deleted in all patients with Williams syndrome.

In addition to its association with Williams syndrome, peripheral pulmonic stenosis can be seen in patients having Alagille syndrome, Noonan syndrome, or Turner syndrome. Alagille syndrome is an autosomal dominant disease with clinical variability, characterized by a paucity of intrahepatic bile ducts resulting in cholestatic jaundice. Infants with Alagille syndrome also have characteristic facial features including a broad forehead and a pointed triangular chin. Additional findings include vertebral anomalies (butterfly vertebrae); posterior embryotoxon; and retarded mental, physical, and sexual development. A mutation in the *JAG1* gene, located at chromosome 20p12, has been identified in approximately 70% of patients with Alagille syndrome. FISH testing to detect a 20p12 microdeletion is available, but is positive in only 7% of patients with Alagille syndrome. Supravalvular aortic stenosis has not been reported in patients with Alagille syndrome.

Velocardiofacial syndrome has an extremely variable phenotype. Physical characteristics may include a cleft palate, a prominent nose with a squared nasal root, minor auricular anomalies, narrow palpebral fissures with "hooded eyelids," a long face, retruded mandible with chin deficiency, long slender fingers, and conotruncal cardiac defects. The most common cardiac defects include interrupted aortic arch, perimembranous ventricular septal defect, truncus arteriosus, and tetralogy of Fallot. The thymus and or parathyroid glands may be hypoplastic or absent resulting in specific T-cell immunodeficiency and/or hypocalcemia. Neurobehavioral characteristics include learning disabilities and mild mental retardation. A microdeletion in the 22q11 region is responsible for velocardiofacial syndrome. A deletion in this region is also seen in patients with DiGeorge syndrome.

Noonan syndrome is an autosomal dominant disorder occurring in 1 in 2,500 newborns. Noonan syndrome should be considered in infants with a normal 46,XY or 46,XX karyotype who demonstrate a "Turner syndrome–like" phenotype, characterized by specific facial features that may include epicanthal folds, ptosis of the eyelids, low nasal bridge, downward slanting palpebral fissures, and low-set and/or abnormal auricles. The neck is short and often webbed and the posterior hairline is low. Infants with this condition have a broad shield-shaped chest. Congenital heart disease associated with Noonan syndrome most commonly involves pulmonic stenosis with valve dysplasia and hypertrophic cardiomyopathy. Additional cardiac defects may include septal defects, patent ductus arteriosus, and peripheral pulmonary stenosis.

Approximately 50% of patients with Noonan syndrome have a mutation in *PTPN11*, a gene that encodes for a nonreceptor-type protein tyrosine phosphatase SHP2. Mutations of *PTPN11* in animals cause abnormal semilunar valve development. The *PTPN11* gene is also involved in signaling pathways leading to cardiomyocyte hypertrophy.

References:

Amenta S, Sofocleous C, Kolialexi A, et al. Clinical manifestations and molecular investigation of 50 patients with Williams syndrome in the Greek population. *Pediatr Res.* 2005;57:789-795

Beck AE, Hudgins L. Congenital cardiac malformations in the neonate: isolated or syndromic? *NeoReviews*. 2003;4(4):e105-113

Jones KL. Chromosomal abnormality syndromes. In: KL Jones, ed. *Smith's Recognizable Patterns of Human Malformation.* 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006

Jones KL. Moderate short stature, facial, +/- genital. In: KL Jones, ed. *Smith's Recognizable Patterns of Human Malformation.* 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006

Jones KL. Facial-limb defects as major feature. In: KL Jones, ed. *Smith's Recognizable Patterns of Human Malformation.* 6th ed. Philadelphia, Pa: Elsevier Saunders; 2006

Lin RJ, Cherry AM, Bangs CD. FISHing for answers: the use of molecular cytogenetic techniques in neonatology. *NeoReviews* 2003;4(4):e94-98

Maschoff K. Elucidating the genetic cause of congenital heart defects. *NeoReviews* 2004;(5)7:e283-288

Wong RJ, DeSandre GH, Sibley E, Stevenson DK. Neonatal jaundice and liver disease. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine, Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier, 2006:1419-1465

Zahka KG. The cardivascular system: causes and association. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine, Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier, 2006:1202-1210

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology, including genetics, of a neonate with a left-sided cardiac obstructive lesion

Be aware of the maternal factors, incidence, and clinical manifestations of Down syndrome

Recognize the karyotype and clinical manifestations associated with the microdeletion syndromes

Recognize the karyotype and clinical manifestations associated with the contiguous gene disorders

Recognize the clinical features of the Noonan syndrome

Recognize the clinical features of the Williams syndrome

Understand the indications and limitations of molecular cytogenetic studies (eg, FISH), specifically in the diagnosis of aneuploidy and microdeletion syndromes

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February: Question 2

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11 November 08

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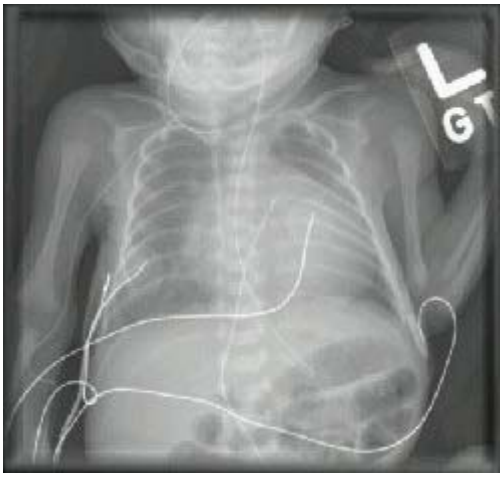
You are providing care to a 12-day-old infant with an estimated gestational age of 30 weeks who has intrauterine growth restriction. He was born by emergency cesarean section for fetal distress. He has been receiving total parenteral nutrition through an umbilical venous catheter and tolerating trophic feeds; his glucose infusion rate is 5 mg/kg per minute and his blood glucose concentration has been normal. You opt to place a peripherally inserted central catheter (PICC) line in anticipation of prolonged parenteral nutrition. A radiograph was obtained to evaluate the PICC line position after insertion (Figure).

Figure



The child subsequently has a precipitous drop in heart rate, develops cyanosis, and appears ashen. Peripheral artery pulses are absent. You immediately place an endotracheal tube (tip palpated in suprasternal notch) and begin conventional ventilation with 100% oxygen (equal breath sounds), but the heart rate drops further. Heart tones are muffled and the voltage on the cardiac monitor is low.

Of the following, the NEXT stage of management of the infant in this vignette should be:

1	fluid bolus through the umbilical line
2	high-frequency ventilation
3	pericardiocentesis
4	repeat chest radiograph
5	thoracocentesis

You selected 3, the correct answer is 3.

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The radiograph demonstrates a peripherally inserted central catheter (PICC) line beginning in the right upper extremity. The umbilical venous catheter (UVC) is also in a position that warrants concern; it projects into the left side of the cardiac shadow. The cardiac silhouette is enlarged, consistent with pericardial effusion, an uncommon but life-threatening complication of catheter insertion. Tamponade from pericardial effusion has been reported in 1% to 3% of neonates with umbilical venous catheters, with mortality rates ranging from 30% to 50%. Pericardial effusion should be considered in any neonate experiencing an acute deterioration with a central venous catheter in place because it represents an emergency situation that can be fatal unless there is a high index of suspicion and rapid diagnosis and intervention.

Most complications of PICC and other central lines are related to suboptimal positioning, hence confirmation of position is important. The recommended position for the tip of a UVC is the junction of the inferior vena cava and right atrium.

The clinical presentation of a line-related pericardial effusion is variable and can present any time after start of infusion. Possible mechanisms of injury include lodging of the tip against the beating heart, direct puncture by catheter tip, or endothelial osmotic damage and subsequent transmural necrosis caused by the hyperosmolar infusates. Correct position of the UVC may not guarantee uneventful catheterization. The most important aspect of the treatment of cardiac tamponade related to central lines is early recognition.

If suspected, infusion through the line should be stopped. Radiography or echocardiography should be performed immediately, and an attempt should be made to aspirate fluid from the catheter. If the response to conventional resuscitative procedures is inadequate, as in the infant in this vignette, diagnostic and therapeutic pericardiocentesis should be considered. Waiting for imaging in this situation is inappropriate.

In the presence of muffled heart tones, cardiomegaly on radiography, and precipitous deterioration, hypovolemia is unlikely. The risk of direct infusion of fluid into the pericardial space, however, is real, making the administration of a fluid bolus inappropriate.

The child's relative respiratory stability before this event suggests an extrapulmonary problem—temporizing by using another form of assisted ventilation such as high-frequency ventilation would delay life-saving treatment.

Repeating chest radiography is unlikely to give additional information helpful to this crisis. The radiograph presented demonstrates an abnormality that requires immediate attention. Any further delay would be dangerous.

Pneumothorax may also result in acute deterioration, but in this vignette the infant was not receiving continuous distending airway pressure or ventilation before the event. His breath sounds were equal and the endotracheal tube position was high in the trachea. This combination makes pneumothorax less likely and thoracocentesis or chest tube placement would likely not be helpful.

References:

Alkhotani A, Khashu M, Osiovich H. *NeoReviews.* 2003;4(7):e194

Beardsall K, White DK, Pinto EM, Kelsall AW. Pericardial effusion and cardiac tamponade as complications of neonatal long lines: are they really a problem? *Arch Dis Child Fetal Neonatal Ed.* 2003;88:F292-F295

Cartwright DW. Central venous lines in neonates: a study of 2186 catheters. *Arch Dis Child Fetal Neonatal Ed.* 2004;89:F504-F508

Nadroo AM, Lin J, Green RS, Magid MS, Holzman IR. Death as a complication of peripherally inserted central catheters in neonates. *J Pediatr.* 2001;138:599-601

Nowlen TT, Rosenthal GL, Johnson GL, Tom DJ, Vargo TA. Pericardial effusion and tamponade in infants with central catheters. *Pediatrics.* 2002;110(1):137-142

Onal EE, Saygili A, Koc E, Türkyilmaz C, Okumus N, Atalay Y. Cardiac tamponade in a newborn because of umbilical venous catheterization: is correct position safe? *Pediatr Anaesth.* 2004;14:953-956

Paster S, Middleton P. Roentgenographic evaluation of umbilical artery and vein catheters. *JAMA.* 1975;231:742-746

American Board of Pediatrics Content Specification(s):

Understand the indications for and management of intravascular fluid volume replacement

Understand the indications and contraindications of drugs used for neonatal resuscitation

Understand the pathophysiology of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Recognize the clinical features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Recognize the laboratory and radiographic features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Formulate a differential diagnosis of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Understand the total management plan and associated potential complications of such management for an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

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11 November 08

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March: Question 10

A full-term male infant is born to a mother with chorioamnionitis. Because of severe respiratory distress and persistent cyanosis, the infant is intubated and placed on high ventilatory support. He appears mottled and is hypotensive. His blood pressure improves after he receives two normal saline boluses and a dopamine drip at a rate of 20 µg/kg per minute. A few hours later, he again becomes hypotensive and echocardiography is performed. The study reveals a structurally normal heart, normal right ventricular function, hyperdynamic left ventricular function, and a high cardiac index.

Of the following, the MOST effective medication to treat this infant's hypotension is:

1	digitalis
2	dobutamine
3	epinephrine
4	isoproterenol
5	milrinone

You selected 3, the correct answer is 3.

Infants with symptomatic hypotension may have cardiogenic, hypovolemic, or distributive shock. *Cardiogenic* shock occurs when inadequate tissue perfusion is attributable to cardiac dysfunction manifested by impaired contractility, ventricular emptying, and cardiac filling. *Hypovolemic* shock is a common type of shock in the neonate and occurs when an infant's blood volume is below a critical threshold; this leads to decreased ventricular filling and reduced stroke volume. Cardiac output will wane unless the heart rate and/or stroke volume increase. *Distributive* shock is the result of an inadequate relative intravascular volume because of severe vasodilation.

In this vignette, the infant's hypotension is most likely because of either hypovolemic shock with sepsis-induced capillary leakage and third spacing or distributive shock with sepsis-induced vasodilation. This infant's blood pressure would most likely improve with volume resuscitation and/or another vasoconstrictor, such as epinephrine. Increasing the infant's inotropic ability would have little additional benefit, because the infant's echocardiogram showed appropriate cardiac function. Medications that lower systemic vascular resistance might further exacerbate the infant's hypotension.

Cardiac pharmacologic agents are classified by their sympathetic receptor activity (Table).

Table

Table. Adrenergic Receptors*		
Receptor	**Action Site**	**Major Cardiac Effect**
Alpha-1	Arterial and venous smooth muscle Cardiac myocytes	Vascular smooth muscle contraction Positive inotropy
Alpha-2	Sympathetic nerves (pre- and postsynaptic) Central nervous system	Vascular smooth muscle relaxation
Beta-1	Cardiac myocytes Conduction cells (e.g., Purkinje fibers, sinoatrial and AV nodes)	Positive inotropy Positive chronotropy Conduction velocity induction
Beta-2	Peripheral vascular smooth muscle (both arterial and venous) Bronchial smooth muscle cells	Vascular smooth muscle relaxation

* Adapted from Brodsky and Martin (2003).

Epinephrine has a dose-dependent effect on both beta- and alpha-adrenergic receptors. Lower doses of epinephrine induce beta-receptor activity and lead to increased inotropic and chronotropic effects, which result in increased cardiac output with decreased systemic vascular resistance and variable effects on the mean arterial blood pressure. Higher doses bind alpha-adrenergic receptors, inducing vasoconstriction in addition to increasing cardiac output. The increased afterload is associated with enhanced diastolic pressure, creating an additional benefit of improving coronary artery perfusion.

Digitalis, an extract of the foxglove plant, generates a positive inotropic effect by inhibiting the Na+/K+ ATPase pump in cardiac myocytes, indirectly increasing the intracellular calcium concentration. Digitalis has a negative chronotropic effect because it decreases atrioventricular nodal conduction velocity and enhances the refractory period, reducing the transmission of atrial impulses to the ventricles. Additional chronotropic suppression occurs because digitalis increases vagal tone.

Dobutamine is a synthetic catecholamine with potent direct beta-1 and some beta-2 adrenergic action. These adrenergic effects lead to a mild increase in chronotropism, enhanced inotropism with an increase in stroke volume, and peripheral vasodilation. This latter effect is probably secondary to production of the metabolite 3-*O*-methyldobutamine, which is a potent inhibitor of alpha-adrenoreceptors. Dobutamine is an effective medication for cardiogenic shock or myocardial dysfunction because it does not increase afterload. However, it may decrease coronary perfusion because of this decrease in systemic vascular resistance.

Despite having a similar name to dobutamine, the endogenous catecholamine dopamine acts differently than dobutamine. Dopamine has a dose-dependent action, leading to renal vasodilation by dopaminergic receptor activation; enhanced inotropy and chronotropy by stimulating beta-1 adrenergic receptors; and increased systemic vascular resistance by alpha-1 action at low, medium, and high doses, respectively. As a precursor of norepinephrine, dopamine leads to increased release of endogenous norepinephrine and thus, with prolonged use, it is less effective, correlating with lower norepinephrine stores.

Isoproterenol is a synthetic catecholamine with nonspecific beta-agonist activity and minimal alpha-adrenergic effects. It has a positive inotropic effect, leads to significant chronotropic action, and decreases systemic vascular resistance. Isoproterenol use is limited by its potent increase in heart rate, which precedes its inotropic effect, and also its potential decrease in coronary blood flow because of cardiac muscle vasodilation.

Milrinone is a non–receptor-mediated agent, acting by selective inhibition of phosphodiesterase type III, which results in cyclic adenosine monophosphate (cAMP) accumulation in the myocardium. cAMP increases the force of myocardial contraction as well as the rate and extent of myocardial relaxation. It is an excellent inotropic medication that can be used long term without the development of tolerance because its action is receptor-independent. cAMP-induced relaxation of the vascular smooth muscle cells also leads to vasodilation. Milrinone can reduce the afterload of both the left and right ventricles.

The actions of the aforementioned cardiotropic agents are based on data from older children and adult studies. It is possible that neonates have a different response to these medications because of variations in receptor number and myocyte function. Premature infants also may have unique

responses compared with full-term infants. In addition to needing age-based comparison studies, further research is warranted to determine whether treatment of systemic hypotension using any agent in premature infants is effective at increasing cerebral perfusion and/or decreasing cerebral injury.

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References:

Brodsky D, Martin C. Cardiology. In: *Neonatology Review*. Philadelphia, Pa: Hanley & Belfus; 2003:85-121

Engle WD, LeFlore JL. Hypotension in the neonate. NeoReviews.org Web site. Accessed July 15, 2007, at: http://www.neoreviews.org/ (subscription required)

Gooneratne N, Manaker S. Use of vasopressors and inotropes. UpToDate Web site. Accessed July 11, 2007, at: http://www.uptodate.com (subscription required)

Sladen RN. Pharmacology of shock: an update. *Can J Anesth.* 2002;49:R1-R5

American Board of Pediatrics Content Specification(s):

Recognize the therapeutic indications for and toxicity of digoxin in treating cardiovascular disease

Recognize the therapeutic indications for and toxicity of inotropic agents in treating cardiovascular disease

Recognize the therapeutic indications for and toxicity of vascular afterload-reducing agents

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11 November 08

12 December 08

March: Question 2

A 4-week-old infant born at 28-weeks' gestation has mild chronic lung disease following respiratory distress syndrome. His umbilical artery catheter was removed at 4 days of age. He has been receiving oral diuretic therapy and low flow nasal cannula oxygen. He has not emptied his stomach after his last three feedings, is irritable, and has had several episodes of opisthotonic posturing. His respiratory rate is 90 breaths per minute and his heart rate is 170 beats per minute. Right arm and left leg blood pressures are 115/85 and 120/88 mm Hg, respectively. Systolic blood pressure has been more than 100 mm Hg for the past 24 hours. Extremities are mottled. Brachial and femoral pulses are equal but weak. A gallop rhythm is heard at the apex. His liver edge is palpable 2 cm below the right costal margin. A chest radiograph shows cardiomegaly and increased interstitial markings. Echocardiography reveals left ventricular hypertrophy with poor myocardial contractility.

Of the following, the MOST appropriate immediate response to the hypertension in this neonate is to:

1	administer an intravenous dose of enalaprilate
2	administer an oral dose of captopril
3	administer an oral dose of furosemide
4	begin a continuous infusion of esmolol
5	begin a continuous infusion of nitroprusside

You selected 5, the correct answer is 5.

Hypertension occurs in approximately 2% of preterm and term neonates admitted to neonatal intensive care units. Determination of the true incidence is hampered by inconsistencies in definitions, variations in measurement techniques, and normal changes with gestational age and weight. Infants with blood pressures consistently greater than two standard deviations for age and gender are defined as having significant hypertension. The neonate in this vignette has a systolic blood pressure (115 mm Hg) well above the 95th percentile for age (Figures 1 and 2).

Figure 1: Systolic blood pressure by postmenstrual age (adapted from Zubrow and colleagues [1995])

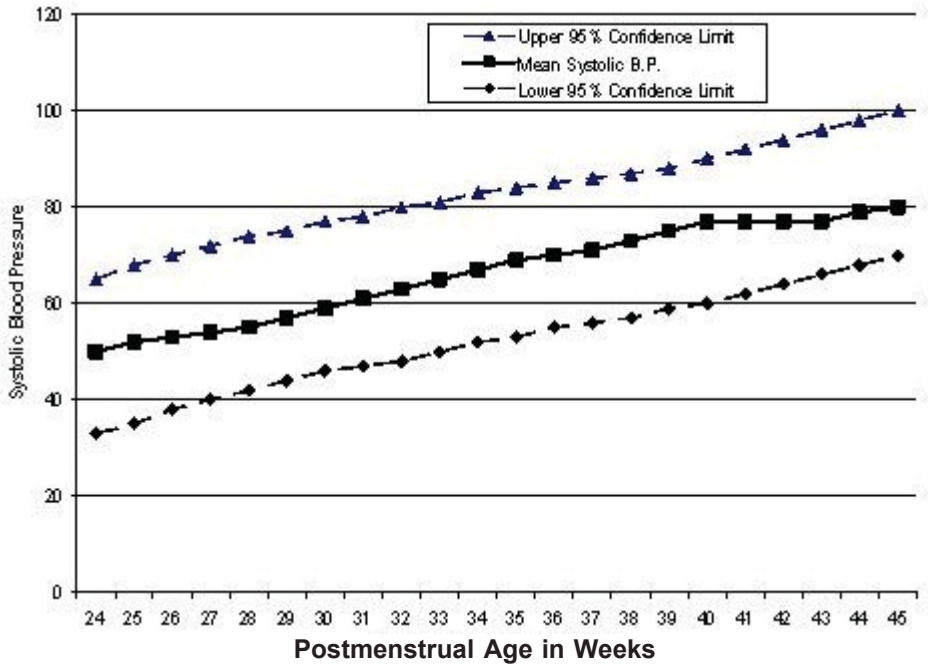
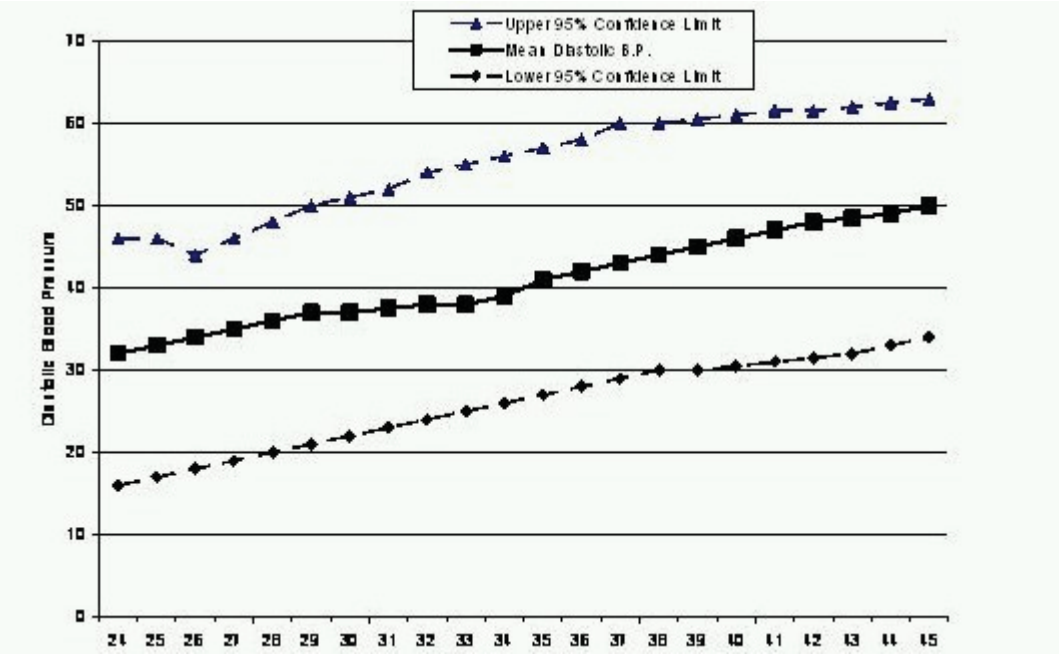


Figure 2: Diastolic blood pressure by postmenstrual age (adapted from Zubrow et al [1995])



Hypertension in the neonate may result from a wide variety of underlying causes (Table 1).

Table 1

Table 1. Common Causes of Hypertension in Neonates*
Causes
Renovascular†
Thromboembolism
Renal artery stenosis
Renal venous thrombosis
Compression of renal artery
Cardiac†
Coarctation of the aorta
Pulmonary†
Bronchopulmonary dysplasia
Renal Disease†
Congenital
Polycystic kidney disease
Multicystic-dysplastic kidney disease
Ureteropelvic junction obstruction
Acquired
Acute tubular necrosis
Hemolytic-uremic syndrome
Obstruction by tumor
Endocrine
Congenital adrenal hyperplasia
Pseudohypoaldosteronism type II
Medications/Intoxications
Maternal
Opioids (cocaine, heroin)
Infant
Dexamethasone
Theophylline
Caffeine
Pancuronium
Phenylephrine
Neoplasms
Wilms tumor
Mesoblastic nephroma
Neuroblastoma
Neurologic
Pain
Intracranial hypertension
Seizures
Miscellaneous
Closure of abdominal wall defect
Adrenal hemorrhage
Hypercalcemia
Extracorporeal membrane oxygenation
Birth asphyxia

* Adapted from Ettinger and Flynn (2002).
† These categories account for most of the cases.

Renovascular hypertension is the most frequent cause of hypertension among premature neonates, accounting for up to 89% of all cases. The most common cause of renovascular hypertension is secondary to umbilical artery catheterization. Hypertension following umbilical catheterization appears with equal frequency among neonates with high or low umbilical catheters. Thrombi have been demonstrated on 25% to 81% of umbilical catheters. An association between the presence of local thrombi and the development of hypertension has been established in at least one trial. Clot fragmentation from thrombi has been documented, suggesting that embolization to the kidneys could cause areas of renal infarction and result in hyperreninemia and hypertension.

The presentation of hypertension in neonates can be quite variable. Nonspecific symptoms

such as poor feeding, irritability, and lethargy are common. In neonates with severe hypertension, significant cardiopulmonary symptoms may develop, including tachypnea, impaired perfusion, congestive heart failure, and hepatosplenomegaly. Hypertensive encephalopathy, presenting with tremors, opisthotonic posturing, hemiparesis, seizures, and coma, may also occur.

A wide variety of oral and intravenous antihypertensive agents may be considered for neonatal hypertension (Table 2).

Table 2

Table 2. Antihypertensive Medications for Neonates*

Drug	Dose	Interval	Action
Intravenous			
Enalaprilate	10-20 µg/kg/dose	Q 8-24 h	Angiotensin-converting enzyme inhibitor
Esmolol	100-300 µg/kg/min	IV infusion	Beta blocker
Hydralazine	0.1-0.4 mg/kg/dose	Q 4-6 h	Vasodilator
Labetalol	0.25-3.0 mg/kg/h	IV infusion	Alpha and beta blockers
Sodium nitroprusside	0.5-8.0 µg/kg/min	IV infusion	Vasodilator
Nicardipine	1-3 mcg/kg/min	IV infusion	Calcium channel blocker
Oral			
Amlodipine	0.1-0.3 mg/kg/dose	Q 12-24 h	Calcium channel blocker
Captopril	0.01-0.5 mg/kg/dose	Q 6-12 h	Angiotensin-converting enzyme inhibitor
Chlorothiazide	5-15 mg/kg/dose	Q 12 h	Distal tubule diuretic
Furosemide	1-6 mg/kg/dose	Q 8-24 h	Loop diuretic
Labetalol	1 mg/kg/dose	Q 8-12	Alpha and beta blockers
Propranolol	0.5-1.0 mg/kg/dose	Q 6-12 h	Beta blocker

* Adapted from: Ettinger and Flynn (2002).

Treatment should be individualized according to the suspected underlying cause and acuteness of the infant's hypertension. As seen in the vignette, infants showing signs and symptoms of cardiopulmonary failure or hypertensive encephalopathy should be given a continuous infusion of an antihypertensive agent such as nitroprusside or nicardipine. These agents have a rapid onset and a very short half-life, allowing titration of the dose for the desired effect. Furthermore, continuously infused antihypertensive agents reduce the wide fluctuations in blood pressure associated with intermittently administered agents. Preterm neonates with immature periventricular circulation are at increased risk for cerebral ischemia and hemorrhage during rapid declines in blood pressure, so slow correction of severe hypertension is optimal. Blood pressure should be lowered by no more than 25% during the first 8 hours of treatment and then maintained at the 95th percentile for 24 to 48 hours.

Sodium nitroprusside, a direct-acting arteriolar and venous vasodilator, effectively lowers blood pressure during a hypertensive crisis in neonates. A rapid onset of action and short half-life (3-4 minutes in adults) allows dose titration of blood pressure within the desired range. Nitroprusside is metabolized to thiocyanate in the liver and kidney, presenting a risk of cyanide toxicity with prolonged treatment (>3 days) and/or high (>3 µg/kg per minute) doses. During treatment, continuous heart rate and intraarterial blood pressure monitoring is recommended. Red blood cell cyanide and serum thiocyanate concentrations also are monitored daily. The infusion is started at 0.25 to 0.5 µg/kg per minute and titrated until the desired response is obtained. The usual maintenance dose is less than 2 µg/kg per minute. Duration of treatment should be as short as possible. Nicardipine has also been reported to be an effective alternative for managing an acute hypertensive crisis in neonates.

Enalaprilate, an intravenous long-acting angiotensin-converting enzyme (ACE) inhibitor, blocks conversion of angiotensin I to the potent vasoconstrictor angiotensin II. It also prevents the breakdown of bradykinin, a potent vasodilator. Vascular resistance is reduced without reflex tachycardia. Enalaprilate can be used in neonates with moderate hypertension, but is generally contraindicated in renal failure because of unpredictable antihypertensive efficacy, prolonged duration of action (8-24 hours), and potential to cause oligouria in neonates with impaired renal function.

Captopril, another ACE inhibitor with a shorter half-life than enalaprilate, is an oral agent used to treat moderate to severe hypertension. Its beneficial effects are attributed to afterload reduction and inhibition of salt and water retention. Loss of renal perfusion and renal failure may occur if it is used in neonates with bilateral renovascular disease or with renal artery stenosis in a solitary kidney. Oral captopril would not be the preferred first-line antihypertensive treatment for the neonate in the vignette who has severe symptomatic hypertension and unknown renal function. In cases of suspected renovascular hypertension, captopril or other ACE inhibitors may be indicated once the acute hypertensive crisis has resolved.

Esmolol is an effective intravenous beta blocker with a rapid onset and short half-life. It has been used in a continuous infusion to treat postoperative hypertension in infants after cardiac surgery. Limited data on the use of this medication in neonates as well as its relative contraindication for use in neonates with chronic lung disease, especially at higher doses, make esmolol a poor candidate for first-line treatment of hypertension in the infant in the vignette.

Furosemide, a loop diuretic, can reduce preload in neonates with congestive heart failure. It is often used in conjunction with other antihypertensive agents to treat hypertension in neonates with congestive heart failure; however, it would not be an effective first-line antihypertensive agent for a neonate with severe hypertension, especially when given orally.

References:

Benitz WE, Malachowski N, Cohen RS, et al. Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr.* 1985;106:102-110

Ettinger LM, Flynn JT. Hypertension in the neonate. *NeoReviews.* 2002;3:e151-156

Gouyon JB, Geneste B, Semama DS, et al. Intravenous nicardipine in hypertensive preterm infants. *Arch Dis Child.* 1997;76:F126-F127.

Jones JE, Jose PA. Neonatal blood pressure regulation. *Semin Perinatol.* 2004;28:141-148

Nafday, SM, Brion LP, Benchimol C, Satlin LM, Flynn JT, Edelmann CM. Renal Disease. In: MacDonald MG, Mullett MD, Seshia MK, eds. *Avery's Neonatology Pathophysiology and Management of the Newborn.* 6th ed. Philadelphia, Pa: Lippincott Williams and Wilkins. 2005:981-1065.

McGonigle LF, Beaudry MA, Coe JY. Recovery from neonatal myocardial dysfunction after treatment of acute hypertension. *Arch Dis Child.* 1987;62:614-615

Milou C, Debuche-Benouachkou V, Semama DS, et al. Intravenous nicardipine as a first-line antihypertensive drug in neonates. *Intensive Care Med.* 2000;26:956-958

Perlman JM, Volpe JJ. Neurologic complications of captopril treatment of neonatal hypertension. *Pediatrics.* 1989;83:47-52

Saland JM, Mahone L, Baum M. Perinatal renal ischemia resulting in hypertensive cardiomyopathy. *Pediatrics.* 2001;107:185-187

Vogt BA, Dell KM, Davis ID. The kidney and urinary tract. In: Martin RJ, Fanaroff AA, Walsh MC,

eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant.* 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1659-1683

Wiest DB, Garner SS, Uber WE, et al. Esmolol for the management of pediatric hypertension after cardiac operations. *J Thorac Cardiovasc Surg*. 1998;4:890-897

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. *J Perinatol.* 1995;15:470-479

American Board of Pediatrics Content Specification(s):

Understand the pathophysiology of an infant with a condition affecting the systemic blood pressure, such as shock and hypertension

Recognize the laboratory and radiographic features of an infant with a condition affecting the systemic blood pressure, such as shock or hypertension

Understand the total management plan and associated potential complications of an infant with a condition affecting the systemic blood pressure, such as shock and hypertension

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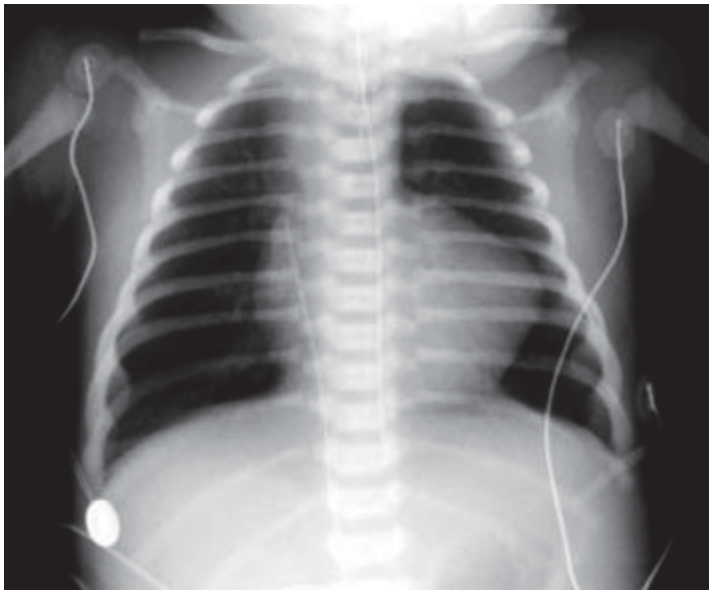
11 November 08

12 December 08

December: Question 7

You are asked to look at a radiograph sent electronically by a pediatrician from an outlying hospital. The 1-day-old infant is delivered at 37 weeks' gestation after an uncomplicated pregnancy. Today, the nurses called the pediatrician after the infant began receiving oxygen because of duskiness. The physician placed an umbilical arterial catheter, inserted an orogastric tube, and ordered the radiograph (Figure 1).



Of the following, this radiograph is MOST consistent with a cardiac diagnosis of:

1	Ebstein anomaly
2	hypoplastic left heart
3	tetralogy of Fallot
4	total anomalous pulmonary venous return
5	tricuspid atresia

You selected 5, the correct answer is 3.

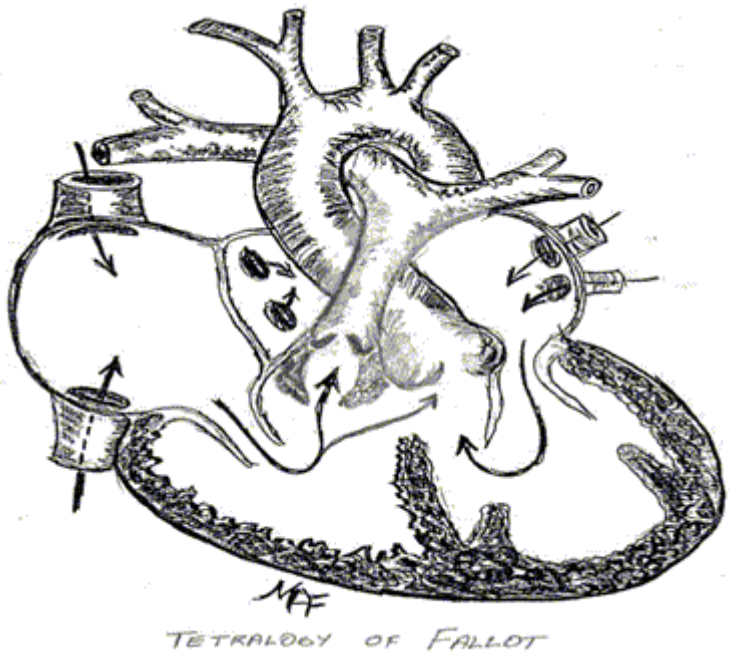
A number of cardiac conditions may result in cyanosis early in the newborn period. Pending consultation with a cardiologist and diagnostic echocardiography, review of the chest radiograph for heart size, pulmonary vascularity and lung fields, and position of the aortic arch may suggest a particular diagnosis and may guide early treatment (Table). The findings of a

normal-sized heart (with upturned apex), clear lung fields, and right aortic arch as noted by the position of the umbilical artery catheter (Figure 1) are most consistent with tetralogy of Fallot (TOF).

Table. Chest Radiography Findings

Lesion	Heart Size	Pulmonary Vascularity	Aortic Arch
Ebstein anomaly of tricuspid valve	Large to very large	Diminished	Usually normal
Hypoplastic left heart	Large	Increased vascular markings	Usually normal
Kartagener syndrome	Dextrocardia	Usually normal	Right arch, also with situs inversus
Tetralogy of Fallot	Normal, may have boot shape	Normal to decreased	25% have right arch
Total anomalous pulmonary venous return	Normal	Hazy lung fields, pulmonary edema	Usually normal
Transposition of the great arteries	Large	Increased vascular markings, congestion	Usually normal
Tricuspid atresia	Normal to enlarged	Diminished	Usually normal

Tetralogy of Fallot consists of a combination of ventricular septal defect (VSD), right ventricular outflow obstruction (infundibular and/or pulmonary valve stenosis), overriding of the aortic root above the VSD, and right ventricular hypertrophy. The aortic arch is right sided in 25% of infants having TOF, as seen in the radiograph, but not in the drawing (Figure 2).



In TOF, the heart shadow may have a characteristic "boot" shape: right ventricular hypertrophy displacing the apex upward and a right aortic arch, both easily seen in this example. The lung fields are underperfused. Not all infants having TOF manifest these "classic" radiographic findings, but cyanosis associated with absence of cardiomegaly and diminished pulmonary blood flow are important features in most cases. If the right ventricular outflow tract is severely obstructed or the pulmonary valve is atretic, pulmonary blood flow is dependent on the ductus arteriosus. With moderate to mild right-sided obstruction, ductal dependency may be present early after birth, while the pulmonary vascular resistance remains high. With TOF as the likely diagnosis and until cardiac anatomy can be ascertained with echocardiography, patency of the ductus arteriosus can be maintained with prostaglandin E infusion pending transfer to a facility

with full cardiology and cardiac surgery services. Knowing the position of the aortic arch is important because Blalock-Taussig shunts, if used, are best placed contralateral to the side of the aortic arch.

Ebstein anomaly of the tricuspid valve consists of variable degrees of displacement of the tricuspid valve into the right ventricle, resulting in dysfunction of the valve, asynchronous contraction of the atrial and ventricular portions proximal to the valve attachment, and variable degrees of right-sided ventricular hypoplasia resulting in right-to-left shunting at the atrial level. Most cases do not present in the neonatal period except those in which the predominance of the tricuspid regurgitation in utero led to massive enlargement of the right atrium. This type of enlargement is associated with life-threatening pulmonary hypoplasia in the early neonatal period. Ebstein anomaly is associated with enlargement of the cardiac shadow, mostly attributed to the right atrium (which can nearly fill the thoracic cavity) and diminished pulmonary markings. Right aortic arch is seldom associated with Ebstein anomaly. Some severely cyanotic infants benefit from a Blalock-Taussig shunt which allows greater pulmonary blood flow as the pulmonary vascular resistance drops after birth. Others, with less severe forms, may go undetected or improve as pulmonary blood flow through the right ventricle increases with decreased pulmonary vascular resistance.

Hypoplastic left heart, occurring in about 10% of infants who present with serious heart disease in the first week after birth, consists of a wide range of anomalies affecting the left side of the intracardiac and extracardiac circulations. Systemic circulation is dependent on patency of the ductus arteriosus. Radiographic findings usually include some degree of cardiomegaly and plethora of the lung fields. A right aortic arch is not commonly found.

Total anomalous pulmonary venous return (TAPVR) accounts for about 2% of neonatal congenital heart disease. Infants having TAPVR present in two forms: (1) unobstructed, in which the common pulmonary vein connects into the right atrium or systemic venous circulation without blockage to flow; and (2) obstructed, wherein the pulmonary veins enter a common channel that is obstructed on its path to the systemic venous circulation. Unobstructed TAPVR usually presents later as the pulmonary vascular resistance drops, resulting in large left-to-right shunting and congestive heart failure. The chest radiograph shows an enlarged heart and pulmonary congestion. Obstructed TAPVR may present shortly after birth with deep cyanosis in a critically ill child. The radiograph may show a normal-sized heart, but the lung fields will be affected, showing pulmonary edema (often confused with primary pulmonary disease, such as respiratory distress syndrome or pneumonia). Right aortic arch is not a common feature of TAPVR. Obstructed TAPVR may be associated with significant deterioration following the use of prostaglandin E_1 because of worsening pulmonary congestion.

Transposition of the great arteries (type D, or d-transposition) (d-TGA) is one of the more common cardiac lesions presenting in the newborn period. The transposed arteries result in pumping of systemic venous return into the aorta and the pulmonary venous return into the pulmonary artery. Survival depends on admixture of the two parallel circulations, which may occur at the atrial, ventricular, or vascular (patent ductus arteriosus) levels. Infants having d-TGA and no VSD present early with profound cyanosis which fails to improve with oxygen supplementation. The chest radiograph may appear normal, but more commonly cardiomegaly is associated with a narrow mediastinum and the lung markings are increased. Prostaglandin E_1 can help to sustain some circulatory admixture pending more definitive treatment using balloon septostomy. If a VSD contributes to admixture of the two circulations, symptoms are often delayed to the early newborn period when congestive heart failure follows massive increase in pulmonary blood flow. By this time, the radiograph will show cardiomegaly and pulmonary edema. Right aortic arch is not a regular feature of d-TGA.

Tricuspid atresia (TA) is an uncommon defect that would be better termed *tricuspid agenesis* based on the total absence of the tricuspid valve in most cases. Infants having TA may present early after birth, especially if there is no VSD, or if a VSD is present but right ventricular outflow is obstructed and pulmonary blood flow is totally dependent on the ductus arteriosus. The chest radiograph may show a normal to slightly enlarged cardiac shadow and diminished pulmonary markings; right aortic arch is not a regular feature of this relatively uncommon anomaly. Some

children having TA also have a large VSD and no obstruction to right ventricular outflow, resulting in later-onset symptoms associated with cardiomegaly and pulmonary congestion on the radiograph.

Definitive diagnosis in any of these instances follows arrival at facilities capable of echocardiography and consultation with a pediatric cardiologist. Of the conditions discussed, blood flow through the ductus arteriosus may be essential or variably helpful for patients with TOF, Ebstein anomaly, hypoplastic left heart, TGA, or TA. Prostaglandin E_1 may be included in pretransport stabilization. However, its use may precipitate the need for ventilatory support and caregivers should be ready to intervene if necessary. Infants having TAPVR, especially the obstructed form, may experience severe exacerbation of pulmonary edema if given prostaglandin E_1.

References:

Flanagan MF, Yeager SB, Weindling SN. Cardiac disease. In: MacDonald MG, Seshia MMK, Mullett MD, eds. *Avery's Neonatology: Pathophysiology and Management of the Newborn.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005:633-709

Greenberg SB. Tetralogy of Fallot. eMedicine.com Web site. Accessed April 24, 2008, at http://www.emedicine.com/radio/TOPIC685.HTM#Multimediamedia1

American Board of Pediatrics Content Specification(s):

Recognize the clinical features of a cyanotic neonate

Recognize the laboratory and radiographic features of a cyanotic neonate

Formulate a differential diagnosis of a cyanotic neonate

Recognize the laboratory and radiographic features of a neonate with a right-sided cardiac lesion

Formulate a differential diagnosis of a neonate with a right-sided cardiac lesion

PREVIOUS NEXT

January: Question 9

1 January 09
2 February 09
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A 6-day-old male infant, who weighed 740 g at birth at an estimated gestational age of 25 weeks, is requiring mechanical ventilation and a fraction of inspired oxygen of 0.6. The infant received surfactant and was briefly weaned off the ventilator and supplemental oxygen, only to require repeat ventilator support and oxygen administration. The infant has received no indomethacin, diuretics, or methylxanthines, and only a short course of antibiotics.

Physical examination reveals tachycardia, increased precordial pulsatility, bounding pulses with wide pulse pressures, and a grade 3/6 pansystolic murmur best heard at the upper left sternal border. Chest radiograph shows an enlarged heart and prominent vascular markings. Echocardiographic evaluation is pending.

Of the following, the vasoactive peptide that MOST correlates with a hemodynamically significant patent ductus arteriosus is:

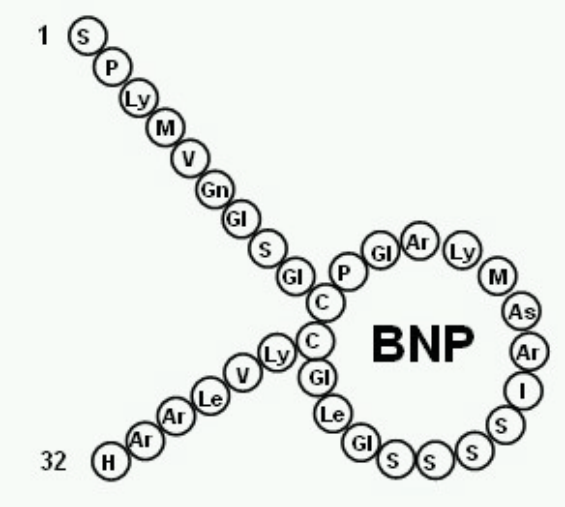
1	adrenomedullin
2	angiotensin II
3	brain natriuretic peptide
4	endothelin-1
5	renin

You selected 2, the correct answer is 3.

Body fluid volume and blood pressure are regulated by integrated actions of the autonomic nervous system, by renal modulation of sodium and water excretion, and by a complex series of interrelated endocrine responses. Traditionally, endocrine regulation has focused on the renal-adrenal axis (renin-angiotensin-aldosterone system), arginine-vasopressin from the neurohypophysis, and circulating levels of norepinephrine under the influence of the sympathetic nervous system. However, recent discoveries have indicated that both cardiac and vascular tissues can synthesize vasoactive peptides that have important local and humoral actions affecting body fluid volume and blood pressure.

Among the vasoactive peptides listed, the brain natriuretic peptide (BNP) is the peptide being studied as a biomarker of hemodynamically significant patent ductus arteriosus (SPDA) in the preterm neonate. The gene encoding BNP is located on the short arm of chromosome 1. Transcription of the BNP gene yields a 134–amino acid precursor (prepro-BNP), which is cleaved to produce a 108–amino acid prohormone (pro-BNP). The latter is cleaved further to a biologically active 32–amino acid peptide (BNP) (Figure 1) and an inactive N-terminal fragment.

Figure 1: Brain natriuretic peptide

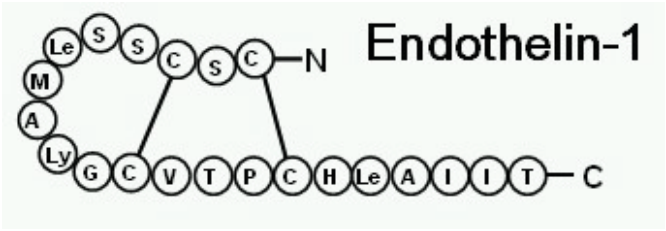


Brain natriuretic peptide is synthesized largely by the ventricular myocardium and secreted as the mature peptide in a constitutive pathway. Approximately 60% to 80% of the cardiac secretion of BNP stems from the ventricle and the remainder from the atrium. Other sites of BNP synthesis include the brain, kidney, lung, thyroid, and spleen. The BNP secretion from the ventricular myocardium is increased nearly 10-fold in response to ventricular pressure and volume overload. This observation has raised the interest in BNP as a biomarker of SPDA in which a large left-to-right shunt across the ductus can cause both left atrial and left ventricular overload. The plasma BNP concentration in the infant in this vignette, who has clinical and radiographic manifestations of SPDA, would be expected to be markedly raised.

The renal effects of BNP include an increase in glomerular filtration rate and fractional excretion of sodium; the net result is diuresis and natriuresis. The hemodynamic effects of BNP include vascular relaxation, particularly involving capacitance veins, and a resultant drop in cardiac preload. Some of this effect is attributed to a reduction in plasma volume from diuresis and natriuresis as well as from a plasma shift from the vascular to the extravascular space secondary to BNP-mediated enhancement of capillary hydraulic conductivity. Cardiac muscle contractility is largely unaffected by BNP, whereas coronary blood flow is increased and myocardial oxygen consumption is decreased. Thus, BNP appears to exert compensatory effects that may be beneficial in the clinical setting of a failing heart.

The gene encoding endothelin-1 (ET-1), the major isoform among three isoforms of endothelin, is located on chromosome 6 (Figure 2).

Figure 2: Endothelin-1



The major site of ET-1 generation is the vascular endothelium, but other cells including epithelial cells, vascular smooth muscle cells, cardiac myocytes, macrophages, and mast cells also secrete ET-1. In addition, ET-1 is distributed among other tissues including the heart, lung, kidney, pancreas, spleen, liver, and central nervous system.

The major hemodynamic effect of ET-1 is vasoconstriction. This effect is particularly notable in the coronary, renal, and cerebral vascular beds. The renal effects of ET-1 include a decrease in renal blood flow and glomerular filtration. Although ET-1 inhibits sodium reabsorption in the renal tubule and water reabsorption in the collecting duct, the marked decrease in renal blood flow from ET-1–induced vasoconstriction produces the net effects of sodium and water retention. Among neonatal diseases, persistent pulmonary hypertension has attracted the most attention with regard to measurements of plasma and tissue concentrations of endothelin isoforms.

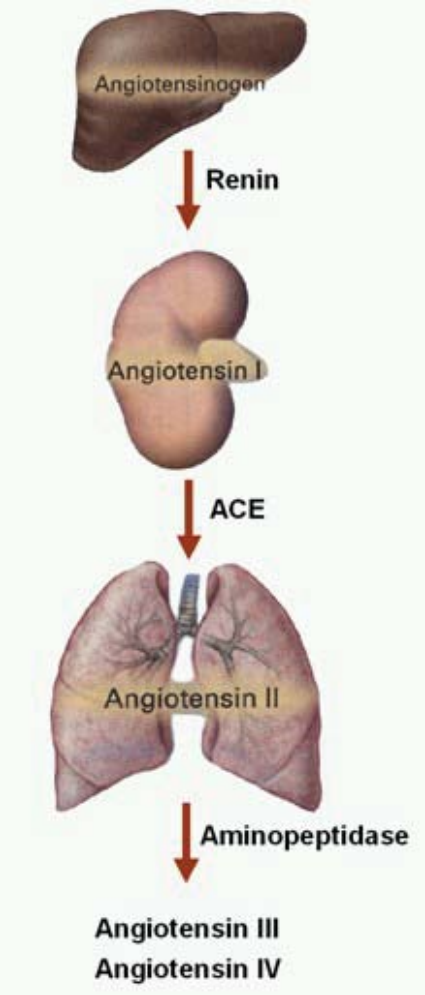
The gene encoding adrenomedullin (AM) is located on chromosome 11 (Figure 2).

The major site of AM generation is the vascular tissue, where the peptide may serve as a vasodilator and an inhibitor of vascular cell proliferation. Highest concentrations of AM are found in the adrenal medulla and anterior pituitary gland. Lower concentrations of AM are found in the heart, lung, kidney, and brain.

The cardiac effects of AM include increases in coronary blood flow and cardiac contractility. The renal effects of AM include increases in glomerular filtration rate (diuresis) and fractional excretion of sodium (natriuresis). The potential clinical application of AM in neonates includes identification of preterm infants at risk for intraventricular hemorrhage and as a marker, in conjunction with other markers of inflammation, of sepsis.

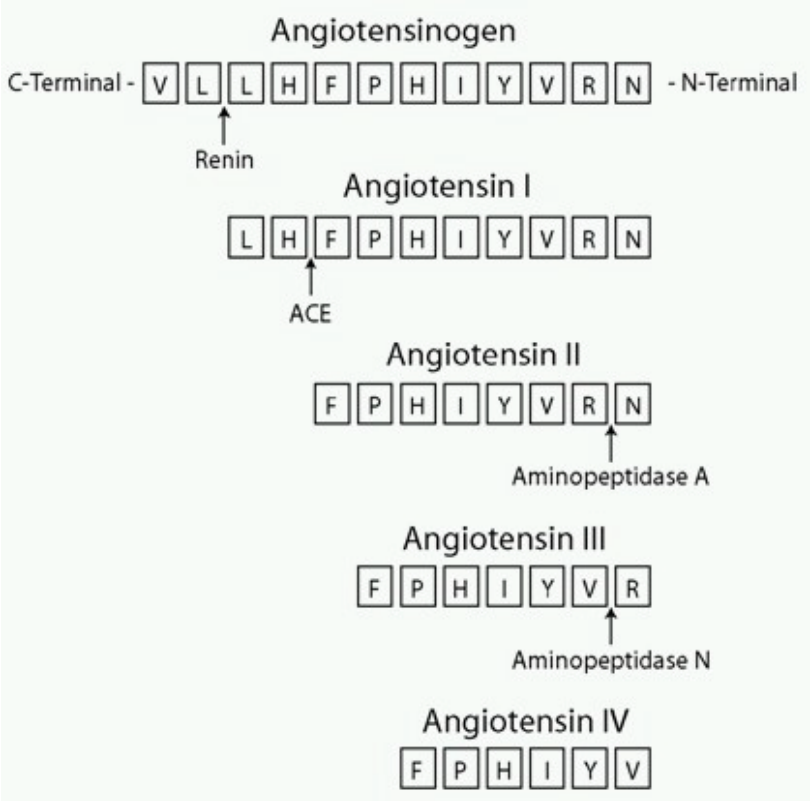
Angiotensin II is an 8–amino acid peptide, the primary effector hormone of the renin-angiotensin-aldosterone system (Figure 3).

Figure 3: Renin-angiotensin system



Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus in the kidney in response to various stimuli, principally a fall in glomerular perfusion. Renin acts on angiotensinogen, a plasma globulin synthesized by the liver, and converts it into a decapeptide, angiotensin I (Figure 4).

Figure 4: Angiotensins I, II, III, IV



Angiotensin I has no appreciable activity, but is converted in the lung by angiotensin-converting enzyme (ACE) to an octapeptide, angiotensin II. ACE is a membrane-bound enzyme on the surface of endothelial cells and is particularly abundant in the lung, which has a vast surface area of vascular endothelium.
Angiotensin II affects blood volume and vascular tone through the following mechanisms:

- Renal absorption of sodium and water, thereby increasing intravascular fluid volume and cardiac preload.
- Systemic arteriolar vasoconstriction, thereby increasing vascular resistance and cardiac afterload.
- Stimulation of sympathetic activity and inhibition of vagal activity.

The sustained action of angiotensin II can result in vascular hyperplasia and cardiac hypertrophy. Angiotensin II is cleaved by aminopeptidase A into a heptapeptide, angiotensin III, which is cleaved further by aminopeptidase N into a hexapeptide, angiotensin IV. Angiotensin III is a potent stimulator of aldosterone secretion, which promotes sodium and water retention. Angiotensin IV is a potent stimulator of plasminogen activator inhibitor-1 from the endothelium, which increases the viscosity of blood.

References:

Czernik C, Lemmer J, Metze B, Koehne PS, Mueller C, Obladen M. B-type natriuretic peptide to predict ductus intervention in infants <28 weeks. ***Pediatr Res.*** 2008;64(3):286-290

Farombi-Oghuvbu I, Matthews T, Mayne PD, Guerin H, Corcoran JD. N-terminal pro-B-type natriuretic peptide: a measure of significant patent ductus arteriosus. ***Arch Dis Child Fetal Neonatal Ed.*** 2008;93:F257-F260

Ko HK, Lee JH, Choi BM, et al. Utility of the rapid B-type natriuretic peptide assay for detection of cardiovascular problems in newborn infants with respiratory difficulties. ***Neonatology.***

2008;94:16-21

Rademaker MT, Espiner EA. Hormones of the cardiovascular system. In: DeGroot LJ, Jameson JL, de Kretser D, et al, eds. ***Endocrinology.*** 5th ed. Philadelphia, Pa: Elsevier Saunders; 2006:2549-2566

Rand HP, Dale MM, Ritter JM, Moore PK. The vascular system. In: ***Pharmacology.*** 5th ed. Edinburgh, UK: Churchill Livingstone; 2003:285-305

American Board of Pediatrics Content Specification(s):

Understand the production sites and actions of various types of vasoactive peptides that affect renal function

Understand the pathway and control of angiotensin peptide production

Know the actions of the components of the renin-angiotensin system

PREVIOUS NEXT

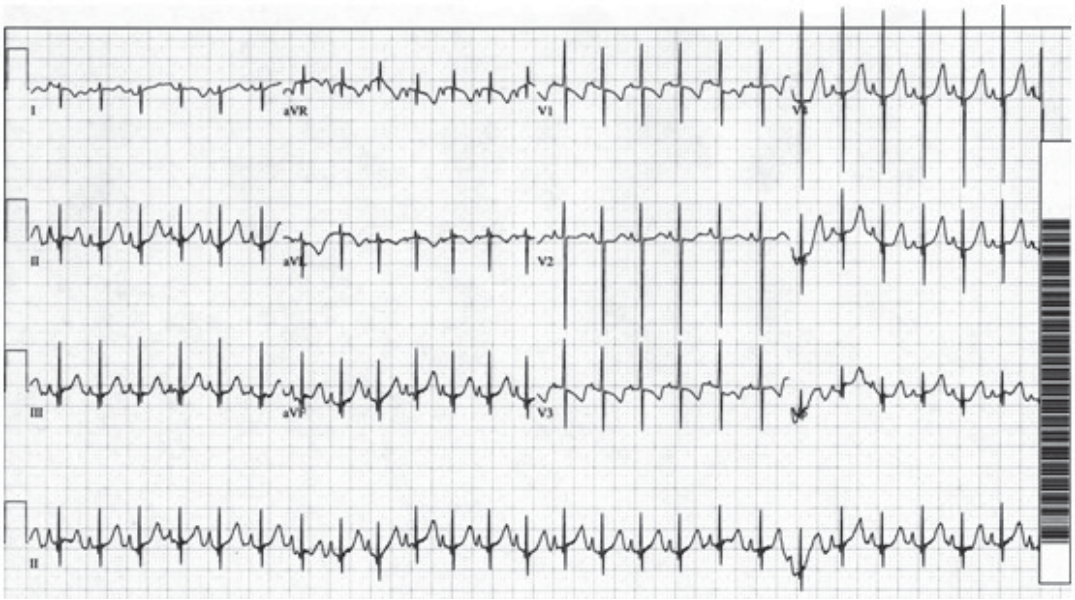
September: Question 10

1 January 09
2 February 09
3 March 09
4 April 09
5 May 09
6 June 09
7 July 09
8 August 09
9 September 09
10 October 09
11 November 09
12 December 09

A 32-week, 1.8-kg premature female infant is born through vaginal delivery to a 42-year-old woman who had had six previous pregnancies, one other preterm delivery, one spontaneous abortion, and three stillbirths. The mother was treated with counseling and relaxation techniques for longstanding fatigue, anxiety, and irritability before this pregnancy. The effect of fluoxetine treatment in the last half of her pregnancy was uncertain. For her premature labor, she was treated with magnesium, and received antibiotics and betamethasone before delivery.

The infant's physical examination findings were normal at birth. Eleven days after birth she was noted to have persistent tachycardia with heart rates as high as 240 beats per minute. Physical examination remained normal otherwise. Her hemoglobin concentration was 9 g/dL (90 g/L), white blood cell count was 10.5×10^3/μL (10.5×10^9/L), and C-reactive protein level was normal. An electrocardiogram was obtained (Figure 1) and chest radiography findings were normal except for a questionably enlarged heart.

Figure 1: Electrocardiography showing sinus tachycardia. Rate is 155 beats per minute; P waves regularly present and P-R interval is 100 milliseconds. No delta wave seen.



Of the following, the MOST likely explanation for the findings in this infant is:

1	anemia of prematurity
2	arteriovenous fistula
3	fluoxetine exposure in utero
4	neonatal hyperthyroidism
5	Wolf-Parkinson-White syndrome

You selected 3, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

The infant in the vignette was described as restless and developed persistent tachycardia in the second week after birth. Her mother had a constellation of problems including a history of stillbirths that should have led to an investigation of her thyroid function. Graves disease, occurring in approximately 1 in 500 pregnancies, is the second most common endocrine disorder of pregnancy after diabetes mellitus. About 1% of infants born to women with Graves disease have neonatal hyperthyroidism.

Most women with Graves disease have nonspecific complaints including nervousness, heat intolerance, restlessness, fatigue, muscle weakness, increased appetite, frequent bowel movements, and sweating. Protruding eyes (proptosis) and goiter are more specific but not necessarily present. Pregnancy itself can reduce the symptoms of Graves disease because of nonspecific immunosuppression. Consequently, the condition is undiagnosed for long periods, and patients are less symptomatic during pregnancy. In fact, more than half of all cases of perinatally acquired neonatal hyperthyroidism are identified before the mother is known to have Graves disease.

Graves disease is an autoimmune disorder in which specific thyroid-stimulating antibodies (TSAb) attach to the thyrotropin receptor (TSH-R) on thyroid epithelial cells, leading to unregulated thyroxine production. The antibodies are in the immunoglobulin G (IgG) class and are transferred to the fetal circulation with similar effect on the fetal thyroid gland. These infants have very high thyroxine (T_4) and very low thyrotropin concentrations. The half-life of transplacentally acquired IgG varies from 3 to 7 weeks. Infants exposed to TSAb most commonly become symptomatic by the 10th day after birth and the clinical condition can persist for 8 to 20 weeks. Restoration of normal laboratory values can take up to 48 weeks after birth.

The fetal thyroid gland develops from an outpouching of the floor of the primitive pharynx and starts to secrete thyroxine by the end of the first trimester. Transfer of IgG across the placenta starts slowly around the 17th week and increases gradually over the next 4 months. Therefore, transplacentally acquired hyperthyroidism (Graves disease) can start in the fetus as early as the second half of pregnancy (early onset). Fetal manifestations include death in utero, preterm delivery, intrauterine growth restriction, fetal tachycardia, goiter, accelerated bone maturation, cardiac failure, and hydrops.

The onset of disease is delayed in the newborn and is most commonly recognized in the second week after birth. Signs and symptoms can include:

- **Irritability, jitteriness, restlessness**
- **Tachycardia, arrhythmias, cardiac failure, pulmonary hypertension**
- **Voracious appetite, weight loss, diarrhea, sweating, flushing**
- **Goiter**
- **Advanced bone age**
- **Periorbital edema, lid retraction, exophthalmos**

The infant in the vignette had restlessness and persistent tachycardia. At 12 days of age her T_4 concentration was more than 6 ng/dL (reference range, 1-2.6 ng/dL) and her thyrotropin concentration was 0.006 mIU/L (reference range, 0.5-10.8 mIU/L). Subsequent testing of the mother revealed that she also had Graves disease.

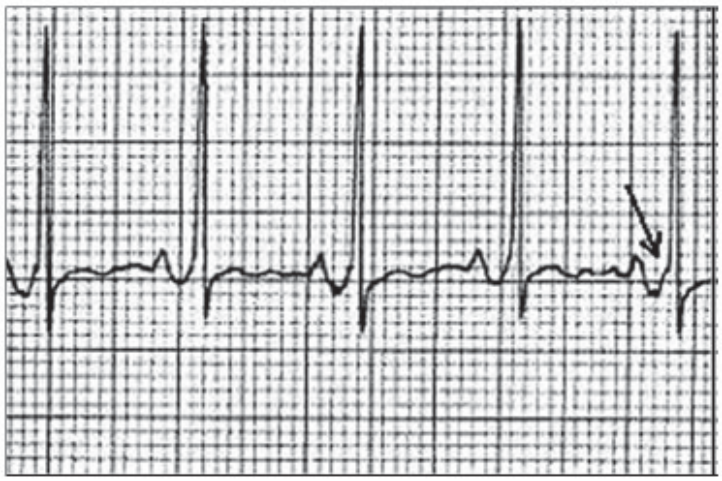
Anemia can cause persistent tachycardia, but rarely causes symptoms by itself when the hemoglobin concentration is 7 g/dL (70 g/L) or higher. Anemia is not a likely cause for this infant's condition.

Arteriovenous fistulae are most often found in the brain (vein of Galen) or in the liver. Infants can have tachycardia and cardiomegaly with heart failure. However, these anomalies are usually found on physical examination as they produce continuous bruits that can be detected with a stethoscope.

Exposure to fluoxetine, a selective serotonin-reuptake inhibitor (SSRI), in the second half of pregnancy can be associated with pulmonary hypertension in the fetus or newborn infant. Anecdotal descriptions of possible SSRI withdrawal symptoms including irritability and gastrointestinal distress have been reported. SSRI exposure is associated with a sixfold higher risk for significant neonatal pulmonary hypertension. Infants with significant pulmonary hypertension have severe respiratory failure requiring ventilatory assistance. They have right to left shunting through fetal channels and often have cyanosis. The infant in the vignette did not show signs of pulmonary hypertension.

The infant in the vignette had an electrocardiogram showing sinus tachycardia (Figure 1) with a normal P-R interval of 100 milliseconds and no delta waves. These findings are inconsistent with the Wolf-Parkinson-White variety of supraventricular tachycardia (Figure 2) in which the P-R interval is abnormally short and delta waves are seen.

Figure 2: Wolf-Parkinson-White syndrome characterized by short P-R interval and delta wave (arrow). (From Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia (SVT). *NeoReviews.* **2005;6;e339-e350)**



References:

Belik J. Fetal and neonatal effects of maternal drug treatment for depression. *Semin Perinatol.* **2008;32(5):350-354.**

Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med.* **2006;354:579-587**

Hernandez MI, Lee K-W. Neonatal Graves disease caused by transplacental antibodies. *NeoReviews.* **2008;9:e305-e309**

U.S. National Library of Medicine and National Institutes of Health. Graves disease. *Medline Plus.* **Accessed January 8, 2009, at: http://www.nlm.nih.gov/medlineplus/ency/article/000358.htm**

Van Hare GF. Neonatal arrhythmias In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant.* **8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:1252-1265**

American Board of Pediatrics Content Specification(s):

Identify the effects of maternal immunologic disease with transplacental passage of immunoglobulins and its treatment on the fetus

Recognize the effects on the fetus of maternal endocrine disorders (other than diabetes mellitus) and their management

Identify the etiology and clinical manifestations of congenital hyperthyroidism

Know the laboratory features and treatment of congenital hyperthyroidism

Recognize the cardiac manifestations of maternal diseases and of common perinatal syndromes in the newborn infant

Differentiate normal from abnormal electrocardiographic voltages, patterns, and rhythms in the fetus and newborn infant, including electrophysiologic characteristics

Understand the clinical features and evaluation of arteriovenous malformations

PREVIOUS NEXT

October: Question 5

1 January 09
2 February 09
3 March 09
4 April 09
5 May 09
6 June 09
7 July 09
8 August 09
9 September 09
10 October 09
11 November 09
12 December 09

You are asked to attend the delivery of a 39-week infant. Prenatal diagnostic evaluations revealed congenital heart disease. To prepare for delivery room management and early neonatal care, you retrieve the results of her antepartum testing.

Of the following, the congenital cardiac lesion MOST likely to require urgent intervention after birth is:

1	atrioventricular canal
2	hypoplastic left heart syndrome with moderate atrial septal defect
3	pulmonary valve stenosis
4	tetralogy of Fallot with absent pulmonary valve
5	truncus arteriosus

You selected 3, the correct answer is 4.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Advances in fetal ultrasonography have led to increasing numbers of infants being diagnosed with congenital heart disease; neonatologists are often asked to attend such deliveries. As such, it is essential to know which cardiac lesions are most likely to require urgent intervention after birth. Of the conditions listed, tetralogy of Fallot (TOF) with absent pulmonary valve will likely require such intervention.

In addition to TOF with absent pulmonary valve, the following cardiac lesions also cause significant compromise after the neonate is separated from the placenta:

- Transposition of the great arteries (TGA) with intact ventricular septum and a restrictive atrial septum
- Hypoplastic left heart syndrome (HLHS) with intact atrial septum
- Obstructed total anomalous pulmonary venous return (TAPVR)

Infants who have TOF with absent pulmonary valve can present with significant respiratory distress after delivery. TOF with absent pulmonary valve is accompanied by an underdeveloped pulmonary valve with severe regurgitation from the branch pulmonary arteries back into the main pulmonary artery and right ventricle. The proximal branch pulmonary arteries become severely dilated secondary to this regurgitation; this dilation results in proximal and distal compression of the airway. It may be possible to maintain patency of the infant's airway with prone positioning; otherwise continuous positive airway pressure or intubation is required.

Infants with TGA with intact ventricular septum and intact or restrictive atrial septum present with severe cyanosis, as the patent ductus arteriosus (PDA) provides the only way to mix pulmonary and systemic blood flow. Often the PDA does not provide sufficient mixing and the

saturation in the ascending aorta is remarkably low. Such infants benefit from a prompt balloon atrial septostomy, which creates a communication between the atria, and can lead to an immediate and significant increase in systemic oxygen saturation.

In HLHS with intact atrial septum, there is no egress from the left atrium so the pulmonary venous blood cannot get to the systemic circulation; infants with this condition can present immediately after birth with severe cyanosis. Infants with HLHS associated with an adequate foramen ovale or atrial septal defect develop symptoms when the ductus begins to close. In these infants, the interatrial communication allows the pulmonary venous return to cross from the left to the right atrium, entering both the pulmonary circulation and the systemic circulation by way of the PDA.

In obstructed TAPVR, the pulmonary veins connect with venous structures either above or below the diaphragm instead of returning to the left atrium. The pulmonary vasculature quickly becomes congested secondary to the obstruction. Cardiac output diminishes rapidly because the left side of the heart cannot fill. As a result, these infants present with metabolic acidosis and severe hypoxemia. Critical surgical intervention is required to alleviate the obstruction and repair the lesion.

The other options in the vignette are less likely to require urgent intervention after birth.

- Atrioventricular canal presents after the immediate newborn period; as the pulmonary vascular resistance decreases, a murmur will be appreciated and symptoms will develop.
- Pulmonary valve stenosis relies on flow through the ductus arteriosus to augment the pulmonary circulation. These infants present with increasing cyanosis as the PDA closes and benefit from prostaglandin treatment. Critical pulmonary valve stenosis may require urgent intervention.
- Truncus arteriosus commonly presents after the pulmonary vascular resistance decreases and pulmonary overcirculation ensues.

References:

Artman M, Mahoney L, Teitel DF. ***Neonatal Cardiology.*** New York, NY: McGraw-Hill; 2002

Friedman AH, Fahey JT. The transition from fetal to neonatal circulation: normal responses and implications for infants with heart disease. ***Semin Perinatol.*** 1993;17:106-121

Johnson BA, Ades A. Delivery room and early postnatal management of neonates who have prenatally diagnosed congenital heart disease. ***Clin Perinatol.*** 2005;32:921-946

Penny DJ, Shekerdemian LS. Management of the neonate with symptomatic congenital heart disease. ***Arch Dis Child Fetal Neonatal Ed.*** 2001;84:F141-F145

American Board of Pediatrics Content Specification(s):

Plan appropriate management for a neonate with a mixed cardiac lesion and understand the potential adverse effects of specific interventions

Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion

Recognize the clinical features of a neonate with a left-to-right shunt lesion

Recognize the clinical features of a neonate with a mixed cardiac lesion

Plan appropriate management of an infant with airway obstruction, such as vascular rings, choanal atresia, and tracheal abnormalities

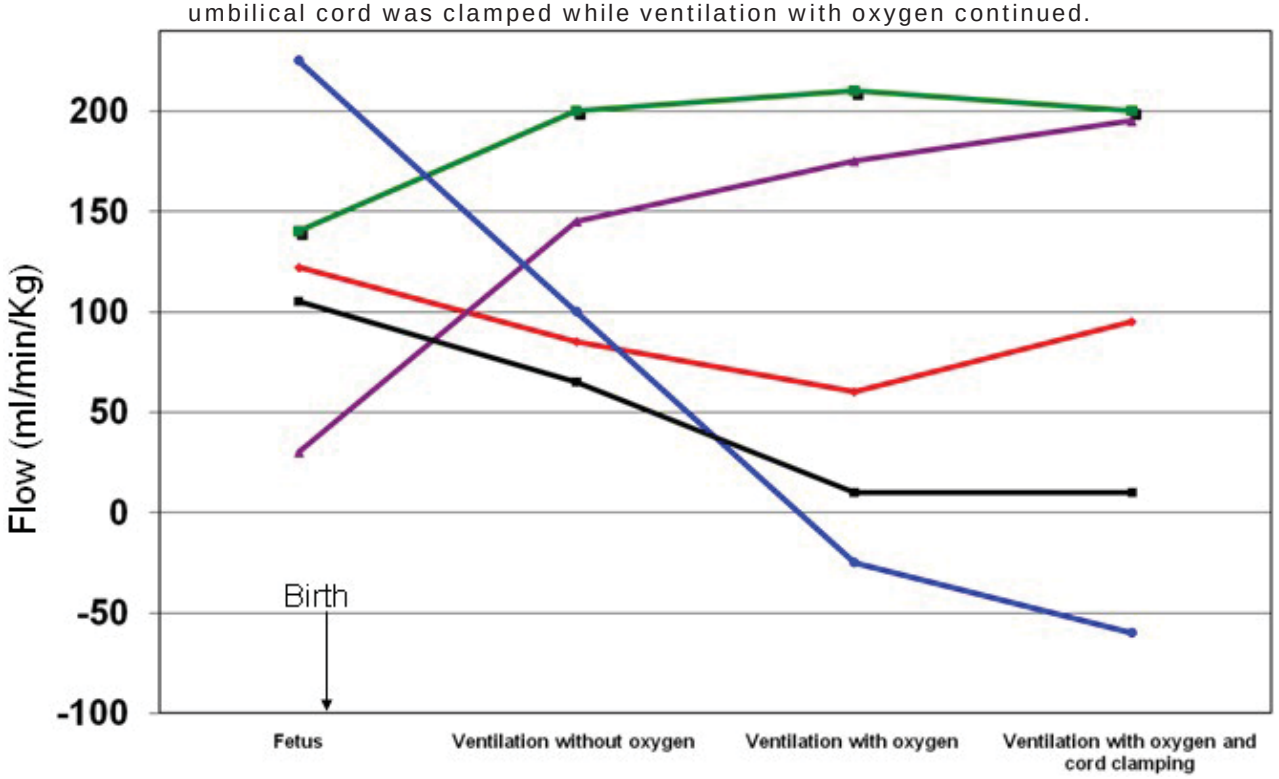
PREVIOUS NEXT

October: Question 3

1 January 09
2 February 09
3 March 09
4 April 09
5 May 09
6 June 09
7 July 09
8 August 09
9 September 09
10 October 09
11 November 09
12 December 09

A term newborn was delivered with the help of vacuum extraction. An inquisitive nursing student asks you why the infant's lower extremities are more cyanotic than the infant's right arm. As the infant's cyanosis is resolving, you illustrate the key physiologic changes in blood flow rates in the ascending and descending aorta, pulmonary artery, ductus arteriosus, and foramen ovale with lung expansion; increase in inspired oxygen concentration; and umbilical cord clamping.

Figure 1: Graph depicting the effects of three components of the birth process on the central blood flow pattern in instrumented fetal sheep. In the model, central blood flow changes were determined, in sequence, during ventilation with and without oxygen and then after the umbilical cord was clamped while ventilation with oxygen continued.



Of the following, the location with dramatic blood flow changes after birth that is MOST accurately depicted by the red line on Figure 1 is the:

1	ascending aorta
2	descending aorta
3	ductus arteriosus
4	foramen ovale
5	pulmonary artery

You selected 2, the correct answer is 2.

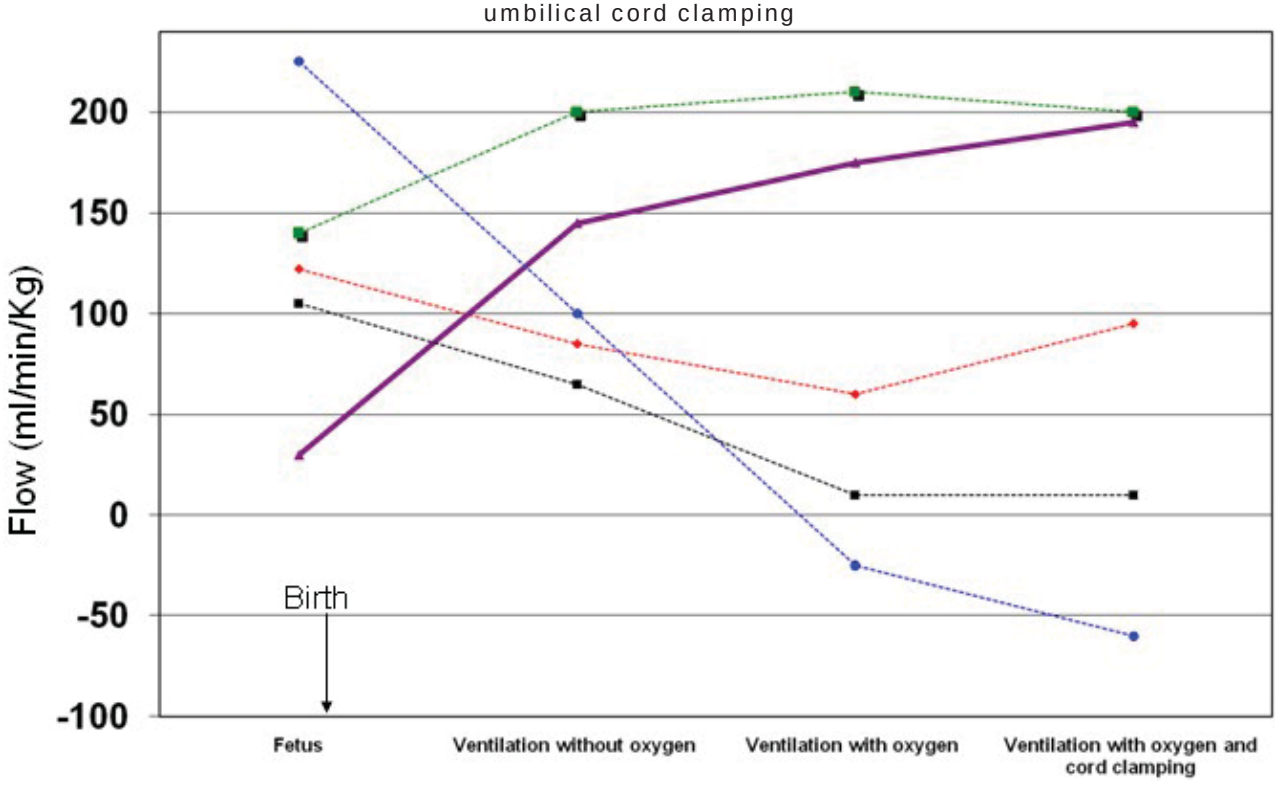
A number of complex and dramatic events must occur at birth to transition from the fetal circulation to the neonatal circulatory pattern. Fetal circulation depends on the placenta for gas exchange and intracardiac and extracardiac shunts to deliver oxygenated blood to the brain. The neonatal circulation provides gas exchange through the infant's lungs, and fetal shunts are close. Two major hemodynamic events, pulmonary vascular vasodilation and closure of fetal shunts, occur after delivery to allow for the transition from a fetal to a neonatal circulation.

The red line on the Figure 1 depicts blood flow changes that occur in the descending aorta and lower body following lung expansion and an inspired oxygen concentration (FiO_2) of 1.0, and clamping of the umbilical cord. Because of an increase in pulmonary blood flow and reversal of blood flow across the ductus arteriosus following lung expansion and an increase in FiO_2, blood flow to the abdominal aorta initially falls. The reversal of blood flow across the ductus arteriosus is not completely compensated by an increase in left ventricular output. Clamping of the umbilical cord stops descending aorta blood flow to the low-impedance placenta and increases blood flow to the abdominal aorta and lower body (Figure 1, red line).

At birth, pulmonary arterial blood flow increases 8- to 10-fold. Pulmonary vascular resistance (PVR) falls by 50% within 24 hours of birth in healthy infants. Pulmonary vascular vasodilation and the resultant increase in pulmonary blood flow play pivotal roles in blood flow changes that occur in the central circulation.

In an animal model, lung expansion with a non–oxygen-containing gas mixture increases pulmonary blood flow (Figure 2, purple line) by exerting dilatory pressure on small pulmonary vessels and stimulating the release of vasoactive substances such as prostacyclin, other prostaglandins, bradykinnin, and nitric oxide (NO). At the same time the production of endogenous vasoconstrictors (such as endothelin-1 (ET-1), thromboxanes, norepinephrine, and angiotensin-1) is reduced.

Figure 2: Graph depicting changes in pulmonary blood flow (purple line) following in sequence: ventilation without oxygen, ventilation with oxygen, and then ventilation with oxygen and umbilical cord clamping

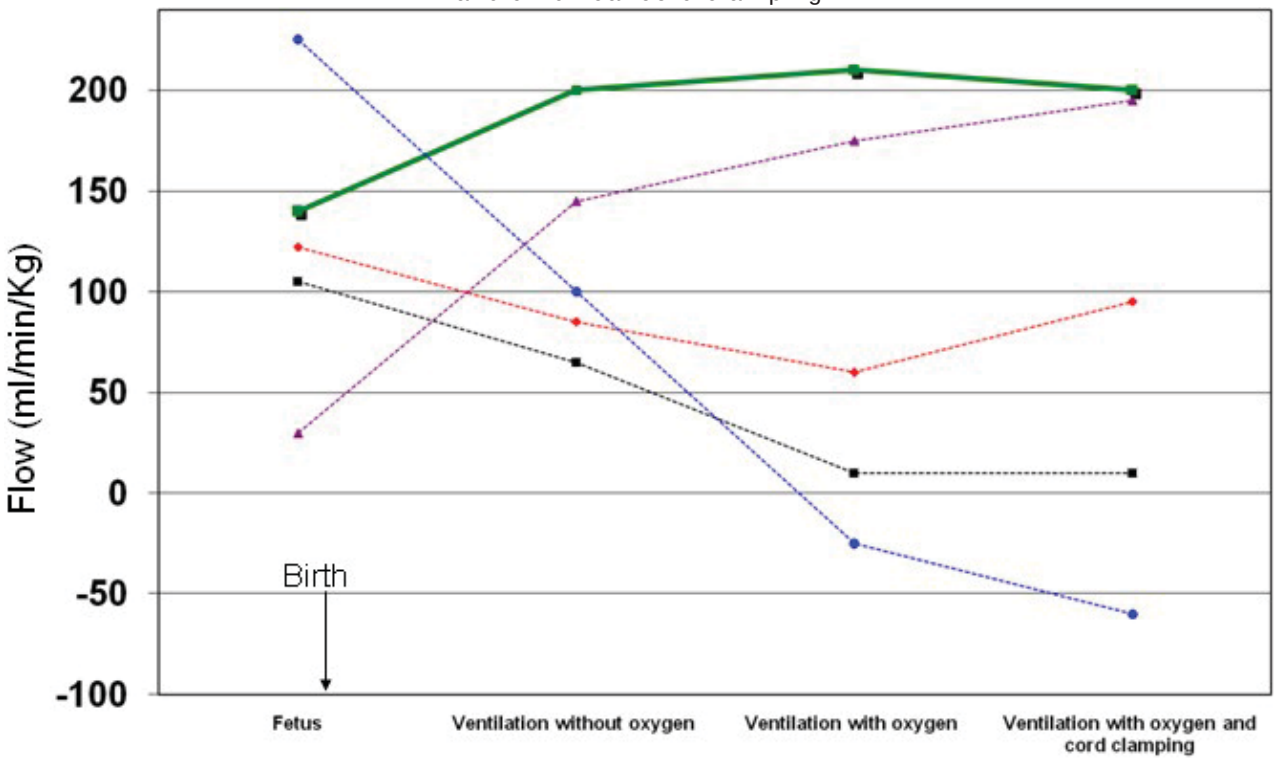


Addition of oxygen to the gas mixture of a ventilated fetal animal model leads to a further increase in pulmonary blood flow (Figure 2, purple line) as the pulmonary vascular bed vasodilates more.

The mechanisms of oxygen-induced pulmonary vasodilation at birth are not fully understood, especially in humans; however, pulmonary vascular tone at birth appears to be regulated by a balance between endothelium-derived mediators that have vasodilator effects (NO, endothelial-derived hyperpolarizing factor [EDHF] and prostacyclin), endothial type B receptors, potassium channels and a few potent vasoconstrictors (ET-1 and leukotrienes). Important physiologic changes in blood flows also occur after birth with the loss of the low-impedance placenta (clamping of the umbilical cord). Removal of the low impedence placenta from the cardiovascular circuit is associated with a marked increase in systemic vascular resistance. Pulmonary blood flow increases slightly (Figure 2, purple line) because of left to right blood flow across the ductus arteriosus.

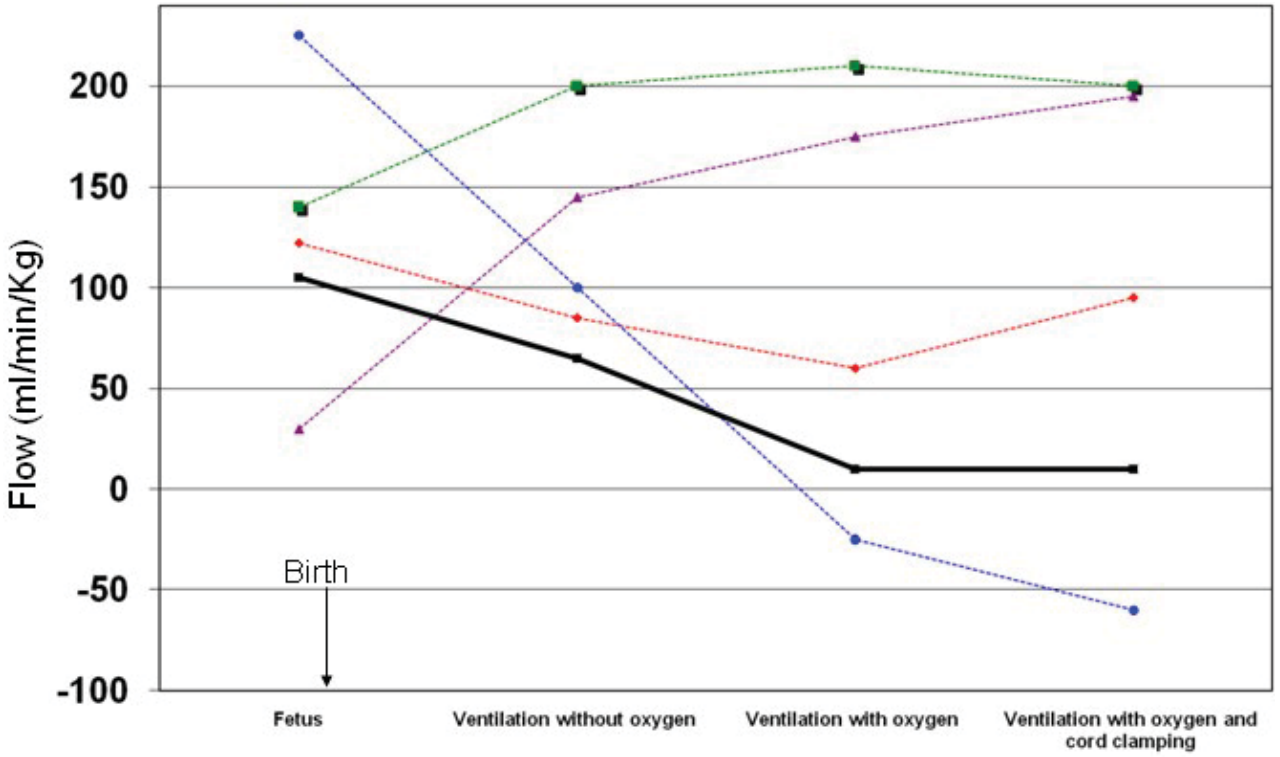
An increase in pulmonary blood flow with lung expansion and with the addition of supplemental oxygen results in an increase in pulmonary venous return to the left atrium and the ascending aorta (Figure 3, green line). Clamping of the umbilical cord has little effect on ascending aorta blood flow after birth.

Figure 3: Graph depicting changes in ascending aortic blood flow (green line) following in sequence: ventilation without oxygen, ventilation with oxygen, and then ventilation with oxygen and umbilical cord clamping



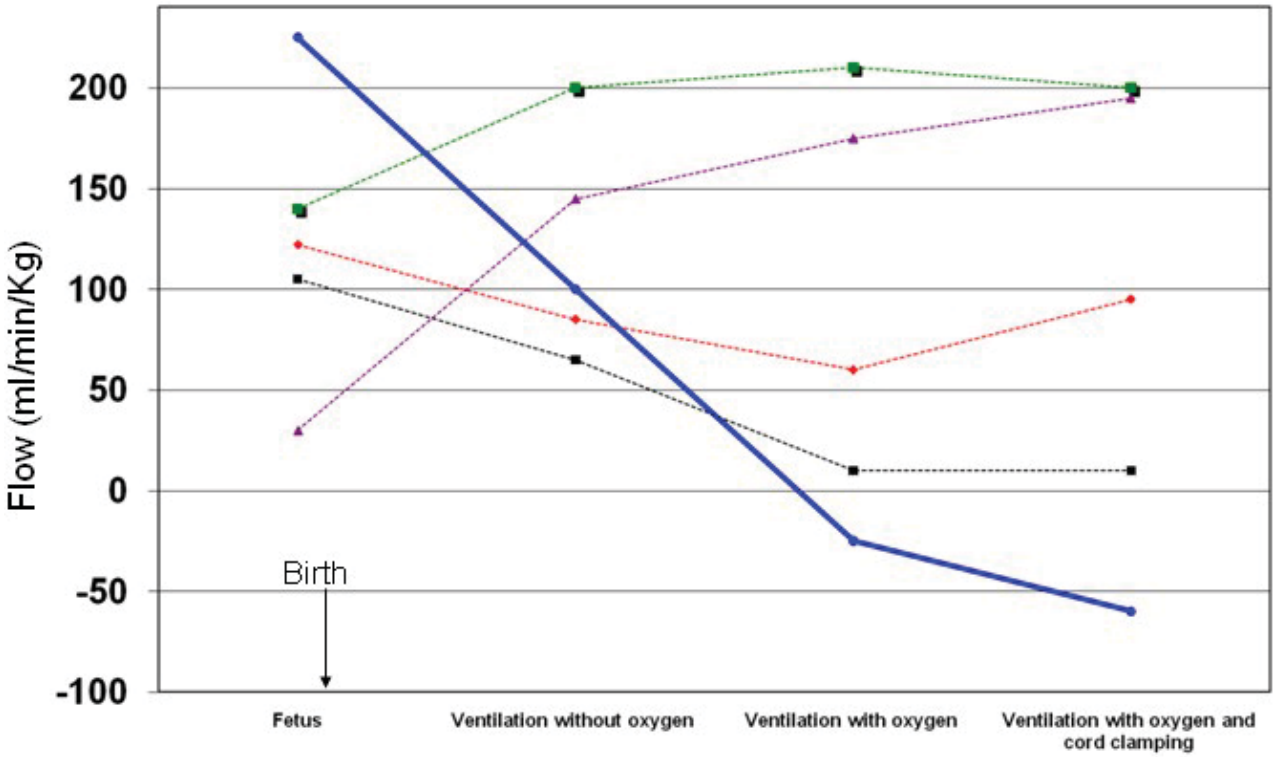
Right-to-left blood flow across the foramen ovale is present in the fetal circulation to supply the brain of the fetus with the most well-oxygenated blood from the placenta. Right-to-left blood flow drops dramatically with the fall in pulmonary vascular resistance following lung expansion and supplemental oxygen (Figure 4, black line). The accompanying increase in pulmonary venous return from the lungs increases left atrial pressure, closes the foramen ovale, and essentially abolishes right to left flow across the foramen. The valvelike flap over the foramen ovale also prevents significant left to right shunting.

Figure 4: Graph depicting changes in right-to-left blood flow across the foramen ovale (black line) following in sequence: ventilation without oxygen, ventilation with oxygen, and then ventilation with oxygen and umbilical cord clamping



With the fall in PVR following the onset of lung expansion, right-to-left blood flow across the ductus arteriosus decreases as blood flows to the lungs rather than into the descending aorta. As PVR declines further with lung expansion and oxygen, the right-to-left shunt across the ductus reverses (Figure 5, blue line). Left-to-right blood flow across the ductus arteriosus continues as systemic vascular resistance increases with the clamping of the umbilical cord.

Figure 5: Graph depicting changes in blood flow across the ductus arteriousus (blue line) following in sequence: ventilation without oxygen, ventilation with oxygen, and then ventilation with oxygen and umbilical cord clamping



References:

Alvaro RE, Rigatto H. Cardiorespiratory adjustments at birth. In: MacDonald MG, Mullett MD, Seshia MMK, eds. ***Avery's Neonatology: Pathophysiology & Management of the Newborn***. 6th ed Philadelphia, PA: Lippincott Williams & Wilkins; 2005:284-303

Cogolludo A, Moreno L, Villamor E. Mechanisms controlling vascular tone in pulmonary arterial hypertension: implications for vasodilator therapy. ***Pharmacology.*** 2007;69:65-75

Haworth SG. Pulmonary endothelium in the perinatal period. ***Pharmacol Rep.*** 2006; 57, suppl: 153-164.

Levy M, Maurey C, Chailley-Heu B, Matinovic J, Jaubert F, Israël-Biet D. Developmental changes in endothelial vasoactive and angiogenic growth factors in the human perinatal lung. ***Pediatr Res.*** 2005;57:248-253

Teitel DF, Iwamoto HS, Rudolph AM. Effects of birth related events on central blood flow patterns. Pediatr Res. 1987; 22: 557-566

Wojciak-Stothard B, Haworth SG. Perinatal changes in pulmonary vascular endothelial function. ***Pharmacol Ther.*** 2006;109:78-91

American Board of Pediatrics Content Specification(s):

Understand the factors affecting and regulating systemic circulation in the fetus and newborn infant and during the transitional period

Understand the factors affecting and regulating the pulmonary circulation in the fetus and newborn infant and during the transitional period

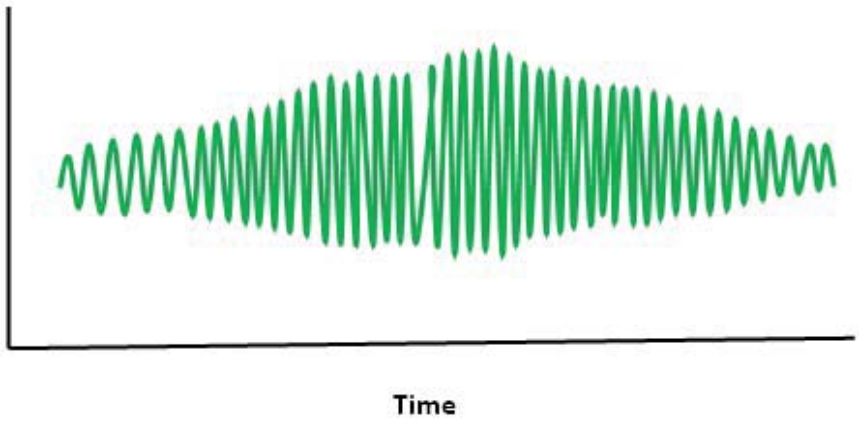
PREVIOUS NEXT

December: Question 9

1 January 09
2 February 09
3 March 09
4 April 09
5 May 09
6 June 09
7 July 09
8 August 09
9 September 09
10 October 09
11 November 09
12 December 09

A full-term female infant was admitted with hypoxic-ischemic encephalopathy. She receives mechanical ventilation and is being treated with whole body cooling. Vital signs and gas exchange are being monitored. A waveform is developed within one of the physiologic monitors and is shown in Figure 1.

Figure 1: Waveform within a physiologic monitor



Of the following, the waveform MOST likely represents measurement of:

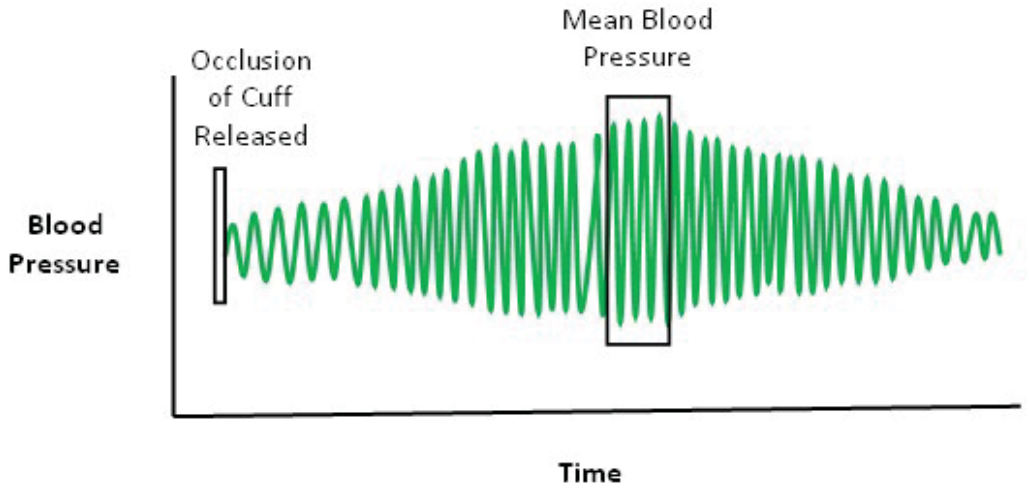
1	arterial oxygen saturation
2	blood pressure
3	carbon dioxide
4	respirations
5	tissue oxygenation

You selected 2, the correct answer is 2.

Do you want to add anything to your Learning Plan?
(You must be an AAP member or PediaLink® Learning Center Subscriber to use this feature.)

Measurements of physiologic parameters are central to intensive treatment of sick infants. Blood pressure can be monitored indirectly using various methods or directly through a catheter-transducer system. Indirect blood pressure measurement using the auscultatory method with a cuff and mercury column is not applicable to newborns because the frequency spectrum of the Korotkoff sounds is not audible. The oscillometric method of measuring blood pressure with a cuff and microprocessor is often used in newborn infants. After inflation, the cuff is allowed to deflate and the oscillations in the cuff pressure form a pattern as increasingly more blood rushes through the narrowed vessel, as depicted in Figure 1 in the vignette. Pulsations peak in size when the mean blood pressure is reached and then taper (Figure 2).

Figure 2: Blood pressure oscillometric waveform. (Adapted from Geddes LA. ***Cardiovascular Devices and Their Applications.*** New York, NY: John Wiley & Sons; 1984.)

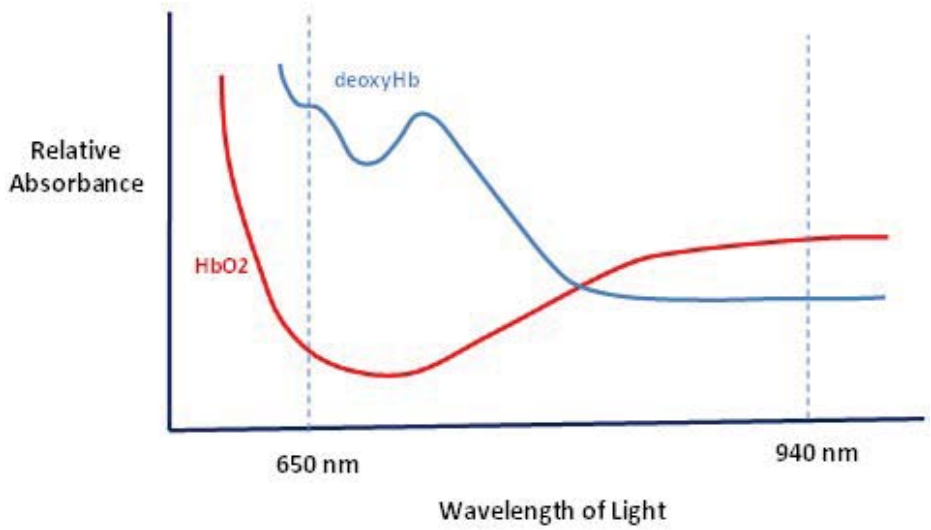


Systolic and diastolic pressures are deduced by extrapolating from the attenuation rate on both sides of the maximum pulsation and internal reference measurements. Because of variation in algorithms of the commercially available oscillometric blood pressure devices, readings may differ. Furthermore, differences with direct measurements of blood pressure in neonates have been shown. Cuff size is an important variable for indirect blood pressure measurements. A cuff width about 40% of the extremity circumference is recommended; cuffs that are too narrow yield falsely elevated readings. Oscillometric measurements of blood pressure are noninvasive, very sensitive to motion, and provide intermittent, not continuous, measurement of blood pressure.

If continuous measurement of blood pressure is indicated, direct measurement with an indwelling catheter connected to a pressure transducer is a preferred option. In such systems, the fluid forces movement in a diaphragm that is converted to an electrical signal. The pressure fluctuations at the tip of the catheter are the same as those within the pressure transducer as long as they are both at the same level. Factors in addition to the blood pressure that affect the transducer response include the mass of the measurement system, stiffness or compliance of the catheter and transducer, and the viscous drag, or damping, of the fluid within the transducer. Air bubbles within the system are compressible and add to the damping caused by viscosity of the fluid. In contrast to indirect blood pressure methods, direct blood pressure measurements of systolic and diastolic pressure are made, and mean blood pressure is calculated by dividing the area under a pulse wave by the width of the wave.

Transcutaneous oxygen saturation (S_pO_2) measurement has become a "fifth vital sign" in patients of all ages. S_pO_2 measurement provides a continuous, noninvasive estimate of arterial oxygen saturation and, secondarily, heart rate. Detection of hemoglobin oxygen saturation is based on relative absorbance of light in the red (approximately 650 nm) and infrared (approximately 940 nm) spectra (Figure 3).

Figure 3: Pulse oximetry, differential absorbance of hemoglobin and deoxyhemoglobin at selected wavelengths

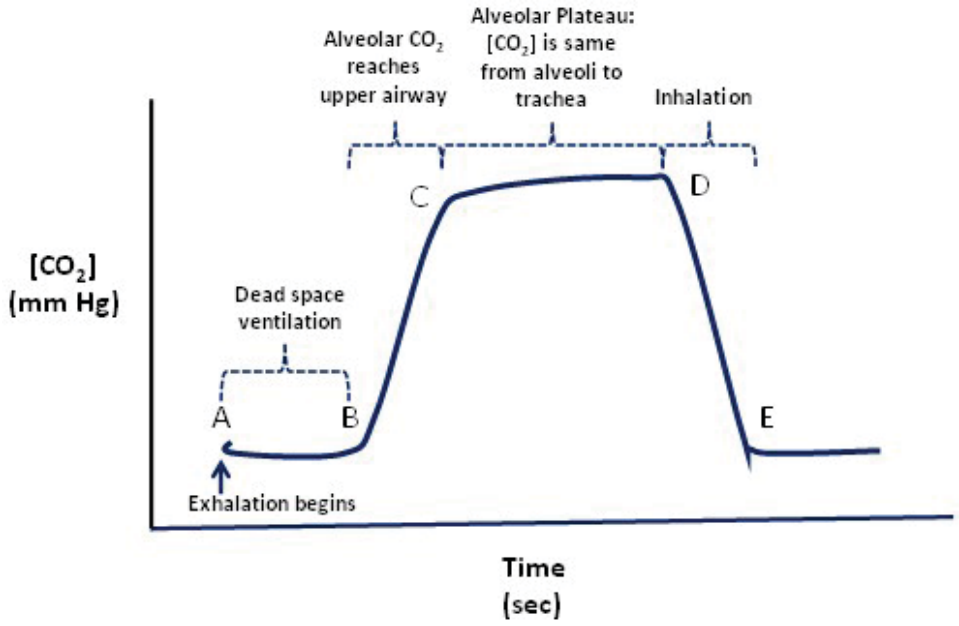


Accuracy of readings is ±2% within the range of 70% to 100%. When S_pO_2 is lower than 70%, accuracy suffers considerably. In neonates, an S_pO_2 range of 85% to 93% correlates closely with a partial pressure of oxygen (PaO_2) range of 50 to 80 mm Hg. When S_pO_2 is greater than 95%, correlation with PaO_2 is poor and hyperoxia may be present. Pulse oximetry is susceptible to motion artifact and readings may be difficult to obtain when poor perfusion or edematous conditions exist. Newly developed algorithms to improve detection during motion and in low flow states have been introduced. Both methemoglobin and carboxyhemoglobin are detected as oxyhemoglobin and will cause readings to be falsely elevated. High concentrations of fetal hemoglobin may also cause inaccurately high readings. Skin pigmentation has little effect on pulse oximetry.

The partial pressure of carbon dioxide can be measured fairly accurately and noninvasively in the exhaled gas from adults and children. The technology to measure end tidal carbon dioxide ($etCO_2$) is not as well adapted to newborn infants because of the high resistance caused by mainstream devices (eg, a sensor indwelling in the ventilator tubing). In sidestream $etCO_2$ devices, CO_2 becomes diluted in high-flow systems or by air entrainment when the patient tidal volume is less than the flow through sidestream systems or around an uncuffed endotracheal tube, as is often found in newborn infants.

Measurements of $etCO_2$ in exhaled gas (capnography) are based on selective absorption of infrared light at specific wavelengths. The presence of $etCO_2$ indicates that metabolic work (carbon dioxide production) and gas exchange (carbon dioxide excretion) are occurring. The presence of $etCO_2$ is also useful to confirm endotracheal tube position in the trachea with the caveat that no $etCO_2$ may be detected if pulmonary blood flow is absent (insufficient cardiac output). Because problems with metabolic function, gas exchange, and perfusion directly affect $etCO_2$ measurements, interpretation can be difficult. For example, a pneumothorax may cause hypercapnea because of impaired gas exchange and low carbon dioxide excretion if cardiac output is reduced by high intrathoracic pressure. Partial pressure of carbon dioxide and $etCO_2$ are often different, especially in patients with lung disease or metabolic abnormalities. A normal $etCO_2$-time waveform is depicted in Figure 4.

Figure 4: Capnography can display a waveform of the carbon dioxide concentration at the proximal end of an endotracheal tube or cannula tip located within a naris. The pattern of the end-tidal carbon dioxide (CO_2) can give insight into CO_2 movement during tidal volume breathing.



Frequently respiration is indirectly monitored through the leads used for monitoring cardiac waveforms during neonatal intensive care, especially for infants with respiratory distress or apnea. Changes in transthoracic electrical impedance with chest wall movement provide an electrical signal that is filtered from the relatively large baseline impedance of the chest wall and sent to a microprocessor, where the signal analyzes for the presence of respiratory efforts and rate of respirations, triggers alarms, and displays the respiratory waveform on the monitor. Artifacts are frequently introduced by improperly placed leads, poor contact of leads with the skin, and during patient movement. The changes in electrical impedance with chest wall movement can be small compared with the impedance of the thorax, which may make it difficult to detect shallow breathing. Changes in impedance caused by changes within organs or blood volume in the thorax may be counted as a breath when none occurs. Obstructive apnea, with continued chest wall movement, is not clearly detected by means of impedance monitoring.

Cerebral tissue oxygenation has been measured using near-infrared spectroscopy for several years in neonates during surgical repair of congenital heart disease. However, measurement of tissue oxygenation in cerebral and other regional tissue beds has not been widely introduced to neonatal intensive care because of the absence of "gold standards" for comparative research, the existence of marked intrapatient and interpatient variability in readings, and the lack of large clinical studies with meaningful outcomes. Nevertheless, near-infrared light (700-1,000 nm) passes easily through tissues and is readily absorbed by oxygen-binding chromophores such as hemoglobin and cytochrome aa3, the terminal enzyme in the mitochondrial electron transport chain. Measurement is based on differential absorption of near-infrared light at specific wavelengths by chromophores with and without bound oxygen. The measurement devices are noninvasive and portable. If the technical limitations of tissue oxygen measurement and outcomes research deficits can be overcome, assessment of absolute tissue oxygen status and other derived variables (such as blood volume, blood flow, vascular vasoreactivity) in the cerebrum, kidney, mesentery, liver, skeletal muscle, and other tissue beds may become possible.

References:

Adams JM, Weisman LE, Kim MS. Oxygen monitoring and therapy in the newborn. UpToDate.com. Accessed March 24, 2009, at: **http://www.uptodate.com/** [subscription required]

Dannevig I, Dale HC, Liestol K, Lindemann R. Blood pressure in the neonate: three non-invasive oscillometric pressure monitors compared with invasively measured blood pressure. ***Acta Paediatr.*** 2005;94:191-196

Hintz S, Wong RJ, Stevenson DK. Biomedical engineering aspect of neonatal monitoring. In: Martin RJ, Fanaroff AA, Walsh MC, eds. ***Fanaroff and Martin's Neonatal-Perinatal Medicine Disease of the Fetus and Newborn***. 8th ed. Philadelphia, Pa: Mosby Elsevier; 2006:609-625

Krauss B, Silvestri S, Falk JL, Walls RM, Torrey SB, Grayzel J. Carbon dioxide monitoring (capnography). UpToDate.com. Accessed March 24, 2009, at: **http://www.uptodate.com/** [subscription required]

Smith J, Elwell C. Near-infrared spectroscopy: shedding light on the injured brain. ***Internat Anesth Res Soc.*** 2009;108(4):1055-1057

Wolfberg AJ, Du Plessis AJ. Near-infrared spectroscopy in the fetus and neonate. ***Clin Perinatol.*** 2006;33:707-728

American Board of Pediatrics Content Specification(s):

Know the appropriate techniques to assess cardiovascular function in the fetus and newborn infant

Understand and be able to interpret the various techniques for assessing lung function including arterial blood gas measurements and noninvasive methods for estimation arterial oxygenation

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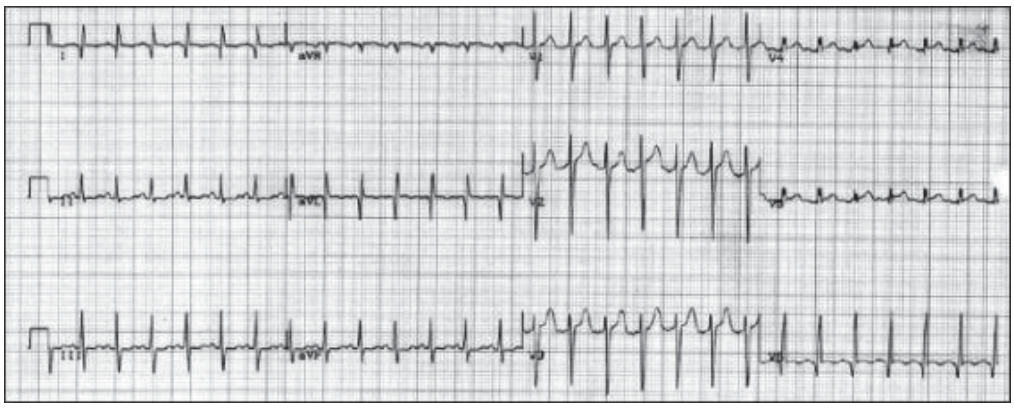
Question 10

A full-term male infant is discharged 2 days after birth following a benign prenatal and postnatal course. At 6 weeks of age, his parents take him to the emergency department because of worsening respiratory distress associated with a cough and nasal congestion. In addition to these symptoms, the family reports that over the past few days he has been crying excessively and becoming diaphoretic at the end of each nursing period.

The infant's vital signs are as follows: rectal temperature, 38°C (100.4°F); heart rate, 180 beats/minute; respiratory rate, 65 breaths per minute; blood pressure, 82/41 mm Hg; and oxygen saturation in the right arm, 99%. His physical examination reveals a pale, lethargic infant in moderate respiratory distress with diffuse expiratory wheezing. Although a murmur is not appreciated, his point of maximal cardiac impulse is laterally displaced and he has cool extremities. The rest of his examination findings are normal except for mild hepatomegaly. A rapid antigen test for respiratory syncytial virus has a positive result. A chest radiograph shows streaky perihilar markings; a 12-lead electrocardiogram is shown in **Figure 1**.

Figure 1: This electrocardiogram tracing is 50% of the standard size in amplitude. (From Epstein and Batra [2002])



Of the following, the MOST likely additional diagnostic finding in this infant is:

- ○ **A.** abnormal right ventricular function evident on echocardiography
- ✓ **B.** increased oxygen saturation in the pulmonary artery evident on catheterization
- ○ **C.** large ratio of pulmonary blood flow to systemic blood flow evident on catheterization
- ○ **D.** normal Doppler color flow evident on echocardiography
- ○ **E.** small cardiac size evident on chest radiography

Correct

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In addition to respiratory syncytial virus bronchiolitis, the infant in this vignette has signs of congestive heart failure. His electrocardiogram (EKG) reveals a lateral wall myocardial infarction. These findings point to an anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) with left-to-right shunting through the coronary circulation resulting in increased oxygen saturation in the pulmonary artery evident on catheterization.

Anomalous origin of the left coronary artery from the pulmonary artery is a rare vascular abnormality occurring in 1 in 300,000 live births, representing 0.25% to 0.5% of congenital heart defects. In this disorder, the left main coronary artery originates abnormally from the pulmonary artery. During development, abnormal division of the conotruncus or abnormal involution of the endothelial buds on the great vessels may lead to ALCAPA. Although ALCAPA is usually an isolated finding, additional congenital heart defects may be observed.

Four pathophysiologic stages of ALCAPA have been identified. Stage 1 occurs during the fetal and early neonatal period. With elevated pulmonary vascular resistance, the perfusion from the pulmonary artery to the anomalous left coronary artery is adequate and myocardial ischemia does not occur; while blood to the left coronary artery is under relatively normal pressure, it is slightly hypoxic because it is supplied by the poorly oxygenated pulmonary artery. The pulmonary vascular resistance decreases appropriately during the first few weeks after birth; therefore pulmonary arterial pressure is no longer sufficient to force blood into the anomalous left coronary artery. During this second stage, flow to the left coronary arterial system relies on collateral oxygenated flow from the right coronary arterial system. Patients who do not develop enough collateral flow will bypass stage 3 and progress rapidly to stage 4.

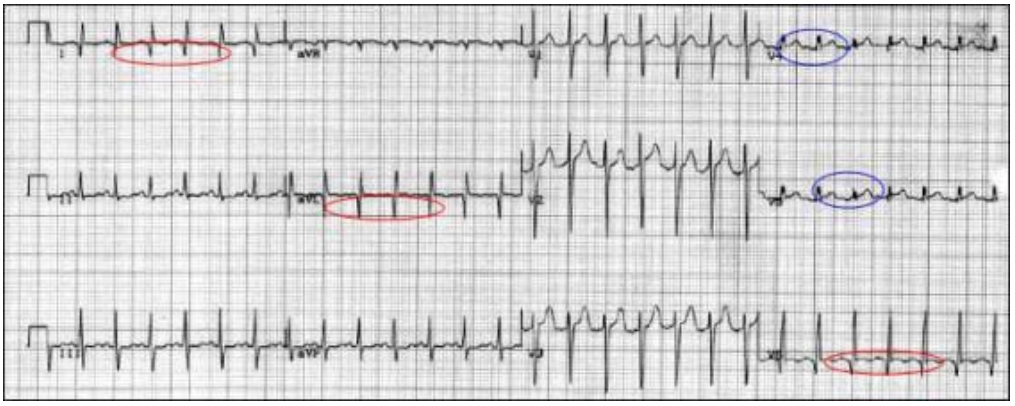
Infants who form a large collateral system between the right and left coronary circulation will advance to stage 3. During this uncommon stage, the collateral system may provide adequate perfusion, with patients remaining asymptomatic into adulthood. In stage 4, as the pulmonary vascular resistance decreases even further, the collateral from the right coronary arterial circulation preferentially flows into the low-resistance pulmonary artery instead of the left coronary arterial system which has a relatively higher resistance. This reversal of flow, also known as the pulmonary-coronary steal, leads to left ventricular myocardial ischemia and possibly infarction. The myocardial ischemia occurs in an anterolateral distribution, leading to global left ventricular dysfunction, following which, mitral valve regurgitation, left atrial dilation, and pulmonary venous congestion develop.

The clinical findings in patients with ALCAPA depend on the degree of pulmonary vascular resistance, presence or absence of collateral vessels between the right and left coronary arterial systems, and degree of myocardial ischemia and/or infarction. Symptoms usually appear at approximately 2 to 3 months of age. As the pulmonary vascular resistance decreases, an infant with ALCAPA will develop respiratory distress, feeding intolerance, and/or failure to thrive. Transient ischemia may lead to periods of pallor, paroxysmal crying, diaphoresis with feeding, and severe agitation. Infants with symptomatic ALCAPA develop signs of congestive heart failure, and may have a displaced apical impulse and/or a holosystolic murmur of mitral valvar regurgitation. Further increased myocardial oxygen demand from stressors such as a viral infection, may lead to myocardial infarction, as occurred in the infant in this vignette. If the myocardial injury is delayed because of a large collateral system, an older child or adult may present with chest pain upon exertion, dyspnea, arrhythmias, and/or syncope.

The chest radiograph of an infant with ALCAPA typically shows evidence of congestive heart failure with cardiomegaly and interstitial pulmonary edema. If the infant's disease progresses to an anterolateral myocardial infarction, the classic EKG findings show abnormal Q waves in leads I, aVL, V4, V5, and V6 (**Figure 2**).

Figure 2: This electrocardiogram is consistent with a lateral wall myocardial infarction. Red circles denote the Q waves evident in leads I, aVL, and V6. ST segment elevations are evident in leads V4 and V5.

Feedback



In addition, ST segment elevations are evident in leads V4 through V6. If the EKG findings are indicative of ALCAPA, echocardiography with Doppler color flow can confirm the diagnosis by showing blood flowing from the left coronary artery into the pulmonary artery. With a ventricular infarction, mitral valve insufficiency, decreased left ventricular function, and regional left ventricular wall motion abnormalities also can be observed on echocardiography.

If the diagnosis is not clear with echocardiography, cardiac catheterization with selective coronary cineangiography, will assist with the diagnosis by identifying the origin and course of the coronary arteries. Cardiac catheterization may also detect a small left-to-right shunt with a ratio of pulmonary blood to systemic blood flow ranging between 1 and 1.5. With low pulmonary vascular resistance, the flow in the ALCAPA is retrograde and enters the pulmonary artery; this well-oxygenated blood from the left coronary arterial circulation leads to a small increase in oxygen saturation in the pulmonary artery.

Thus, the infant in this vignette most likely will have cardiomegaly evident on chest radiography; normal right ventricular function, abnormal left ventricular function, and abnormal Doppler color flow evident on echocardiography; and a mildly increased ratio of pulmonary blood flow to systemic blood flow evident on catheterization. Cardiac catheterization showing an increase in oxygen saturation in the pulmonary artery as a result of flow from the well-oxygenated anomalous left coronary artery is the most likely additional finding in the infant in this vignette.

Surgical repair is the definitive treatment for ALCAPA. Currently, establishment of two coronary arteries is the preferred surgical approach. This is currently performed by anastomosis of the anomalous left coronary artery directly to the aorta. While this technique can be performed without difficulty in patients with ideal positioning of the anomalous vessel, some patients may require a more complicated procedure such as creation of an intrapulmonary aortocoronary tunnel.

Prognosis for patients with ALCAPA is dependent on prompt recognition and diagnosis as well as the degree and duration of preoperative mycocardial injury. Indeed, if cardiac dysfunction is severe, cardiac transplantation may be required. For symptomatic infants who remain undiagnosed, the mortality rate is higher than 90%.

References:

Epstein D, Batra AS. Index of suspicion: case 3. *Pediatr Rev*. 2002;23:393-400

Lee AC, Foster E, Yeghiazarians Y. Anomalous origin of the left coronary artery from the pulmonary artery: a case series and brief review. *Congenit Heart Dis*. 2006;1:11-15

Mancini MC, Rosen K, Mart C, Myers J. Anomalous left coronary artery from the pulmonary artery: surgical perspective. eMedicine.com Web sit. Accessed March 26, 2009, at: http://emedicine.medscape.com/article/905229-overview

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the pathophysiology (including genetics) of a neonate with an arterial vascular abnormality

03_Cardiovascular: Recognize the clinical features of a neonate with an arterial vascular

abnormality

03_Cardiovascular: Know the evaluation and management plans (medical and/or surgical) and associated potential complications or adverse effects of such management for a neonate with an arterial vascular abnormality

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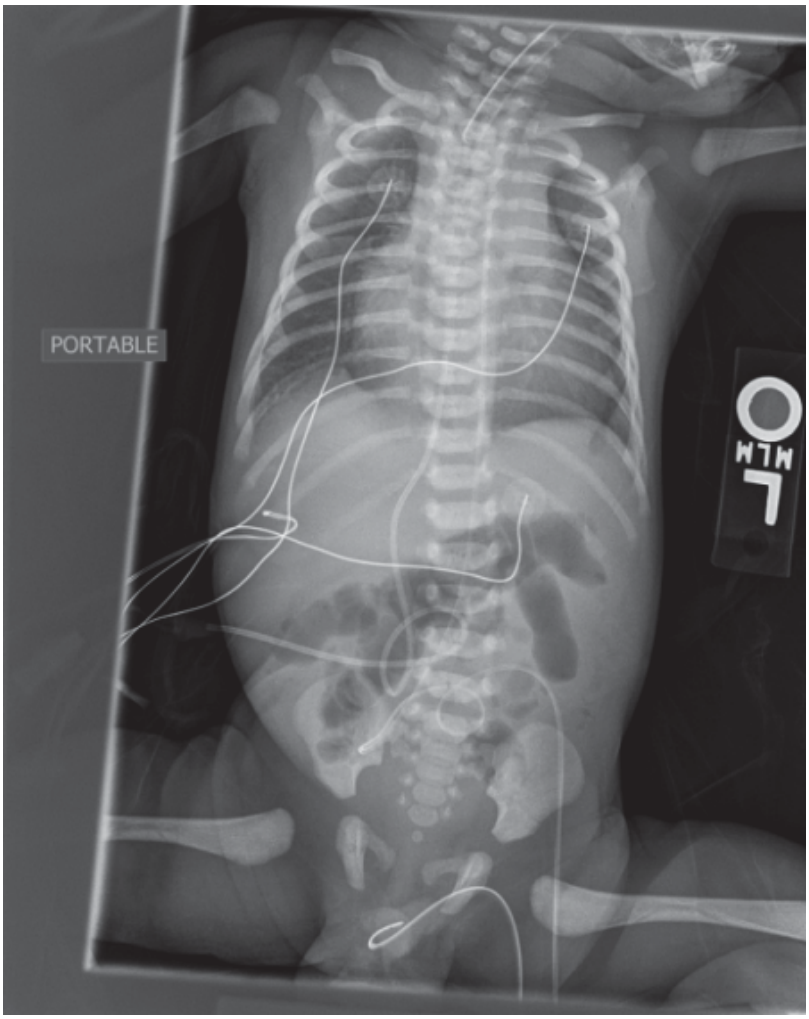
Question 9

A full-term newborn develops tachypnea and tachycardia 2 hours after birth. Cardiac examination reveals a systolic ejection murmur; pulses are equal and bounding in the upper and lower extremities. Echocardiography reveals normal cardiac anatomy and biventricular enlargement (**Figure 1**).

Figure 1: Radiograph of the chest demonstrating cardiomegaly



Of the following, the test MOST likely to lead to the diagnosis of this child's condition is:

- A. abdominal radiography
- B. cardiac computed tomography
- C. chest radiography
- D. cranial ultrasonography
- E. electrocardiography

Incorrect:

Correct Answer: D

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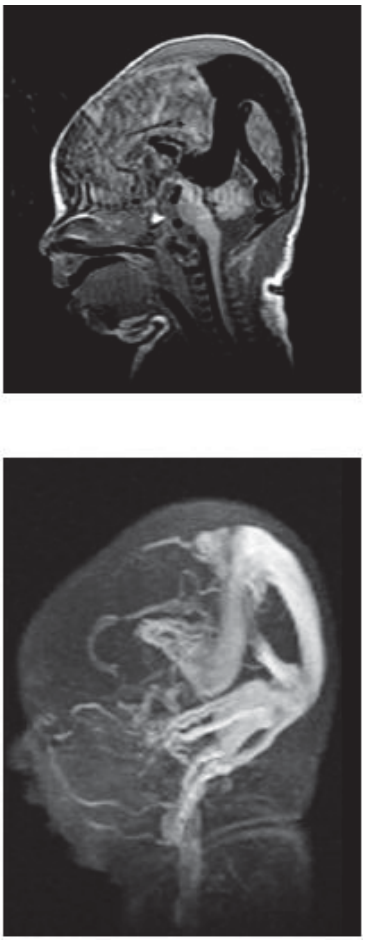
The infant in the vignette presents after birth with high-output heart failure. High-output cardiac failure occurs when demands for cardiac output exceed the ability of the cardiovascular and endocrine systems to respond. The major causes of congestive heart failure (CHF) presenting on the day of birth include severe anemia, arrhythmias, infection, severe atrioventricular valve insufficiency, and large systemic arteriovenous malformations (AVM). Of the tests listed, cranial ultrasonography would elucidate the most likely reason for early neonatal CHF in this infant (**Figure 2**).

Figure 2: Magnetic resonance imaging with and without contrast depicting large vein of Galen malformation



With an AVM, the systemic vascular resistance is decreased as blood from a high-pressure artery is shunted to a low-pressure vein. Total cardiac output is increased by the quantity of blood flowing through the AVM, resulting in increased heart rate, stroke volume, and total plasma volume. The systemic blood

Feedback

flow into the venous system results in increased volume work for both ventricles. The development of CHF depends on the magnitude of the shunt, determined by the flow resistance of the AVM. AVMs causing neonatal CHF are most commonly found in the intracranial and intrahepatic locations and should be considered in any newborn who has unexplained CHF, especially high-output heart failure. Intracranial AVMs most commonly connect the arterial flow to the vein of Galen, but they also can be seen in the cerebral hemispheres, thalamus and third ventricle, and choroid plexus.

On clinical examination, a continuous bruit usually can be heard over the vascular malformation. Otherwise, the clinical findings are similar to those of any infant with high-output CHF. The large volume of blood returning to the right side of the heart and then to the left after traversing the pulmonary bed can be associated with a third heart sound or gallop. Tachypnea results from increased pulmonary blood flow and abnormal diastolic filling of the overloaded ventricle. Widening of the pulse pressure may result from the low diastolic pressure in the arterial system caused by “run off” of the arterial flow. Prerenal azotemia, a consequence of the CHF, may occur. Seizures and other neurologic signs are very rare. The associated neuropathologic findings observed with vein of Galen malformations (VGM) are a direct result of the ischemic, hemorrhagic, and mass effects of the malformation. The ischemia is caused by the absence, or even the reversal, of diastolic cerebral blood flow. The high-output heart failure therefore may be potentiated by marked cardiac ischemia from decreased coronary blood flow. While VGMs can be diagnosed in utero with color Doppler studies and magnetic resonance imaging (MRI), most VGMs are diagnosed after birth.

Cranial ultrasonography often is used for the initial diagnostic evaluation when VGM is suspected. The vein is dilated like an aneurysm and presents as a large echolucent area in the region of the vein of Galen.

Magnetic resonance angiography (MRA) and MRI are extremely sensitive for confirming the diagnosis and for delineating the position, secondary effects (such as ischemia), and the anatomic particulars of the VGM. A few cases involving VGM have associated hydrocephalus or subarachnoid hemorrhage. VGMs only occasionally present with parenchymal or intracranial hemorrhage in the neonatal period. If intracranial hemorrhage is present, computed tomography may demonstrate a dilated, blood-filled third ventricle with normal-appearing lateral ventricles suggestive of VGM as the source of an intraventricular hemorrhage. Identifying the course of arterial feeders and the size and location of the venous malformation is critical for determining the best intervention. The most common feeding arterial vessels are the posterior choroidal artery, anterior cerebral artery, middle cerebral artery, anterior choroidal artery, and posterior cerebral artery.

The infant in this vignette had a normal cardiac anatomy on echocardiography. Although congenital heart defects are the most common cause of pediatric heart failure, the resultant CHF most often presents after the first day after birth. Structural defects impose an excessive workload on the cardiac muscle. Some cardiac lesions may impose an excessive volume load on the left ventricle, as seen with a large ventriculoseptal defect (VSD); infants with this condition usually present weeks to months after birth. Other cardiac defects may impose an excessive pressure load on the heart, as seen in critical aortic stenosis; these patients usually present earlier, often within the first week after birth. Occasionally, CHF results from a process with impaired myocardial contraction as seen in an infiltrative disease (Pompe disease), or an infectious process (echoviruses). AVMs may occur in other locations, and ultrasound, Doppler flow examination, and MRI or MRA may help in their diagnosis as well. For the newborn in the vignette, abdominal or chest radiography would not reveal the diagnosis, nor would cardiac computed tomography.

Electrocardiography likely would not have findings specific to the diagnosis in high-output CHF. Cardiac failure may result from the myocardial dysfunction or infarction associated with anomalies such as an aberrant left coronary artery. Low-output CHF and q waves and an infarction pattern may be noted on electrocardiography.

References:

Volpe JJ. Intracranial mass lesions: Brain tumors and vein of Galen malformations. In: *Neurology of the Newborn*. 5th ed. Philadelphia, Pa: Saunders Elsevier; 2008:989

Related readings from NeoReviews.org

Fricker FJ. Hypoplastic left heart syndrome: diagnosis and early management. *Neoreviews.* 2008;9:e253-e259. Available at: http://neoreviews.aappublications.org/cgi/content/full/9/6/e253?fulltext [subscription required]. Accessed November 16, 2009

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the pathophysiology (including genetics) of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Recognize the clinical features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion

03_Cardiovascular: Know the evaluation and management plans (medical and/or surgical) and associated potential complications or adverse effects of such management for a neonate with a left-to-right shunt lesion

15_Neurology: Know the clinical features and evaluation, management, complications of management, and outcome of intracranial arteriovenous malformations

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Question 5

You receive a phone call from an emergency room physician at a rural hospital about a potential transfer of an infant. The physician describes the infant as a 6-week old female infant in severe respiratory distress. She has an oxygen saturation of 100% in room air, bilateral diffuse crackles, a holosystolic murmur localized to the left lower sternal border, a loud second heart sound, and normal peripheral pulses. Chest radiography illustrates a large heart with increased pulmonary vascular markings. The infant's electrocardiogram shows bilateral ventricular hypertrophy with a normal QRS axis.

Of the following, this infant's MOST likely diagnosis is:

- **A.** coarctation of aorta
- **B.** tetralogy of Fallot with severe pulmonary valvar stenosis
- **C.** tricuspid atresia with small ventricular septal defect
- **D.** truncus arteriosus
- **E.** ventricular septal defect

Incorrect:

Correct Answer: E

Congenital heart defects can be characterized into three overall groups:

- *Left-to-right shunt lesion*, including atrial septal defect, ventricular septal defect (VSD), patent ductus arteriosus, endocardial cushion defect, and truncus arteriosus
- *Cyanotic heart disease*, which can be further characterized by degree of pulmonary blood flow:
  - Decreased pulmonary blood flow, including tetralogy of Fallot (TOF), tricuspid valve abnormalities, hypoplastic right heart syndrome, pulmonary atresia with intact ventricular septum, valvar pulmonary stenosis (PS), and Ebstein anomaly
  - Increased pulmonary blood flow, including transposition of great arteries, truncus arteriosus, total anomalous pulmonary venous return, pulmonary vascular obstructive disease
- *Left ventricular outflow obstruction*, including coarctation of aorta (COA), hypoplastic

left heart syndrome, and valvar aortic stenosis

The infant in this vignette has clinical, radiographic, and electrocardiographic findings most consistent with a left-to-right shunt lesion and the diagnosis of VSD. A VSD is the most common congenital heart defect, occurring in 20% of individuals with structural heart disease. While infants with a restrictive septal defect (<0.19 inches [0.5 cm^2]) develop a small left-to-right shunt and normal right ventricular output, defects larger than 0.39 inches (1 cm^2) exhibit a large left-to-right shunt when the pulmonary vascular resistance is significantly lower than the systemic vascular resistance. Because this difference in resistance typically occurs by 4 to 12 weeks of age, most infants with a large VSD present with clinical symptoms within this time frame. Whereas 75% of restrictive VSDs close spontaneously by age 2 years, large VSDs remain open. With persistently increased pulmonary blood flow, the infant with a large VSD develops either hyperkinetic pulmonary arterial hypertension or pulmonary vascular obstructive disease. The associated increase in pulmonary artery vascular resistance increases right ventricular pressure leading to right ventricular hypertrophy. If the pulmonary vascular resistance increases so that it is similar to the systemic vascular resistance, the septal shunt can become bidirectional and potentially reverse to a right-to-left shunt with associated cyanosis.

Physical examination findings of infants with a VSD correlate with the size of the VSD, the magnitude of the left-to-right shunt, and the degree of right ventricular and pulmonary hypertension. An infant who has a small VSD with a small shunt and normal or slightly elevated right-sided pressures will have a holosystolic murmur with normal precordial impulses and normal heart sounds. The physical examination of an infant with a moderate or large defect will have an increased right ventricular impulse, a louder second heart sound (S2), and a holosytolic murmur. If the pulmonary blood flow is more than twice the systemic blood flow, a mid-diastolic mitral flow murmur also may be present. Additional clinical findings in these infants include tachypnea, diaphoresis, poor feeding ability, and/or failure to thrive. In addition, infants may have signs of congestive heart failure, hepatomegaly, pulmonary edema, and cyanosis with crying. The chest radiograph may appear normal if the defect is small or may reveal cardiomegaly, increased pulmonary vasculature, and pulmonary edema if the defect is moderate to large in size. Similarly, the electrocardiographic findings correlate with the size of the defect: normal or left ventricular hypertrophy associated with a small defect and biventricular hypertrophy with a large defect.

The clinical presentation of an infant with a COA depends on the severity of the obstruction and the presence of any associated cardiac abnormalities. With closure of the patent ductus arteriosus, the effect of the obstruction manifests itself. If the COA is severe, the infant typically presents within the first few weeks after birth with tachypnea, poor feeding, and congestive heart failure. These findings may progress to cardiogenic shock. Discrepant perfusion, blood pressure, and cyanosis may be apparent between the right arm and either leg. A systolic ejection murmur is audible over the base of the heart and in the left axilla and interscapular region, with radiation to back. Electrocardiographic and radiographic findings may demonstrate left ventricular hypertrophy and cardiomegaly, respectively. The infant described in this vignette is unlikely to have a COA because there is no evidence of cardiogenic shock or differential blood pressure in the upper and lower extremities.

Feedback

The cardiac defect in an infant with TOF consists of an overriding aorta, a subaortic large VSD, right ventricular hypertrophy, and varying degrees of PS. TOF is the most common cardiac defect presenting beyond infancy. Infants with moderate or severe PS have cyanosis with ductal-dependent pulmonary blood flow. In contrast, infants with mild PS are acyanotic and develop pulmonary artery hypertension and heart failure, symptoms similar to the infant in this vignette. The intensity of the infant's systolic murmur correlates indirectly with the degree of the PS; the smaller the degree of PS, the louder the murmur, corresponding to a greater amount of blood flow through the pulmonary valve. Because of the anterior position of the aorta, the S2 is often single and loud. Although infants with TOF and severe PS have a normal-sized heart, the chest radiograph may reveal a "boot-shaped" heart as a result of the right ventricular enlargement, causing lifting of the ventricular apex. Electrocardiographic findings may demonstrate right axis deviation and/or right ventricular hypertrophy. In contrast to the characteristics of a left-to-right shunt described in the infant in this vignette, an infant with TOF has findings consistent with a right-to-left shunt. Indeed, chest radiography shows decreased pulmonary vascularity and a right-sided aortic arch in approximately 20% of infants with TOF.

Tricuspid atresia (TA) is characterized by an obligatory right-to-left shunt at the atrial level and a hypoplastic right ventricle; there is no direct communication between the right atrium and right ventricle. Most infants with TA also have an associated VSD, creating a left-to-right shunt at the ventricular level to augment pulmonary blood flow. As a result of

decreased pulmonary blood flow, infants have cyanosis. Infants with a small VSD will have a limited right ventricular outflow, increasing the degree of cyanosis. If the VSD is large, there will be sufficient intrauterine flow to the right ventricle and potentially a normal-sized right ventricular chamber. Infants with TA also may have varying degrees of PS, which alter clinical manifestations. Chest radiography shows decreased pulmonary blood flow. Because of the small right ventricle, the electrocardiogram reveals a left superior axis. The infant in this vignette is unlikely to have TA because she does not demonstrate findings consistent with decreased pulmonary blood flow.

Infants with truncus arteriosus have a common arterial trunk that supplies the coronary, pulmonary, and systemic circulations; the main pulmonary artery usually arises from the truncus before dividing into two branches. A large VSD is always present, creating complete interventricular mixing. A systolic ejection murmur is audible with a single S2. If the single semilunar valve is regurgitant, a diastolic murmur also may be audible. Infants have bounding peripheral pulses because of the diastolic runoff into the pulmonary circulation. The infant's level of hypoxemia correlates with the degree of pulmonary vascular resistance; severe cyanosis is present in infants with elevated pulmonary vascular resistance. Chest radiography shows increased heart size and increased pulmonary vascular markings as well as an increased likelihood of a right-sided aortic arch. Electrocardiographic findings in infants with truncus arteriosus are nonspecific. The chromosomal 22q11 deletion can be identified in approximately one third of patients with truncus arteriosus. Although the infant in this vignette does have some findings consistent with truncus arteriosus (ie, single S2 and increased pulmonary vascular markings on chest radiography), the absence of cyanosis excludes this diagnosis.

References:

Driscoll DJ. Left-to-right shunt lesions. *Pediatr Clin North Am*. 1999;46:355-368

Fedderly RT. Left ventricular outflow obstruction. *Pediatr Clin North Am*. 1999;46:369-384

Geggel RL, Armsby LB. Cardiac causes of cyanosis in the newborn. UptoDate.com Web site. Available at: www.uptodateonline.com [subscription required]. Accessed April 9, 2007.

Grifka RG. Cyanotic congenital heart disease with increased pulmonary blood flow. *Pediatr Clin North Am.* 1999;46:405-425

Keane JF, Fyler DC, Lock JE, eds. *Nadas' Pediatric Cardiology*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 2006

Maghsood S, Das BB. Index of suspicion in the nursery. *NeoReviews*. 2007;8:e133-135. Available at: http://neoreviews.aappublications.org/cgi/content/full/8/3/e133?fulltext [subscription required]. Accessed November 16, 2009

Waldman JD, Wernly JA. Cyanotic congenital heart disease with decreased pulmonary blood flow in children. *Pediatr Clin North Am*. 1999;46:385-404

Related readings from Neoreviews.org

Scholz TD, Segar JL. Cardiac metabolism in the fetus and newborn. Neoreviews. 2008;9:e109-e118. Available at: http://neoreviews.aappublications.org/cgi/content/full/9/3/e109?fulltext [subscription required]. Accessed November 16, 2009

Kaplan JH, Ades AM, Rychik J. Effect of prenatal diagnosis on outcome in patients with congenital heart disease. NeoReviews. 2005;6:e326-e331. Available at: http://neoreviews.aappublications.org/cgi/content/full/6/7/e326?fulltext [subscription required]. Accessed November 16, 2009

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Recognize the clinical features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion

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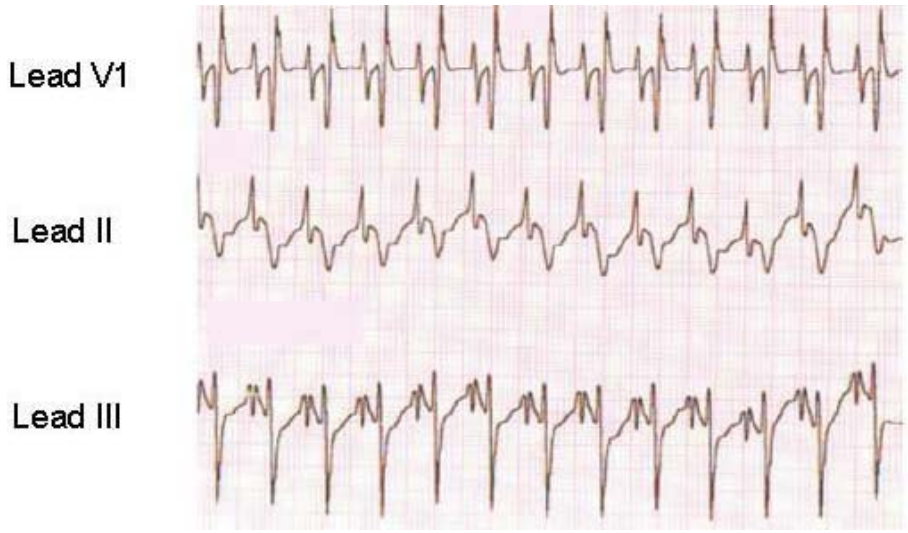
Question 3

While examining a newborn in the nursery, a pediatrician discovers severe tachycardia with a rapid onset and resolution. When the infant's tachycardia recurs, an electrocardiogram is obtained (**Figure 1**).

Figure 1: Electrocardiogram showing a narrow complex QRS tachycardia. (From Killen and Fish [2008].)



Of the following, the MOST likely mechanism for this abnormal rhythm is:

- A. atrial ectopic tachycardia
- B. atrioventricular nodal re-entry tachycardia
- C. orthodromic atrioventricular reciprocating tachycardia
- D. permanent junctional reciprocating tachycardia
- E. sinoatrial nodal re-entry tachycardia

Incorrect:

Correct Answer: C

The normal cardiac conduction wave originates in the sinus node and travels antegrade through the atria to the atrioventricular (AV) node. The impulse is delayed at the AV node and then propagates through the His bundle into the right and left bundle branches.

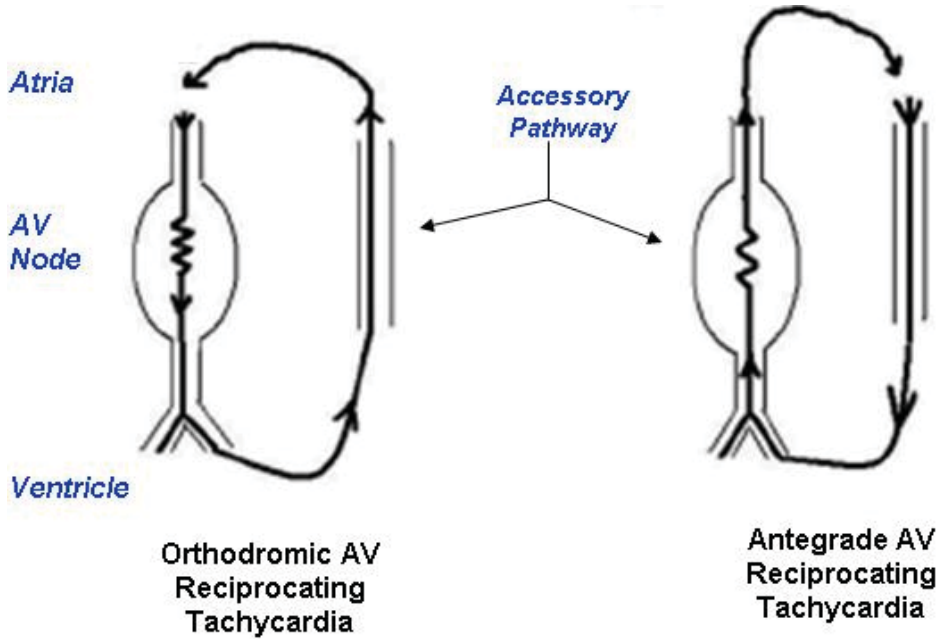
Supraventricular tachycardia (SVT) is a tachyarrhythmia that originates proximal to the bundle of His, arising from either the atrium, AV junction, or an accessory pathway. It is the most common symptomatic pediatric arrhythmia and occurs in 1 in 200 to 250 neonates. The electrocardiographic findings of the infant in this vignette are most consistent with SVT because of the regular R-R intervals, the rapid ventricular rate, and the displaced P waves. Because the QRS wave is narrow, ventricular tachycardia is not a possible diagnosis. In contrast to sinus tachycardia, infants with SVT have a heart rate greater than 230 beats per minute and typically range between 260 and 300 beats per minute; an abnormal P-wave axis, atypical location of the P-wave relative to the QRS wave, or an absent P-wave; a rapid onset and termination of the tachycardia; a consistent rate; and/or the potential to respond to vagal maneuvers.

Atrioventricular re-entry tachycardia (AVRT) is the most common type of SVT, representing approximately 70% of SVT rhythms. Infants can have orthodromic or antegrade (also known as *antidromic*) AV reciprocating tachycardia. In either type, there is a re-entry (or reciprocating) circuit between the atria and ventricles. The term *re-entry* describes a single stimulus or excitation wave that can return to reactivate the same tissue from which it came. Because cardiomyocytes require a refractory period after initial depolarization, a second pathway is needed to produce severe tachycardia. Furthermore, the excitation must be sufficiently delayed to enable recovery of the original tissue. Finally, the retrograde pathway must be protected against the initial depolarization. Thus, three prerequisites are required for a re-entry pattern:

- Dual pathways
- Conduction delay
- Unidirectional block

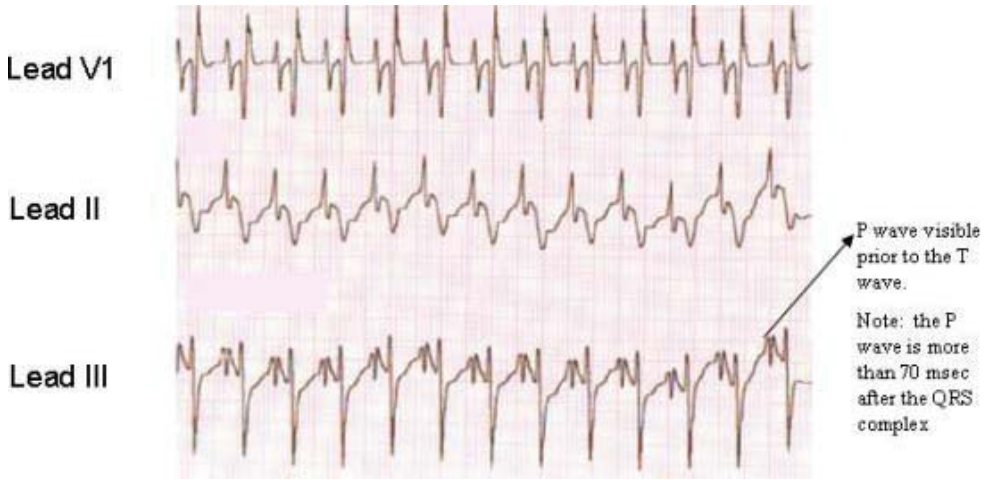
In orthodromic AVRT, the AV node forms the antegrade pathway, and an accessory connection between the ventricle and atria provides retrograde conduction of impulses (**Figure 2**).

Figure 2: Two mechanisms of atrioventricular re-entry tachycardia are shown: orthodromic and antegrade atrioventricular (AV) reciprocating tachycardia. In the orthodromic type, the AV node pathway is antegrade with a retrograde accessory pathway while the antegrade circuit consists of an antegrade accessory pathway associated with a retrograde pathway through the AV node. (From Singh and colleagues [2005].)



In contrast to the orthodromic mechanism, neonates with the less common antegrade AVRT have an accessory connection that serves as the antegrade pathway, and the AV node is the accessory pathway (Figure 2). While the electrocardiographic findings in infants with the orthodromic type of SVT reveal a narrow QRS wave, the antegrade type is more likely to be associated with a wide QRS complex. In addition to a narrow QRS complex, this infant's electrocardiogram also reveals a P wave that is more than 70 msec after the QRS wave and thus, located within the ST segment, typical of AVRT rhythms (**Figure 3**).

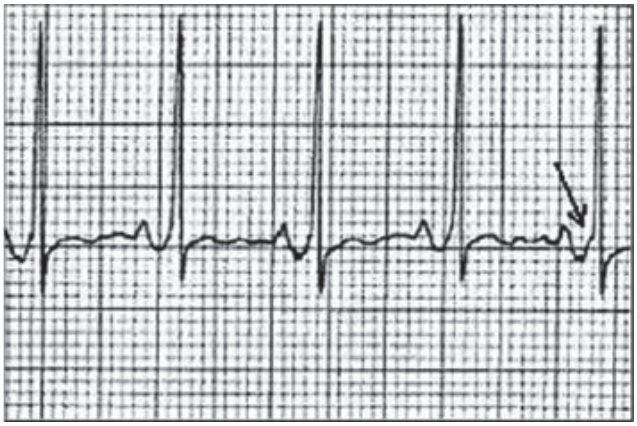
Figure 3: This rhythm reveals supraventricular tachycardia resulting from orthodromic atrioventricular re-entry. In this electrocardiogram, the QRS complex is normal and the atrial depolarization follows the preceding QRS wave by more than 70 msec. (From Killen and Fish [2008].)



Because of the higher incidence of this condition and the associated electrocardiographic findings, orthodromic AVRT is the most likely mechanism to explain the electrocardiogram of the infant in this vignette.

Some infants with AVRT may exhibit Wolff-Parkinson-White (WPW) syndrome. Infants with this rhythm lack an AV nodal delay after the impulse is conducted through the accessory pathway. Thus in the resulting dual ventricular conduction, part of the ventricular myocardium is initially depolarized by the accessory pathway and the remaining ventricular myocardium is depolarized through the normal pathway. In contrast to most of the SVT rhythms that reveal normal electrocardiographic findings between tachycardic events, infants with WPW syndrome will demonstrate specific rhythm abnormalities while the heart rate is normal; these findings include a short PR interval and a slurred upstroke of the QRS complex, known as the delta wave (**Figure 4**). This delta wave results from fusion of distinct ventricular complexes.

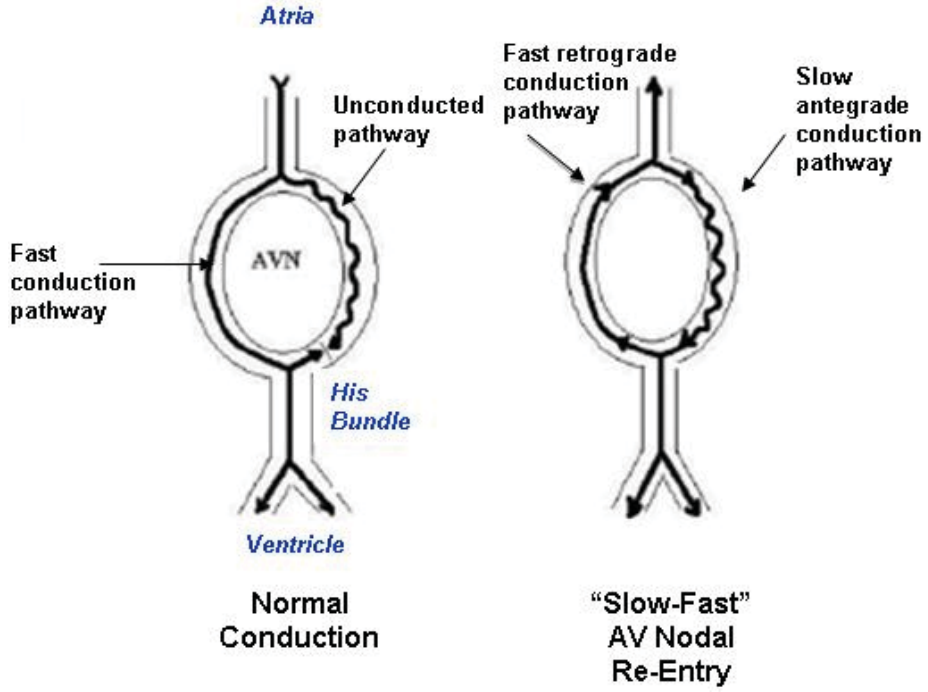
Figure 4: This electrocardiogram is consistent with Wolff-Parkinson-White syndrome characterized by a short PR interval and a delta wave (arrow). (From Singh and colleagues [2005].)



Atrial tachycardia is responsible for 14% of SVT rhythms and includes both atrial flutter and *atrial ectopic tachycardia* (AET). While atrial flutter results from a re-entry pathway within the atrial muscle, AET results from an ectopic atrial focus with abnormal automaticity. The corresponding electrocardiogram of AET demonstrates an abnormal P-wave axis with rates up to 300 beats per minute. The AV node is not a component of either types of atrial tachycardia, and ventricular rates depend on how often the atrial impulses are conducted through the AV node; conduction may be 1:1, with the ventricular rate being as high as the atrial rate or, more likely, conduction is lower because of limited atrial beats conducting through the AV node.

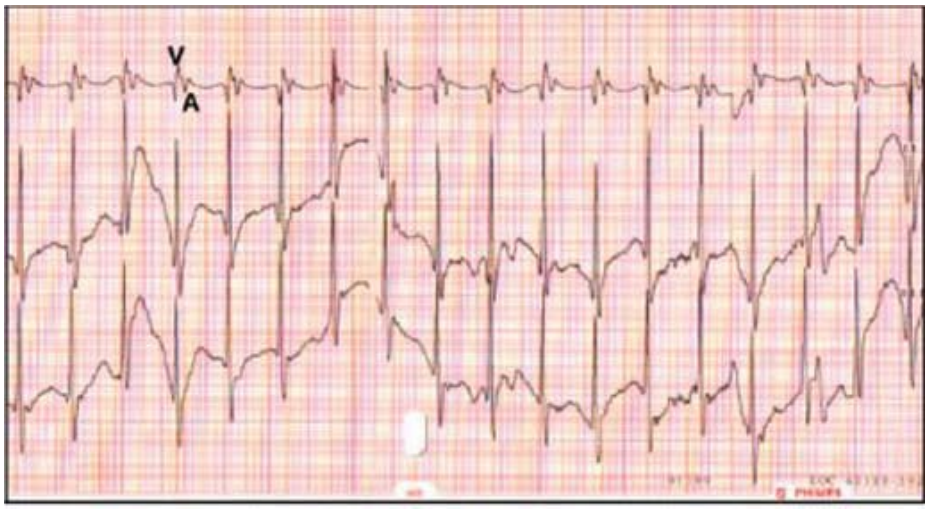
Atrioventricular nodal re-entry tachycardia (AVNRT) is another type of SVT, representing about 13% of SVTs. Similar to AVRT, two pathways exist in AVNRT, but both are located within or near the AV node. The antegrade pathway typically moves slowly across the AV node to stimulate the ventricles and has a short refractory period, whereas the retrograde pathway has a faster conduction with a longer refractory time, often termed *slow-fast* AVNRT (**Figure 5**).

Figure 5: Comparison of normal conduction with atrioventricular nodal re-entry tachycardia pathway. In this type of supraventricular tachycardia, there are two conduction pathways but both are located within or near the atrioventricular (AV) node. The antegrade pathway typically moves slowly across the AV node to stimulate the ventricles, and the retrograde pathway has a faster conduction, often termed "slow-fast" AVNRT. (From Singh and colleagues [2005].)



The corresponding electrocardiogram reveals a QRS complex followed by a T wave; the P wave may be concealed within the QRS complex but more commonly, the P wave is apparent immediately (ie, within 70 msec) after the complex (**Figure 6**).

Figure 6: This rhythm is attributable to atrioventricular (AV) nodal re-entry tachycardia. In this rhythm, the P wave (designated as "A") is apparent immediately (ie, within 70 msec) after the QRS complex (designated as "V"). (From Killen and Fish [2008].)

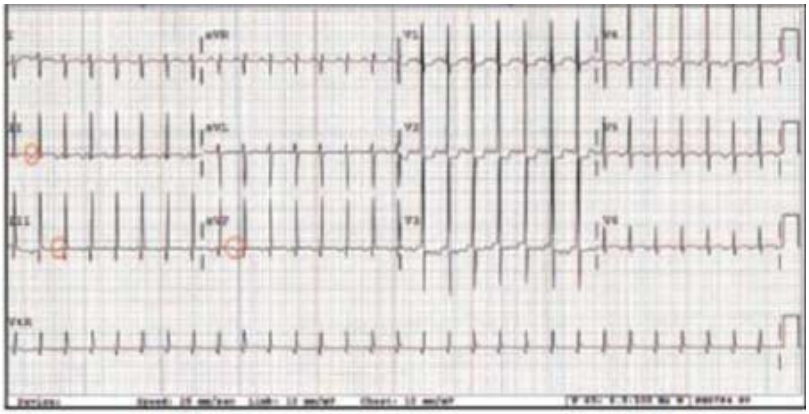


This is in contrast to the reciprocating tachycardias discussed earlier, in which the accessory pathway traverses a longer circuit and the P wave, if visible, is more than 70 msec after the QRS complex. Atypical AVNRT exhibits a slower retrograde conduction compared with the antegrade pathway (ie, fast-slow) whereby the P wave becomes visible as an inverted complex after the QRS wave.

Permanent junctional reciprocating tachycardia is an uncommon type of SVT, accounting for approximately 1% of cases. Most of these tachycardias result from an orthodromic AVRT involving a posterior-septal accessory connection with slow conduction that enables recovery of the AV node. Electrocardiographic findings reveal a variable rate, a dramatically prolonged interval between the QRS and the inverted P wave, and a normal or short PR interval (**Figure 7**). As the name suggests, this form of SVT is very difficult to treat.

Figure 7: This supraventricular tachycardia is the result of permanent junctional

reciprocating tachycardia evident by an inverted P wave (red circles) in leads II, III, and AVF with a short PR interval. (From Killen and Fish [2008].)



Sinoatrial (SA) nodal re-entry tachycardia is a rare form of SVT, accounting for fewer than 5% of cases. In this rhythm, the re-entry is seen within the sinus node or perinodal tissue. It produces electrocardiographic findings similar to those seen in sinus tachycardia with a P wave axis of approximately 60°. However, unlike sinus tachycardia, SA nodal re-entry begins abruptly and has minimal rate variation.

A comparison of the electrocardiographic features of the different types of SVT is shown in the **Table**.

Table: Electrocardiographic Features of Supraventricular Tachycardia (SVT)*

Type of SVT	Baseline EKG	Onset and Termination	Atrial Rate	P Wave Axis
Atrial ectopic tachycardia	Normal	Gradual	Variable	Ectopic Atypical appearance
AV nodal re-entry tachycardia	Normal	Abrupt	Fixed	P waves not typically seen Retrograde P wave immediately after QRS complex, if seen
Orthodromic AV reciprocating tachycardia	May have WPW	Abrupt	Fixed	Retrograde P wave may be seen more than 70 msec after QRS complex
Antegrade AV reciprocating tachycardia	May have WPW	Abrupt	Fixed	Retrograde Inverted P wave may be seen more than 70 msec after QRS complex
Permanent junctional reciprocating tachycardia	Usually without period of normalcy	Incessant	Fixed	Retrograde Inverted P wave usually > 70 msec after QRS complex and may seem to be before the QRS wave
SA nodal re-entry	Normal	Abrupt	Fixed	Normal appearance and timing of P wave

AV = atrioventricular; EKG = electrocardiogram; SA = sinoatrial; WPW = Wolff-Parkinson-White syndrome.
* Adapted from Keane and colleagues (2006) and Singh and colleagues (2005)

References:

Keane JF, Fyler DC, Lock JE, eds. *Nadas' Pediatric Cardiology*. 2nd ed. Philadelphia, Pa: WB Saunders Co; 2006

Related readings from Neoreviews.org
Killen SAS, Fish FA. Fetal and neonatal arrhythmias. *NeoReviews*. 2008;9:e242-252. Available at: http://neoreviews.aappublications.org/cgi/content/full/9/6/e242?fulltext [subscription required]. Accessed November 16, 1009

Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia. *NeoReviews*. 2005;6:e339-350. Available at: http://neoreviews.aappublications.org/cgi/content/full/6/7/e339?fulltext [subscription required]. Accessed November 16, 1009

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Differentiate normal from common abnormal electrocardiographic patterns and rhythms in the fetus and newborn infant

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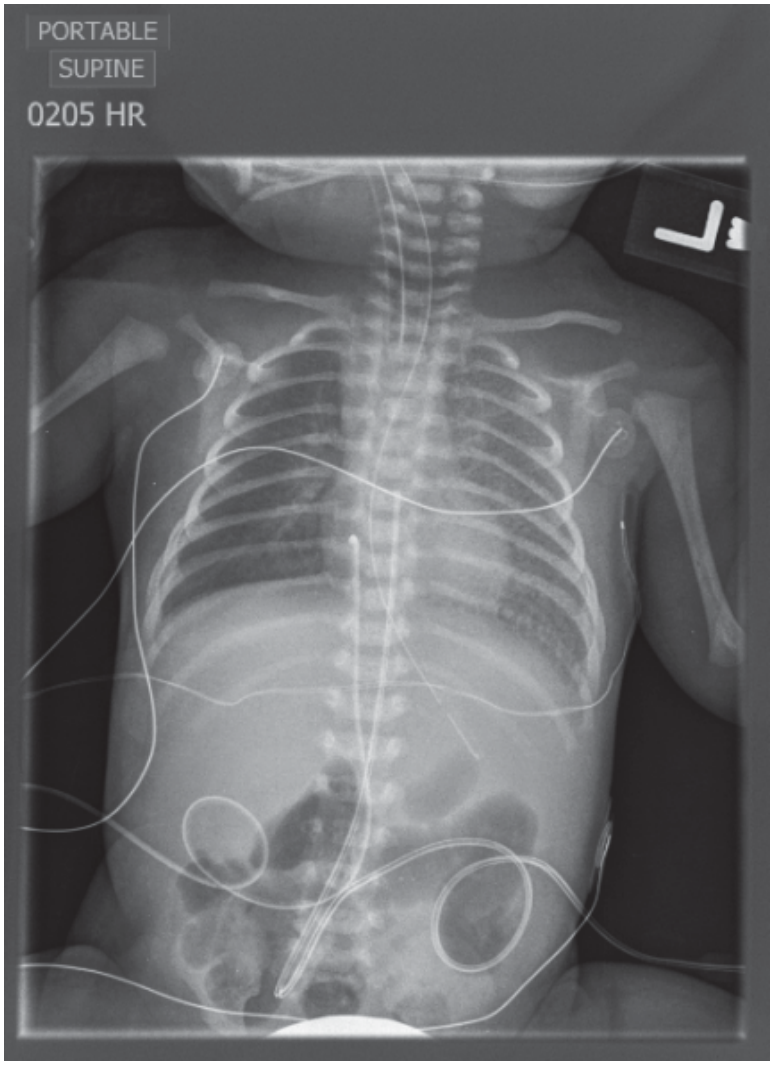
Question 2

A full-term male newborn presents 6 hours after birth with moderate respiratory distress and cyanosis. The infant is treated with positive pressure ventilation and oxygen. Umbilical catheters are placed; the partial pressure of oxygen (PO_2) from the umbilical artery catheter is 80 mm Hg and the PO_2 from the umbilical venous catheter is 200 mm Hg. A chest radiograph is obtained (**Figure 1**).

Figure 1: Radiograph of the chest



Of the following, the MOST likely diagnosis in this infant is:

- A. hypoplastic left heart syndrome
- B. pulmonary hypertension
- C. total anomalous pulmonary venous return
- D. transposition of the great arteries
- E. truncus arteriosus

Correct

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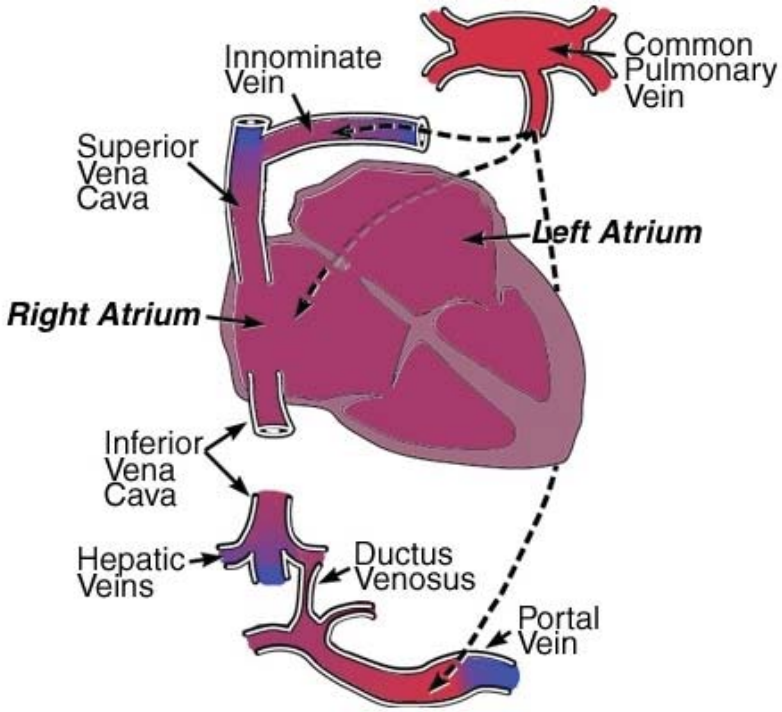
The umbilical venous catheter blood may have higher oxygen saturations than the umbilical artery catheter blood in infants with infradiaphragmatic total anomalous pulmonary venous return (TAPVR; **Figure 2**).

Figure 2: Graphic representation of the three types of total anomalous pulmonary venous return. (Courtesy of the Media Lab at Doernbecher Children's Hospital, Portland, Ore).



In a patient with a large inferior vena caval connection, the highest oxygenated blood will be returning from the lungs and emptying into the inferior vena cava where the umbilical venous catheter is positioned. A partial pressure of oxygen (PO_2) of 200 mm Hg may lead the clinician to believe that the cause of hypoxemia is noncardiac in origin. The hyperoxia test is thought to be useful in differentiating cardiac from pulmonary sources of hypoxemia based on the premise that supplemental oxygen does not increase the PO_2 value in the presence of an intracardiac shunt as much as it does in isolated pulmonary disease.

The hyperoxia test is performed by placing the neonate in 100% oxygen for 10 minutes and sampling the right radial arterial blood to distinguish cyanotic from acyanotic cardiac lesions and pulmonary disease. The preductal PO_2 while breathing 100% oxygen concentration

Feedback

rarely exceeds 150 mm Hg in cyanotic cardiac lesions. The level of PO_2 may be helpful in distinguishing among types of cyanotic heart disease as well. With transposition of the great arteries and severe right ventricular outflow tract obstructions (pulmonary atresia, tetralogy of Fallot, tricuspid atresia) the PO_2 values are often less than 60 mm Hg. In lesions that display intracardiac mixing (truncus arteriosus, TAPVR, and hypoplastic left heart syndrome), PO_2 values may be 75 to 150 mm Hg. In some pulmonary conditions, the PO_2 may be less than 150 mm Hg (persistent pulmonary hypertension with severe right-to-left shunting), as well as in lung disease with significant ventilation-perfusion mismatch (meconium aspiration syndrome, pneumonia).

As a result of high resistance in the hepatic microcirculation, infracardiac TAPVR usually presents during the first days after birth with signs of obstructed pulmonary venous return.

Total anomalous pulmonary venous return is seen in approximately 1.5% of infants with cardiovascular malformations. This lesion results from embryonic failure of connection between the fetal pulmonary venous sinus and the left atrium. The pulmonary veins may take one of several pathways to establish an anomalous connection that delivers pulmonary venous blood to the right side of the heart instead of the left. A patent foramen ovale or an atrial septal defect provides a right-to-left shunt so that an admixture of oxygenated and deoxygenated blood eventually reaches the left side of the heart. Patients with TAPVR show oxygen desaturation to varying amounts depending on the anomalous pathway, atrial mixing, and pulmonary congestion.

Depending on the type of venous connection, TAPVR may be either obstructed or nonobstructed. Seventy-five percent of patients with TAPVR have a widely patent connecting vein with no obstruction of venous return; the remaining 25%, however, have narrowed and obstructed pulmonary venous blood flow.

Total anomalous pulmonary venous connection is classified according to the site at which the connection occurs (supracardiac, cardiac, infracardiac, or a mixture of two or more types). It is estimated that more than 50% of TAPVR cases are supracardiac, which involve connections to the right or left superior vena cava, azygous vein, or to the left innominate vein. Cardiac connections involve the coronary sinus or right atrium. Infracardiac connections occur below the diaphragm (the portal venous system, ductus venosus, or the inferior vena cava).

When the connection is infradiaphragmatic, some degree of obstruction to blood flow is almost always present. In infracardiac TAPVR, the vein is compressed with swallowing and diaphragmatic contraction because the connection traverses the diaphragm through the esophageal hiatus. Obstruction also occurs with connection to the portal vein; the high resistance of the parenchymal circulation in the liver generates a barrier to blood flow for the pulmonary vein.

An infant with obstructed TAPVR will develop early signs and symptoms of marked cyanosis, tachypnea, hypoxemia, and acidosis, as seen in the vignette. A chest radiograph may reveal a small heart size and interstitial edema (Figure 1). With echocardiography, the connections of all the pulmonary veins may be determined.

References:

Enriques AM, McKay R, Arnold RM, Wilkinson JL. Misleading hyperoxia test. *Arch Dis Child.* 1986;61(6):604-606

Geva T, Van Praagh S. Anomalies of the pulmonary veins. In: *Moss and Adams' Heart Disease in Infants, Children, and Adolescents: Including the Fetus and Young Adult.* 7th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2008

Jones RW, Baumer JH, Joseph MC, Shinebourne EA. Arterial oxygen tension and response to oxygen breathing in differential diagnosis of congenital heart disease in infancy. *Arch Dis Child.* 1976;51(9):667-673

*Related readings from Neoreviews.org*Kaplan JH, Ades AM, Rychik J. Effect of prenatal diagnosis on outcome in patients with congenital heart disease. *NeoReviews.* 2005;6:e326 - e331. Available at: http://neoreviews.aappublications.org/cgi/content/full/6/7/e326?fulltext [subscription required]. Accessed November 16, 2009

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the pathophysiology (including genetics) of a cyanotic neonate

03_Cardiovascular: Recognize the clinical features of a cyanotic neonate

03_Cardiovascular: Recognize the laboratory, imaging, and other diagnostic features of a cyanotic neonate

03_Cardiovascular: Formulate a differential diagnosis for a cyanotic neonate

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Question 6

You are called to the bedside of a 12-hour-old male infant with cyanosis. Blow-by oxygen delivery has been started. Pulse oximetry shows 80% saturation in the right hand, 93% saturation in the left leg. A quick check of the pulse oximetry cables confirms that the connections are correct.

Of the following, the MOST likely condition associated with pulse oximetry readings is:

- **A.** hemoglobin M disorder
- **B.** patent ductus arteriosus with pulmonary hypertension
- **C.** transposition of the great arteries with interrupted aortic arch
- **D.** truncus arteriosus
- **E.** unobstructed supracardiac total anomalous pulmonary venous return

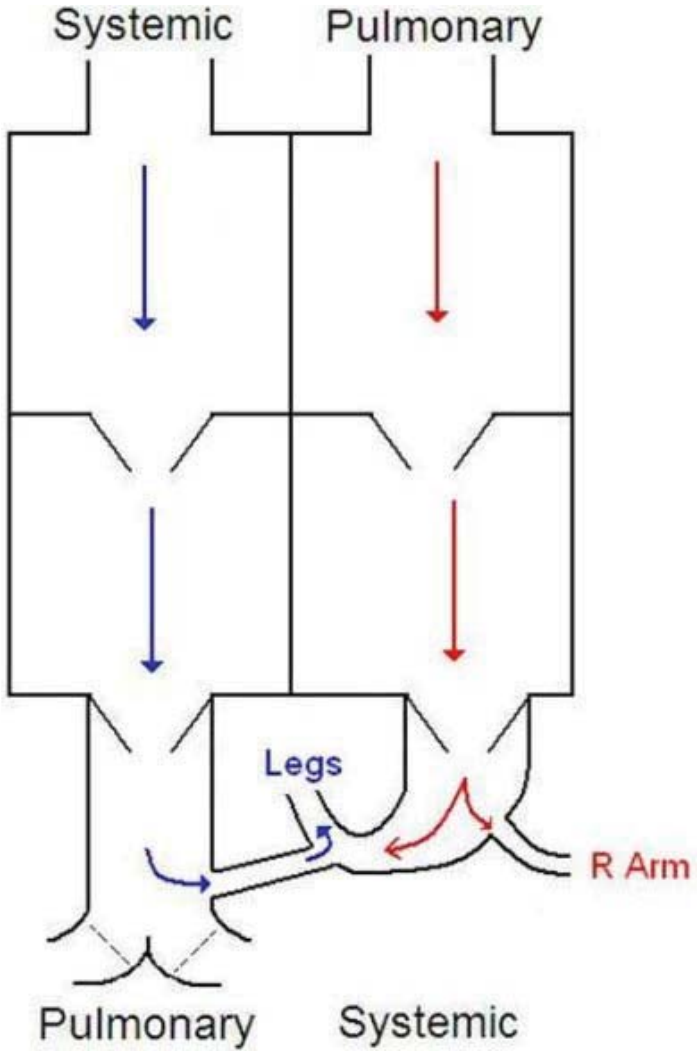
Feedb

Incorrect:

Correct Answer: C

Differential cyanosis is seen when preductal oxygen saturation exceeds postductal oxygen saturation by a significant amount, usually defined as at least 10 percentage points of saturation. Patent ductus arteriosus (PDA) with pulmonary hypertension (**Figure 1**) is an example where this is often seen.

Figure 1: Schematic representation of patent ductus arteriosus with pulmonary hypertension, an example of differential cyanosis



Reverse differential cyanosis, as seen in the vignette, is when the postductal saturation is higher than preductal. Most often, the pulse oximetry leads are mislabeled and the child has (nonreverse) differential cyanosis. Causes of reverse differential cyanosis include transposition of the great arteries (TGA) with interrupted aortic arch (IAA, **Figure 2**), and unobstructed supracardiac total anomalous pulmonary venous return (TAPVR, **Figure 3**). Of these two, TGA with IAA is seen more frequently.

Figure 2: Schematic representation of transposition of the great arteries with interrupted aortic arch, an example of reversed differential cyanosis

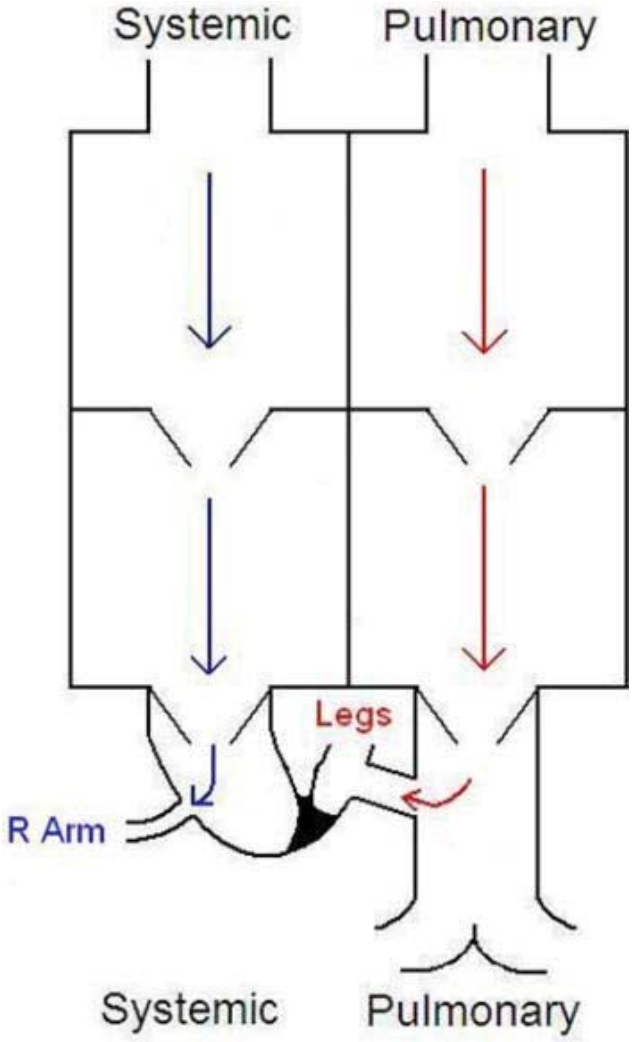
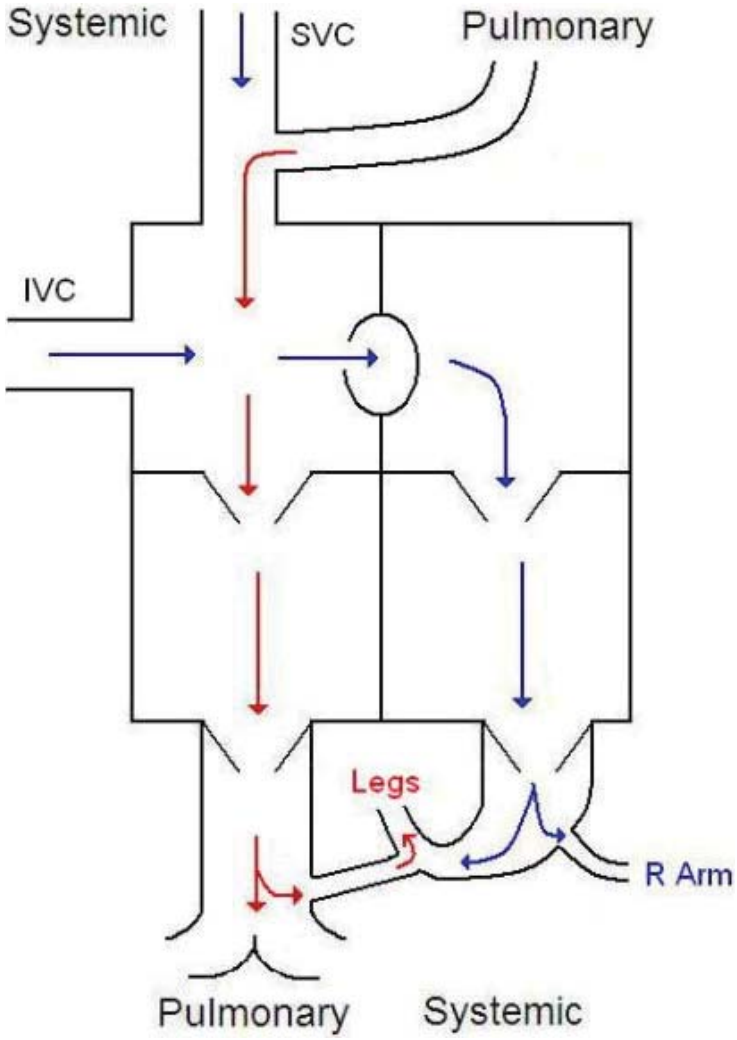


Figure 3: Schematic representation of supracardiac unobstructed total anomalous pulmonary venous return, an example of reversed differential cyanosis



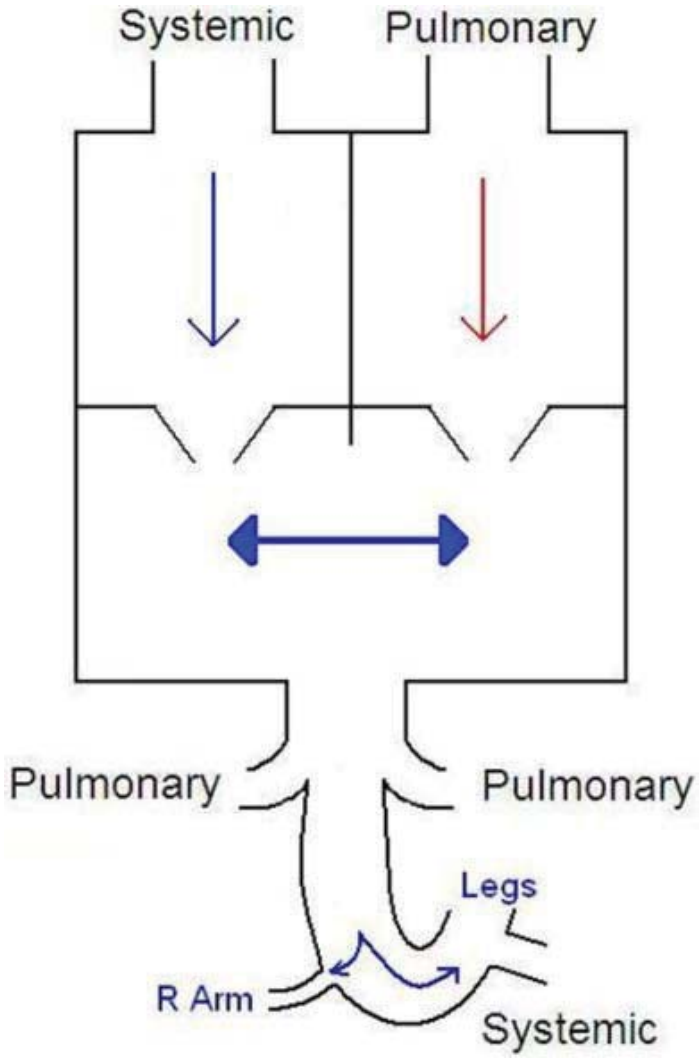
Patent ductus arteriosus with pulmonary hypertension (Figure 1) diverts some of the deoxygenated blood in the pulmonary artery across the ductus into the lungs. This right-to-left shunt delivers the deoxygenated blood to the descending aorta and causes cyanosis in the legs. The ascending aorta only receives oxygenated blood from the lungs via the left ventricle, giving a higher oxygen saturation in the right arm than in the legs. The legs appear more cyanotic than the right arm.

Transposition of the great arteries with IAA (Figure 2) allows deoxygenated blood from the systemic circulation to cross through the right ventricle, out through the ascending aorta and into the right arm. Oxygenated blood from the lungs passes through the left ventricle, out the pulmonary artery, and down the descending aorta to the legs. The right arm appears more cyanotic than the legs. This pattern of reversed differential cyanosis also can be seen in TGA with preductal coarctation or TGA with pulmonary hypertension.

Unobstructed supracardiac TAPVR (Figure 3) has only recently been described in a case report as a cause of reversed differential cyanosis. Oxygenated blood from the lungs returns to the superior vena cava (SVC) and then to the right atrium. Deoxygenated blood from the inferior vena cava (IVC) also returns to the right atrium. Then, as in fetal life, the SVC flow is preferentially directed to the tricuspid valve and the IVC flow is directed to the foramen ovale. The oxygenated blood traverses the right ventricle and the pulmonary artery, and a portion crosses the PDA into the descending aorta. Deoxygenated blood crosses into the left side of the heart and then into the ascending aorta and the right subclavian artery.

Truncus arteriosus (**Figure 4**) represents single-ventricle physiology. Mixing of oxygenated and deoxygenated blood is complete, and cyanosis is the same in the arms and legs.

Figure 4: Schematic representation of truncus arteriosus, an example of cyanosis with no differential



Hemoglobin M disorder is caused by an autosomal dominant abnormality in which heme iron is maintained in the ferric (+3) state instead of the normal ferrous (+2) state. Oxygen binds almost irreversibly to the affected molecules, causing impaired release of oxygen to the tissues and eventual hypoxia. The molecule of hemoglobin M shows a gray to blue color, whether oxygen is bound or not. Children appear cyanotic over the whole body, with no differentiation between the arms and legs. The homozygous state is not viable.

References:

Aziz K, Sanyal SK, Goldblatt E. Reversed differential cyanosis. *Br Heart J.* 1968;30:288-290

Sasidharan P. An approach to diagnosis and management of cyanosis and tachypnea in term infants. *Pediatr Clin N Am.* 2004;51:999-1021

Tingelstad J. Nonrespiratory cyanosis. *Pediatr Rev.* 1999;20:350-352

Wernovsky G. Transposition of the great arteries. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, eds. *Moss and Adam's Heart Disease in Infants, Children, and Adolescents.* 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001:1027-1084

Yap SH, Anania N, Alboliras ET. Reversed differential cyanosis in the newborn: a clinical finding in supracardiac total anomalous venous connection. *Pediatr Cardiol.* 2009;30:359-362

Related readings from Neoreviews.org

Mastropietro CW, Tourner SP. Parallel circulations: managing single-ventricle physiology. *Neoreviews.* 2009;10:e239-e244. Available at: http://neoreviews.aappublications.org/cgi/content/full/10/5/e239?fulltext [subscription required]. Accessed November 17, 2009

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American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the pathophysiology (including genetics) of a cyanotic neonate

03_Cardiovascular: Recognize the clinical features of a cyanotic neonate

14_Hematology_Oncology: Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias

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Question 7

A 4-day-old late preterm infant (gestational age 35 weeks, birthweight 2.2 kg) with hypoxemic respiratory failure secondary to meconium aspiration syndrome is receiving high-frequency oscillatory ventilation with a mean airway pressure of 18 cm H_2O. His echocardiogram shows elevated right ventricular systolic pressures with right-to-left shunting across a ductus arteriosus and foramen ovale and normal cardiac contractility. He is being sedated, is receiving continuous infusions of dopamine and dobutamine to maintain systemic blood pressure, and receives inhaled nitric oxide. After documenting the oxygenation index to be greater than 40 on two arterial blood gases, a decision is made to place the infant on extracorporeal membrane oxygenation (ECMO) support. You are trying to decide whether to use venoarterial or venovenous ECMO.

Of the following, compared with the venoarterial approach, venovenous ECMO is MOST likely to be associated with:

- **A.** decreased pulmonary artery blood flow
- **B.** decreased right ventricular preload
- **C.** increased left ventricular afterload
- **D.** increased oxygen content in pulmonary arteries
- **E.** increased risk of cerebral reperfusion injury

Incorrect:

Correct Answer: D

Extracorporeal membrane oxygenation (ECMO) requires the diversion of blood from a major systemic vessel through a membrane oxygenator and back to a major vessel. ECMO is administered to neonates using two principal modes: venovenous (VV), which provides respiratory and, indirectly, cardiac support, and venoarterial (VA) bypass, which provides both cardiac and respiratory support. VV-ECMO offers several advantages over VA-ECMO: avoidance of arterial cannulation, ligation, or repair; preserved blood flow and improved oxygenation in the pulmonary circulation; and lack of hemodynamic effects. A comparison of VV and VA bypass is shown in **Tables 1** and **2**.

Table 1: Comparison of V-V & V-A ECMO

VV-ECMO	VA-ECMO

Advantages	
Requires venous access only	Better O_2 and CO_2 exchange
Pulsatile flow as heart in series	ECMO circuit in parallel & series
Good CO_2 removal	Partial cardiac bypass & rest
Easy to wean off ECMO	Rapid ↓ ventilator/inotropes
Disadvantages	
Dependence on cardiac function	Nonpulsatile flow
Flow limited by smaller cannula	Cannulation of right carotid artery
↓ O_2 delivery to peripheral circulation	More difficult to wean off ECMO
↓ flow if mediastinum displaced	

VA-ECMO = venoarterial extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation.

Table 2: Comparison of VV- and VA-ECMO: Hemodynamic Effects

	V-V ECMO	V-A ECMO
O_2 delivery capacity	Moderate	High
PaO_2 achieved	40-80 torr	60-150 torr
Cardiac effects	Negligible effects, CVP and pulse pressure unaffected, may improve coronary oxygenation, may ↓ RV afterload	↓ preload, ↑ afterload, CVP varies, pulse pressure low, coronary oxygenation provided by LV blood, "cardiac stun" possible
Circulatory support	No direct effect, but improved delivery of O_2 to coronary and pulmonary circulation can improve cardiac output	Partial to complete
Effect on pulmonary circulation	No direct effects, but improved delivery of O_2 to coronary and pulmonary circulation can improve cardiac output	Moderately to markedly decreased
Recirculation	Major impact on O_2 delivery	None

VA-ECMO = venoarterial extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation.

Venoarterial ECMO has served as the primary mode of cannulation for neonates and infants since the advent of prolonged extracorporeal support. VA bypass removes systemic venous blood from the right atrium via the right internal jugular vein and returns the blood to the systemic arterial circulation in the aortic arch via the right common carotid artery. When VA-ECMO is begun, the right and left ventricular preloads are substantially decreased by diverting flow through the ECMO circuit. Left ventricular afterload is increased by the return of pump flow directly into the aortic arch. VA-ECMO is associated with "cardiac stun," defined by a decrease in pulse pressure to less than 10 torr, more frequently (5% of cases) than with VV-ECMO (<1% of cases). Furthermore, during VA-ECMO, cardiac contractility and ejection fraction are significantly depressed at high ECMO flow rates.

In VV-ECMO, a single double-lumen catheter often is used in neonates and young infants to both drain and return blood to the right atrium through the internal jugular vein. Blood flows

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from the right atrium into the side holes of the cannula, through the ECMO circuit before being returned to the right atrium via the end of the double-lumen catheter. Catheters that drain blood from the superior and inferior vena cavae and return blood by way of the right atrium were recently introduced; such catheters significantly reduce the recirculation that occurs with traditional double-lumen venous cannulae. In VV perfusion using traditional double-lumen cannulae, the oxygenator blood is returned to the right atrium where it mixes with the blood returning from the tissues, raising the saturation of blood in the right ventricle, pulmonary artery, and ultimately in the arterial circulation. The flow of highly oxygenated blood through the lungs assists in dilation of the vascular bed, improves cardiac function by increasing oxygen content ejected from the left ventricle into the coronary circulation, and decreases right-to-left shunt. Avoidance of increased left ventricular afterload and improved oxygen delivery to the coronary arteries indirectly improve myocardial performance. Thus, VV-ECMO provides indirect cardiac support without ligation of a major artery.

Venovenous ECMO is increasingly being applied for neonatal respiratory failure because it provides several advantages over VA-ECMO:

- Avoidance of arterial cannulation eliminates the potential for arterial embolization, and arterial ligation or repair is unnecessary.
- Because the volume of blood drained from and returned to the central venous system is equal, VV-ECMO does not decrease right ventricular preload, pulmonary blood flow, left atrial return, or left ventricular output. The absence of a change in LV afterload with VV support may eliminate the isolated left ventricular “stun” syndrome seen in a subset of patients receiving VA-ECMO support.
- VV-ECMO allows the native circulation to provide physiologic pulsatile flow. Compared with nonpulsatile flow, pulsatile flow decreases vascular resistance, decreases afterload, and improves organ perfusion.
- During VV-ECMO, blood entering the cerebral circulation is not as highly oxygenated nor is it under as much pressure as during VA-ECMO. This decreases the risk for cerebral reperfusion injury, particularly in infants with altered cerebral blood flow autoregulation. Persistently decreased cerebral flow velocities have been demonstrated during VA compared with VV-ECMO. This decline in cerebral blood flow is believed to be related to decreased endogenous cardiac output, increased cerebrovascular resistance, and diminished cerebrovascular pulsatility.

Venovenous ECMO is very good at removing carbon dioxide from the circulation, but it is not as effective as VA-ECMO at oxygenation because of the mixing of ECMO return blood with desaturated systemic venous blood in the right atrium. Therefore, during VV-ECMO, the systemic arterial partial pressure of oxygen (Po_2) is no higher than pulmonary arterial Po_2 when there is no native lung function. Consequently, it is necessary to treat VV-ECMO patients at arterial saturation levels between 80% and 95%, with Po_2 of 40 to 55 mm Hg. Oxygen delivery is maintained by means of red blood cell transfusion to keep hematocrit levels above 40%.

A significant disadvantage of VV-ECMO is the absence of direct cardiovascular support. For neonates whose cardiac function is severely compromised because of illness or postoperative myocardial depression, VV-ECMO will not provide the level of cardiac support required for systemic and pulmonary perfusion. It is important to understand that no specific level of inotropic or ventilator support has been identified which definitely precludes VV-ECMO for neonatal respiratory failure. In fact, cardiac performance has been shown to improve after initiation of VV-ECMO, and inotropic support can frequently be weaned. Other disadvantages of VV-ECMO include flow limitation because of the smaller lumen of the double-lumen cannula and decreased end-organ oxygen delivery because of admixture of blood from the native circulation bypassing the pump. Also, in infants who weigh less than 2.5 kg or those with extremely small jugular vessels, it may not be technically feasible to place a double-lumen VV cannula. Recirculation is a disadvantage unique to VV-ECMO. Recirculation is defined as the portion of blood returning to the ECMO circuit immediately after being infused to the patient from the ECMO circuit. All patients receiving VV-ECMO through traditional double-lumen cannulae have some degree of recirculation, with the average recirculation fraction being 30%. Higher fractions of recirculation may affect oxygen delivery.

References:

Fortenberry JD, Pettignano R, Dykes F. Principles and practice of venovenous ECMO. In: Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:85-

105

Heard ML, Labuz M. Principles and practice of veno-venous ECMO. In: Van Meurs K, ed. *ECMO Specialist Training Manual.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 1999:51-63

Hilt T, Graves D, Zwischenberger JB. ECMO physiology. In Van Meurs K, ed. *ECMO Specialist Training Manual.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 1999:19-40

Hopper AO, Pageau J. Management of the neonate on ECMO. In Van Meurs K, ed. *ECMO Specialist Training Manual.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 1999:123-140

Lewis FC, Reynolds M, Arensman RM. Extracorporeal Membrane Oxygenation. In Goldsmith JP, Karotkin E, eds. *Assisted Ventilation of the Neonate.* Philadelphia, Pa: WB Saunders; 2003:261-277

Pranikoff T, Hines MH. 2005 Vascular Access for Extracorporeal Support. In: Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:121-132

Van Meurs K, Hintz SR, Sheehan AM. ECMO for neonatal respiratory failure. In: Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:273-295

American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the indications, techniques, effects, and risks of extracorporeal membrane oxygenation (ECMO)

04_Respiratory: Know the management of persistent pulmonary hypertension including assisted ventilation, pharmacologic approaches, and ECMO

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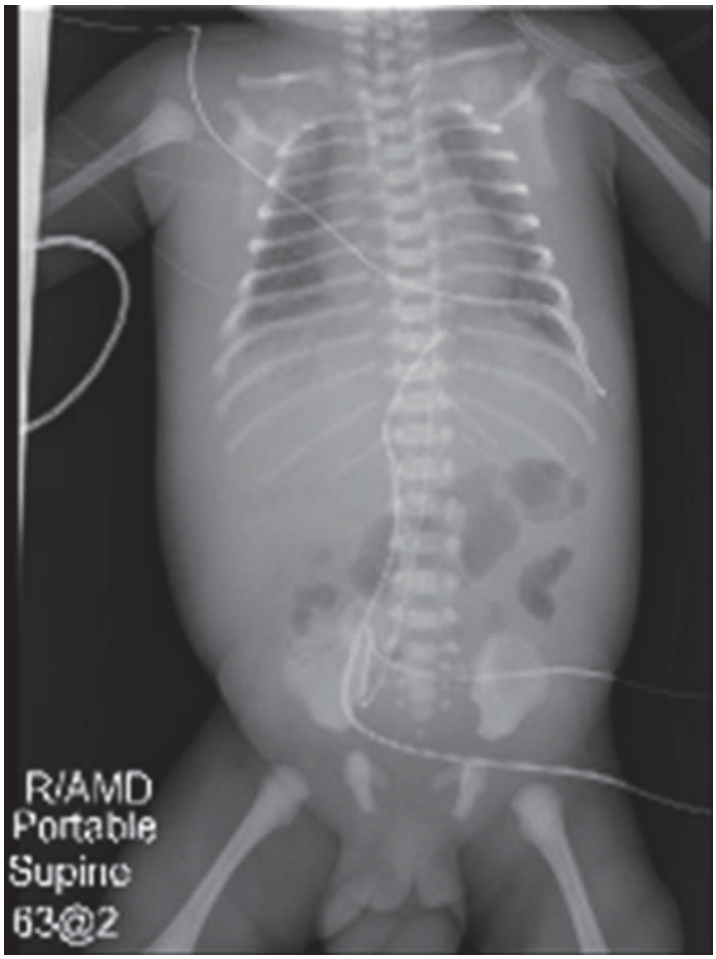
ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **4** Correct Answers: **1**

Question 4

A male infant is born at 36 weeks' gestation by emergency cesarean delivery to a 36-year-old healthy woman of western European descent. She received prenatal care from the eighth week of pregnancy, which had been uneventful until 3 days before delivery when she noted decreased fetal movement. Ultrasonography on the day of delivery showed pulmonary effusions and massive ascites. The neonate's birthweight was 3.7 kg; his Apgar scores were 1, 1, and 3 at 1, 5, and 10 minutes after birth, respectively. He responded gradually to resuscitation efforts and was breathing and crying spontaneously at 12 minutes. Temperature was normal, heart rate varied from 133 to 180 beats per minute, and respirations were 35 to 62 breaths per minute during the first 10 days. He had generalized edema. The rest of the physical examination findings were normal. He required supplemental oxygen for the first 3 days only. Initial blood count showed a hematocrit of 42%. Both the mother and infant were of blood type A positive and the infant's Coombs test result was negative. Pleural effusions and ascites were confirmed on radiography (**Figure 1**) but cleared spontaneously over the first week.

Figure 1: Hydrops: massive subcutaneous edema, ascites, and small bilateral pleural effusions.



Of the following, the investigation MOST likely to reveal the cause of this infant's fluid accumulation is:

- **A.** chromosomal analysis
- **B.** cranial imaging
- **C.** electrocardiography
- **D.** hemoglobin electrophoresis
- **E.** parvovirus titers

Incorrect:

Correct Answer: C

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Hydrops fetalis or hydrops in the newborn infant is defined as generalized dermal edema associated with fluid collection(s) in at least one other body compartment (pleural, peritoneal, or pericardial space) and/or the placenta. The incidence today is 1 in 2,500 to 4,000 pregnancies. Before the mid-1960s it occurred much more frequently, most commonly caused by erythroblastosis fetalis arising from Rh isoimmunization. The introduction of anti-Rh antibody prophylaxis during pregnancy dramatically reduced the incidence to its current rate, and nonimmune hydrops fetalis (NIHF) became the most prevalent cause of this condition. Rarely hydrops is also caused by other isoimmune causes (antibodies to Kell, Duffy, etc).

Fluid accumulation in extravascular spaces is regulated by six factors. Promoting fluid accumulation are hydrostatic pressure within capillaries (*Pcap*) and oncotic

pressure in the interstitium (*Otiss*). The filtration coefficient (*k*) across the capillary controls the rate at which water might pass through the capillary wall. The reflection coefficient (*r*) controls the rate at which solute might pass. Opposing fluid accumulation in the interstitium are oncotic pressure within the capillary (*Ocap*) and hydrostatic pressure in the tissues (*Ptiss*). This relationship can be succinctly represented as follows:

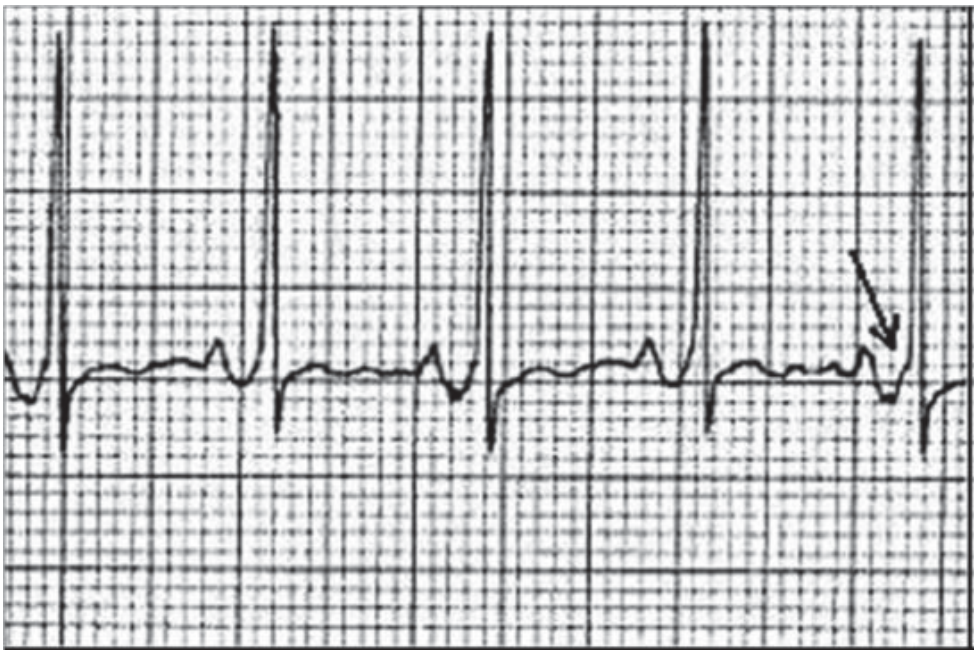
Filtration of fluid = k[(Pcap – Ptiss) – r(Ocap – Otiss)]

Physiologic mechanisms leading to extravascular fluid accumulation include:

- Increase in central venous pressure
- Venous obstruction
- Marked increase in arterial pressure
- Malformation of lymphatic drainage
- Severe hypoalbuminemia
- Fluid overload (IV or oral)

Congestive heart failure (CHF) is the most common cause of NIHF, accounting for 22% of cases in one large series. CHF may be the result of a cardiac malformation (eg, pulmonary atresia, Ebstein anomaly), myocardiopathy, or a cardiac arrhythmia. Malformations or myocardiopathy (primary or infectious) should be evident on chest radiography as an enlarged or abnormally shaped heart and abnormal pulmonary vascular pattern, neither of which was present in the vignette. Supraventricular tachycardia has been reported in 1 in 200 to 250 newborn infants. Cardiac arrhythmias, such as supraventricular tachycardia, can produce cardiac failure in utero without manifesting at the time of birth. At birth, chest radiography would not show cardiac enlargement or pulmonary congestion. Because cardiac disease is the most common underlying cause of NIHF, electrocardiography would provide the best chance to find the cause of the hydrops, perhaps showing a variant in the normal electrical pathways of cardiac excitation. For example, electrocardiography may show no tachycardia, but still demonstrate the delta waves of Wolff-Parkinson-White syndrome (**Figure 2**). Without treatment, a repeat episode of tachycardia leading to heart failure would be likely.

Figure 2: Wolff-Parkinson White syndrome characterized by short P-R interval and delta wave (arrow)



Chromosomal disorders accounted for 13% of cases in a large series of NIHF. Turner syndrome (45XO) and trisomy 21 are the most common of these. Trisomies 18, 13, 15, and

16 have also been reported with NIHF. However, in these cases hydrops is detected in the first trimester or shortly after and results in fetal death most often. The physical examination of the infant in the vignette did not reveal typical dysmorphia.

Arteriovenous malformations such as a vein of Galen malformation are very rare (less than 1 in 25,000 births) and can produce congestive cardiac failure in utero with hydrops. However, the malformation would still be causing cardiac failure at the time of birth. CHF was not evident on radiography in the vignette.

Homozygous alpha-thalassemia is a common cause of hydrops among Southeast Asians, accounting for 31% or more of cases in that population. However, the infant in the vignette was not anemic, nor was he likely to have homozygous alpha-thalassemia because his mother's ancestry was eastern European. Likewise, the lack of anemia makes it unlikely that parvovirus titers would help with the diagnosis of NIHF in the vignette. Human parvovirus B19 can cause an aplastic anemia in utero. However, half of our population is immune and very few pregnant women infected during pregnancy have infants with NIHF. Other infections (syphilis, toxoplasmosis, cytomegalovirus) also produce anemia. Genetic causes of red cell hemolysis (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase, and glucosephosphate isomerase deficiencies) can lead to NIHF, but, again, anemia was not present in the case in the vignette.

Other rare causes of NIHF such as congenital cystic adenomatoid malformation of the lung, congenital diaphragmatic hernia, congenital pulmonary lymphangiectasia, and bronchopulmonary sequestration would have been evident on the chest radiography if present.

References:

Hamden AH. Hydrops fetalis. eMedicine.com Web site. Available at: http://emedicine.medscape.com/article/974571-print. Accessed April 12, 2010

Murphy JH. Nonimmune hydrops fetalis. *NeoReviews.* 2004;5:e5-e15. Available at: http://neoreviews.aappublications.org/cgi/content/full/5/1/e5? Accessed May 19, 2010

Sheth RD. Vein of Galen malformation. eMedicine.com Web site. Available at: http://emedicine.medscape.com/article/1179888-overview. Accessed April 12, 2010

Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia (SVT). *NeoReviews.* 2005;7:e339-e350. Available at: http://neoreviews.aappublications.org/cgi/content/full/6/7/e339? Accessed May 19, 2010

American Board of Pediatrics Content Specification(s):

01_Maternal_Fetal: Know the differential diagnosis and the plan of evaluation and management of a fetus with non-immune hydrops

10_Infectious_diseases: Know the clinical manifestations, diagnostic features, treatment, and complications of perinatal parvovirus infections

03_Cardiovascular: Know the physiologic consequences of a dysrhythmia in a fetus or newborn infant

03_Cardiovascular: Differentiate normal from common abnormal electrocardiographic patterns and rhythms in the fetus and newborn infant

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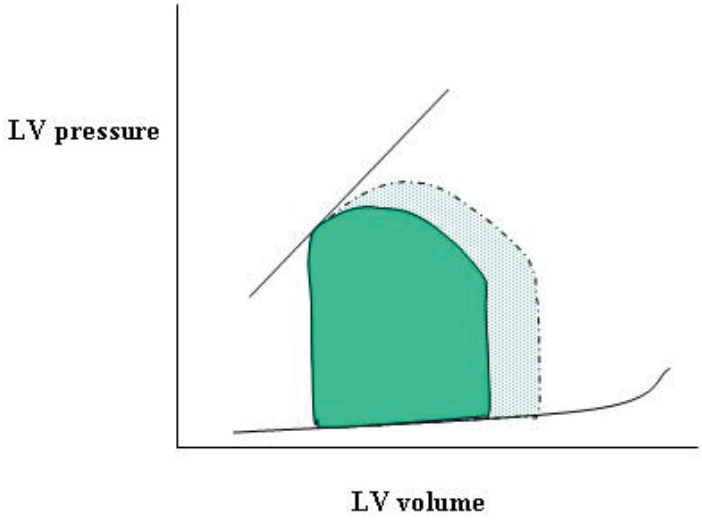
ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **5** Correct Answers: **3**

Question 5

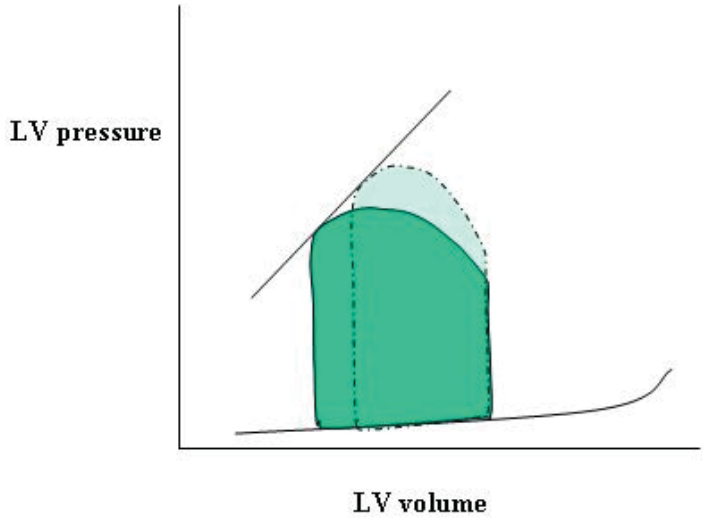
A pediatric resident performs an exchange transfusion on a full-term infant because of severe unconjugated hyperbilirubinemia resulting from Rh isoimmunization. At the completion of the exchange transfusion, you suggest that the pediatric resident end with a net positive infusion. This infusion results in an increase in preload to the infant. You then discuss with the resident the anticipated cardiovascular effects resulting from the increase in preload, assuming that afterload and inotropy remain constant.

Of the following, the Figure that MOST likely corresponds with this clinical scenario is:

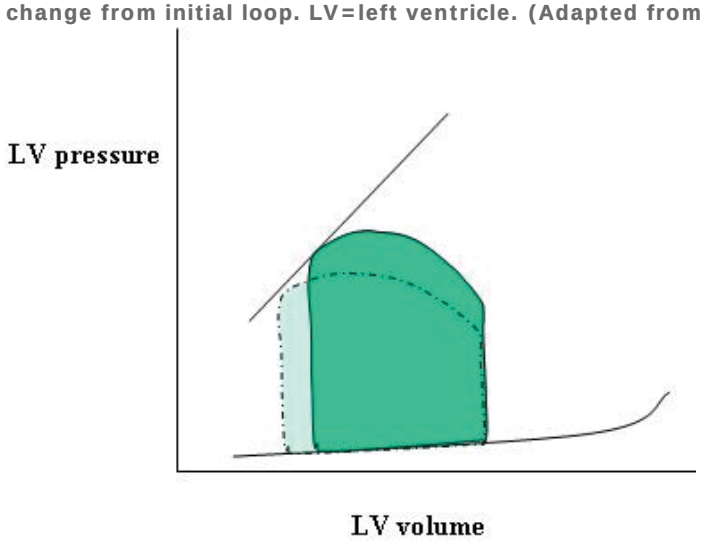
A. Figure 1: Green pressure-volume loop is baseline; dotted green graph with dashed lines represents change from initial loop. LV=left ventricle. (Adapted from Klabunde [2005].)



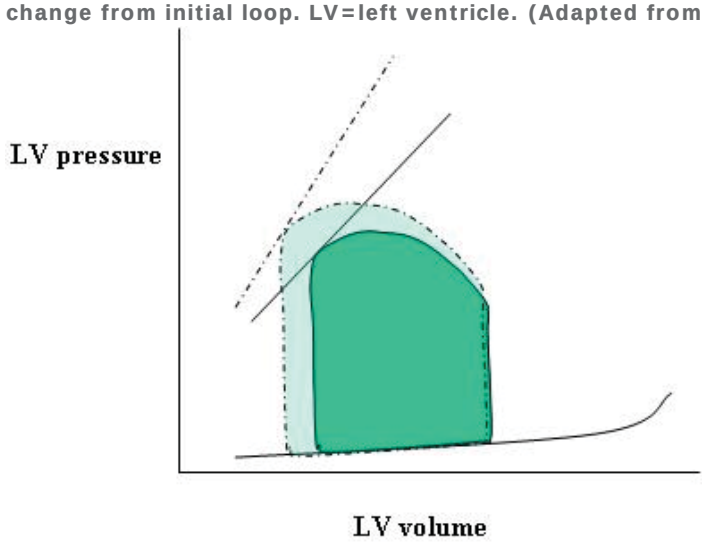
B. Figure 2: Green pressure-volume loop is baseline; dotted green represents change from initial loop. LV=left ventricle. (Adapted from Klabunde [2005].)



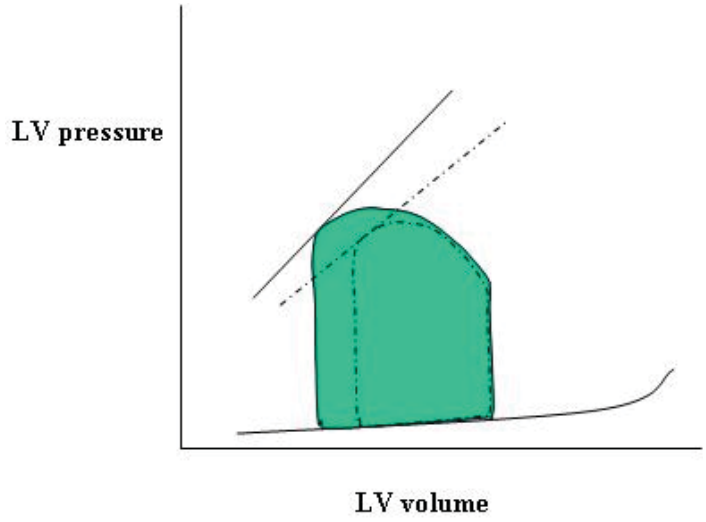
C. **Figure 3: Green pressure-volume loop is baseline; dotted green represents change from initial loop. LV=left ventricle. (Adapted from Klabunde [2005].)**



D. **Figure 4: Green pressure-volume loop is baseline; dotted green represents change from initial loop. LV=left ventricle. (Adapted from Klabunde [2005].)**



E. **Figure 5: Green pressure-volume loop is baseline; dotted green represents change from initial loop. LV=left ventricle. (Adapted from Klabunde [2005].)**



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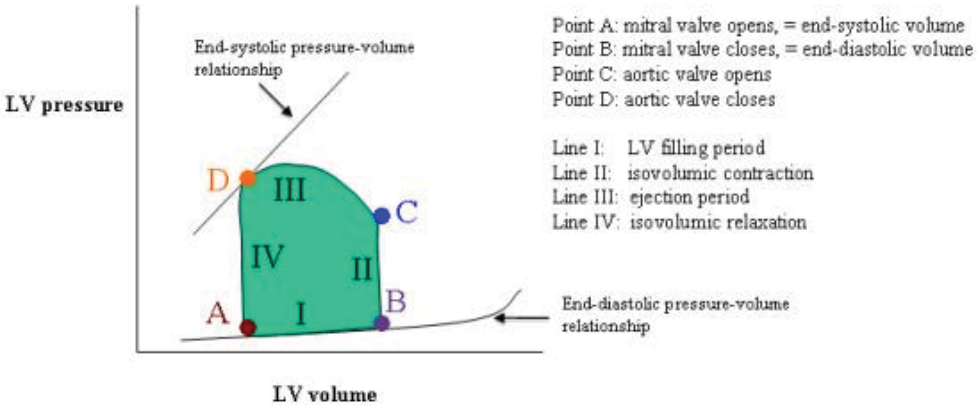
Ventricular pressure-volume loops can be used as a tool for visualizing changes in ventricular function as preload, afterload, and inotropy change. The pressure-volume loop formed from points A to B to C to D in **Figure 6** represents one cardiac cycle. Point A denotes the volume of the left ventricle (LV) after a contraction, also known as the end-systolic volume; the diastolic pressure at this point is close to zero. At this time, the mitral valve opens and the heart begins to fill until it reaches the end-diastolic volume at point B. The line between point A and point B (ie, line I) represents the LV filling period. This period ends when the mitral valve closes. The intraventricular pressure then increases until it becomes greater than the aortic pressure, which forces the aortic valve to open (designated as point C). Line II, which connects points B and C, represents the isovolumic, or isovolumetric, contraction period. With ventricular ejection, the LV volume decreases along line III as blood is ejected from the LV. During this systolic period, the intraventricular pressure increases. The aortic valve closes when the intraventricular pressure is lower than the aortic pressure, designated as point D. With a closed chamber, the intraventricular volume remains constant at the end-systolic volume and as the cardiac muscle relaxes, there is a decrease in ventricular pressure; this period shown as line IV represents the isovolumic relaxation period of the heart. When the LV pressure falls below the atrial pressure, the mitral valve opens and the cycle continues from point A.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Figure 6: This figure represents the ventricular pressure-volume loop. Roman numerals represent adjacent line or curve; letters represent points. LV=left ventricle. (Adapted from Klabunde [2005].)



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The filling phase moves along the end-diastolic pressure-volume relationship, which is the passive filling curve for the LV, shown in Figure 6. The slope of the end-diastolic pressure-volume curve is indirectly correlated with ventricular compliance. Thus, if the ventricle undergoes hypertrophy and ventricular compliance is low, the slope of the end-diastolic pressure volume curve will be increased. In contrast, if the infant has a dilated cardiomyopathy with increased ventricular compliance, the slope of this curve will be decreased.

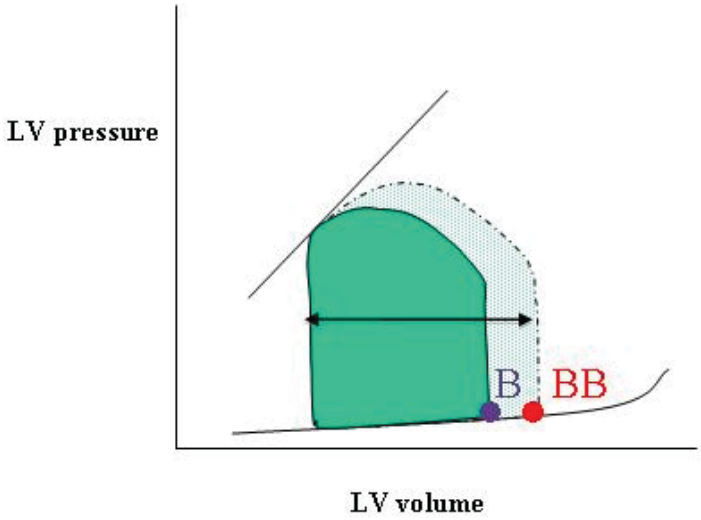
The end-systolic pressure-volume relationship depicts the inotropic state of the ventricle (shown in Figure 6). This curve is created by using the maximal pressures developed by the LV at any given LV volume. The slope of this line correlates directly with LV contractility; while a steeper slope of the end-systolic pressure-volume curve demonstrates greater LV contractility, a lower slope correlates with decreased LV contractility.

The volume difference between point C and point D corresponds to the stroke volume of that cycle. Three factors affect stroke volume: ventricular preload, ventricular afterload, and contractility. Ventricular preload is the volume of the ventricle at the end of filling, also known as end-diastolic volume. Preload is increased by several factors including the following:

- Increased circulating blood volume
- Skeletal muscle contraction, which propels blood within veins *toward* the heart (one-way valves within veins act to return blood to the heart)
- Deep inspiration, which leads to a decrease in intrathoracic pressure and an increase in abdominal pressure; both changes increase venous return to the thorax
- Atrial contraction, which ensures that the maximal amount of blood is ejected from the atria into the ventricles

Figure 1 represents the change in the pressure-volume loop of the infant in the vignette who has an increase in preload without a change in afterload or inotropy. With increased diastolic filling, cardiac muscle undergoes greater stretching, resulting in a greater force of ventricular contraction, which allows the ventricle to eject the additional blood; this effect is known as the *Frank-Starling principle*. As shown in **Figure 7**, this is represented by an increase in the end-diastolic volume from point B to point BB, a greater stroke volume (double arrow), and a greater LV systolic pressure (upwards move of line III). A decrease in preload will lead to the opposite effects with a decrease in end-diastolic volume and stroke volume.

Figure 7: In this figure, the dotted green graph with dashed lines represents changes that occur to the ventricular pressure-volume loop with an isolated increase in preload. The end-diastolic volume increases from point B to point BB, and a greater stroke volume (double arrow) and greater LV systolic pressure (upward move of line III) are seen. A decrease in preload will lead to the opposite effects with a decrease in end-diastolic volume and stroke volume. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in preload. LV=left ventricle. (Adapted from Klabunde [2005].)



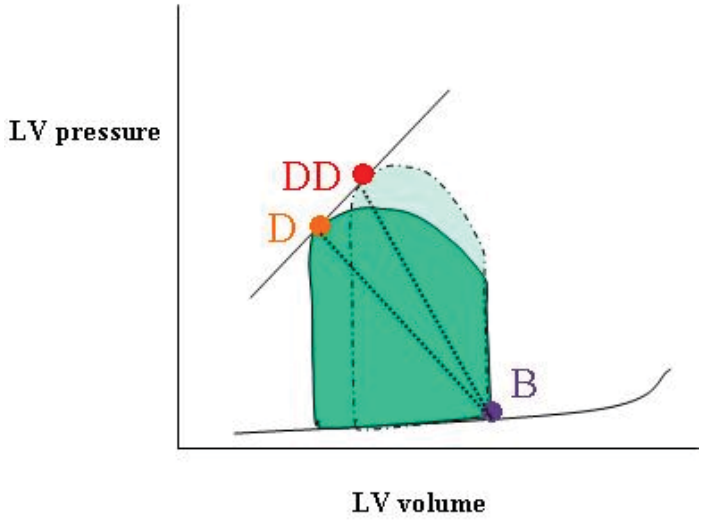
The second factor that influences stroke volume is ventricular afterload. Afterload is defined as the force that resists myocardial fiber contraction at the beginning of systole. It is influenced by ventricular pressure, ventricular volume, and ventricular wall thickness at the time the aortic valve opens. Afterload correlates directly with ventricular wall stress. Ventricular wall stress is calculated using the following equation:

$$\text{Wall stress} = \frac{\text{Ventricular pressure} \times \text{Ventricular radius}}{\text{Wall thickness}}$$

Afterload, or peak systolic wall stress, is mostly affected by changes in the resistance of systemic blood vessels or heart valves. For example, increased aortic vascular resistance creates a greater afterload for the LV. A pathologic example of increased afterload occurs with a hypoplastic aortic arch. At a given ventricular pressure, if ventricular dilation occurs with a correspondingly larger ventricular radius, the afterload is also increased. In contrast, a ventricle with hypertrophy with a thickened wall reduces wall stress and thus afterload.

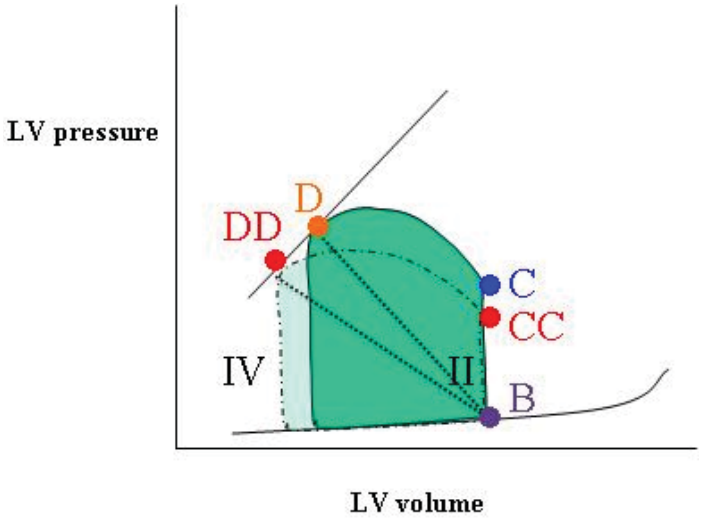
Figure 2 shows the change that occurs in the ventricular pressure-volume loop when afterload increases at a constant rate of preload and inotropy. In this situation, the left ventricular pressure needs to be greater than that at baseline to overcome the increased aortic vascular resistance and cause the aortic valve to open. The stroke volume is decreased because the increase in afterload reduces the velocity of muscle fiber shortening as well as the velocity by which the blood is ejected. As shown in **Figure 8**, afterload is reflected in the slope of the line between points B and D. With an increase in afterload, this slope becomes steeper as the ventricle develops more pressure but delivers a smaller stroke volume, shown as the line between points B and DD in Figure 8.

Figure 8: In this figure, the dotted green graph with dashed lines represents changes that occur to the ventricular pressure-volume loop with an isolated increase in afterload. The dotted lines reflect the afterload slope, which becomes steeper when the ventricle develops greater pressure but delivers a smaller stroke volume. This increased afterload slope is represented by the line between points B and DD. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in afterload. LV=left ventricle. (Adapted from Klabunde [2005].)



The effect of decreased afterload on the pressure-volume loop is shown in Figure 3. With a decrease in afterload, the left ventricular pressure that is required to overcome the aortic vascular resistance is less, decreasing the length of line II with point CC being reached earlier than the original point C (**Figure 9**). Stroke volume increases because there is a greater velocity of muscle fiber shortening, allowing more blood to be ejected. Line IV moves to the left as stroke volume increases. The slope of the line between points B and DD is more gradual with a decrease in afterload.

Figure 9: In this figure, the dotted green graph with dashed lines represents changes that occur to the ventricular pressure-volume loop with an isolated decrease in afterload. In addition to an increase in stroke volume, the afterload slope (shown as the dotted line) becomes more gradual with a decrease in afterload. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents a decrease in afterload. LV=left ventricle. (Adapted from Klabunde [2005].)



In addition to preload and afterload, contractility is a factor that influences ventricular stroke volume. Cardiac contractility is defined as the force and velocity of a contraction. Using the pressure-volume loop, contractility can be determined by the rate at which the end of systole is attained. Contractility is represented by the slope of the end-systolic pressure-volume curve (**Figure 10**), which is created by using the maximum LV pressures at each LV volume. For the same preload and afterload, an increase in contractility leads to a steeper slope of this line because of the relatively greater increase in stroke volume compared with the increase in systolic pressure that is observed with increased contractility. This pressure-volume loop change as a result of increased contractility is shown in Figure 10; the end-systolic pressure-volume line is steeper because the maximum LV pressure (DD) is greater than the original maximum LV pressure (D). Decreased inotropy has the opposite effect (**Figure 11**) and leads to a higher end-systolic volume and lower stroke volume, reflected

as a more gradual slope of the contractility line.

Figure 10: This figure shows changes that occur in the ventricular pressure-volume loop as contractility increases for the same preload and afterload. The greater stroke volume and lower end-systolic volume are reflected as a steeper slope of a line from a point of zero pressure to point DD. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in inotropy. LV=left ventricle. (Adapted from Klabunde [2005].)

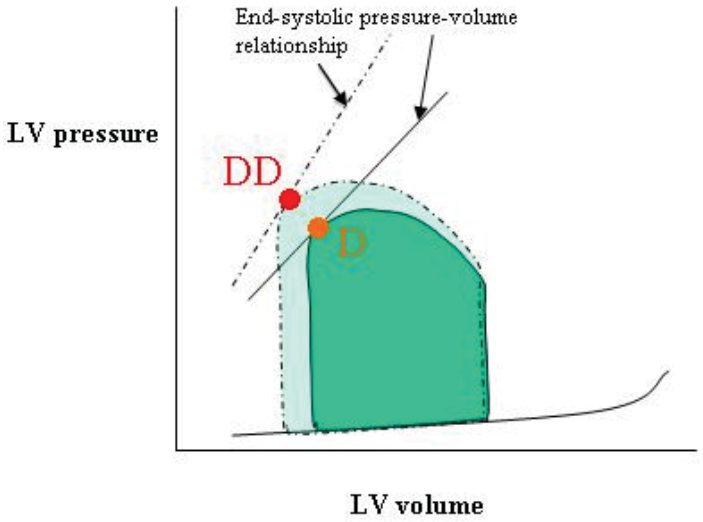
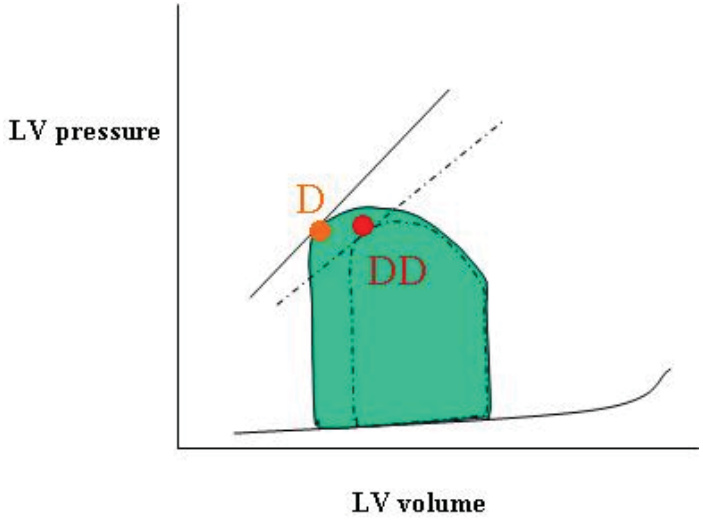


Figure 11: This figure shows changes that occur in the ventricular pressure-volume loop as contractility decreases for the same preload and afterload. The lower stroke volume and a higher end-systolic volume are reflected as a more gradual slope of a line from a point of zero pressure to point DD. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents a decrease in inotropy. LV=left ventricle. (Adapted from Klabunde [2005].)



Figures 1 through 11 demonstrate changes in the pressure-volume ventricular loop if preload, afterload, or contractility is altered, while the remaining two factors are held constant. However, in reality, these factors are interdependent, and changing one will affect the others. For example, an increase in preload will not just increase stroke volume but the greater cardiac output will lead to greater arterial pressure and a greater afterload, which partially offsets the increased stroke volume by increasing the end-systolic volume. This is shown in **Figure 12**. Similarly, increased afterload does not only lead to a decrease in stroke volume and increase in end-systolic volume but the increased end-systolic volume leads to a secondary increase in end-diastolic volume because there is more blood volume left inside the ventricle (**Figure 13**). This secondary increase in preload partially offsets the reduction in stroke volume caused by the initial increase in afterload. Finally, changes in inotropy will have a secondary effect on end-diastolic volume. For example, increased inotropy leads to a greater stroke volume and thus, a decrease in end-systolic volume, but this secondarily

leads to a lower end-diastolic volume and lower preload, with a shift in line II to the left (**Figure 14**).

Figure 12: This figure shows the differences between the ventricular pressure-volume loops of an isolated increase in preload compared with the interdependent effects of increased preload. An increase in preload will not just increase stroke volume but also the cardiac output, which in turn, will lead to greater arterial pressure and a greater afterload, which partially offsets the increased stroke volume by increasing the end-systolic volume (point DD has a greater volume compared with isolated preload graph). Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in preload. LV=left ventricle. (Adapted from Klabunde [2005].)

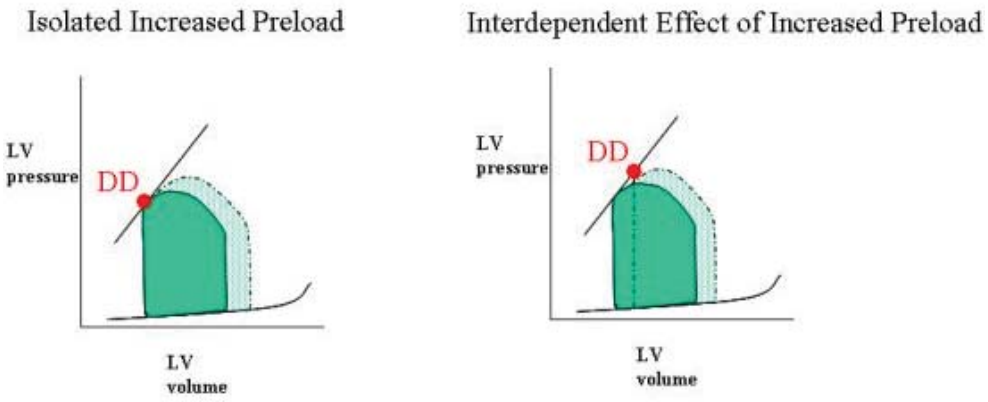


Figure 13: This figure shows the differences between the ventricular pressure-volume loops of an isolated increase in afterload compared with the interdependent effects of increased afterload. Increased afterload will not only decrease stroke volume and increase end-systolic volume (shown on the graph on the left); this increased end-systolic volume leads to a secondary increase in end-diastolic volume because more blood volume is left inside the ventricle, as shown by the shift in line II. Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in afterload. LV=left ventricle. (Adapted from Klabunde [2005].)

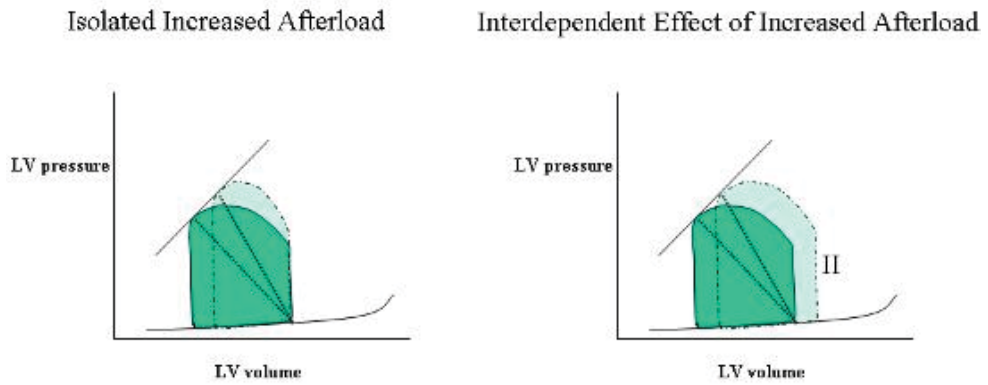
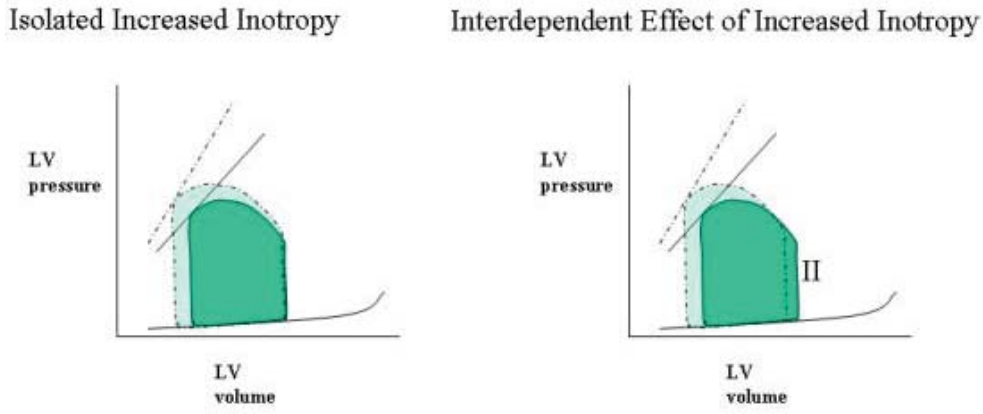


Figure 14: This figure shows the differences between the ventricular pressure-volume loops of an isolated increase in inotropy compared with the interdependent effects of increased inotrope. An increase in inotropy leads to a greater stroke volume and thus, a decrease in end-systolic volume but this secondarily leads to a lower end-diastolic volume and lower preload, with a shift in line II to the left . Green pressure-volume loop is baseline; dotted green graph with dashed lines represents an increase in inotropy. LV=left ventricle. (Adapted from Klabunde [2005].)



References:

Brodsky D, Martin C. *Neonatology Review*. 2nd ed. Philadelphia, Pa: Elsevier; 2010

Guyton AC. *Textbook of Medical Physiology*. Philadelphia, Pa: WB Saunders Co; 1986

Kibble JD. *Medical Physiology: The Big Picture*. Philadelphia, Pa: McGraw-Hill; 2009

Klabunde RE. *Cardiovascular Physiology Concepts*. Philadelphia: Lippincott, Williams & Wilkins; 2005. Available at: http://www.cvphysiology.com. Accessed February 1, 2010

American Board of Pediatrics Content Specification(s):

03_Cardiovascular: Know the factors affecting and regulating myocardial performance and function in the fetus and newborn infant and during the transitional period

03_Cardiovascular: Know the factors affecting and regulating the systemic circulation in the fetus (including umbilical vessels) and newborn infant during the transitional period

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ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **7** Correct Answers: **2**

Question 7

A term male newborn with normal physical examination findings was discharged from the hospital 48 hours after birth. He was seen 2 days after discharge and his physical examination findings remained normal. At 12 days, the parents report that his feeding changed from vigorous to weak. He stopped feeding often to catch his breath and sweat appeared on his forehead. His breathing was labored even between feedings.

The infant was taken to a pediatric emergency service. Vital signs included an axillary temperature of 36.8°C, heart rate of 186 beats per minute, and respiratory rate of 72 breaths per minute. Blood pressures were 76 mm Hg systolic, 36 mm Hg diastolic, and equal in all limbs. His weight was 5% greater than his birthweight. He was pink in room air. He had chest retractions and a holosystolic murmur most prominent at the left sternal border. Fine rales were heard over the posterior lungs. A chest radiograph (**Figure 1**) and Doppler echocardiography (**Figure 2**) were obtained.

Figure 1

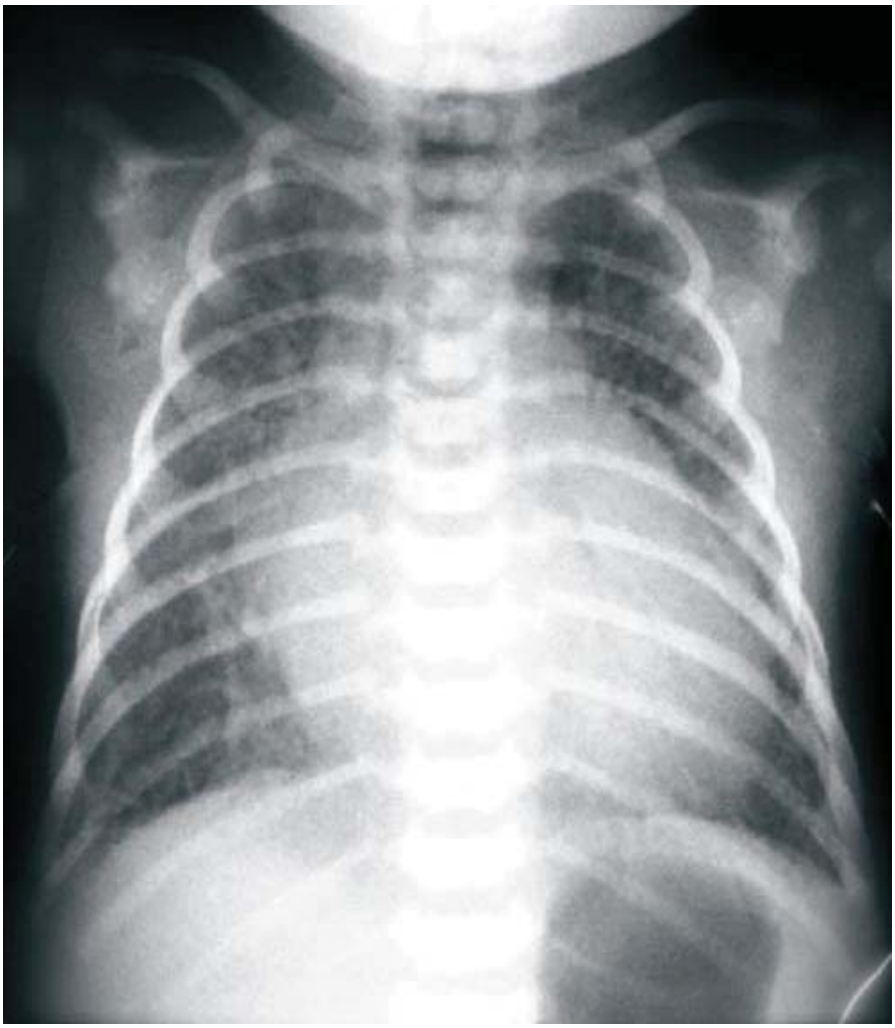

Figure 2

Of the following, the MOST likely cause of this infant's problem is:

- A. bacterial sepsis
- B. chronic lung disease
- C. congestive heart failure
- D. group B Streptococcus pneumonia
- E. obstructive pulmonary veins

Correct

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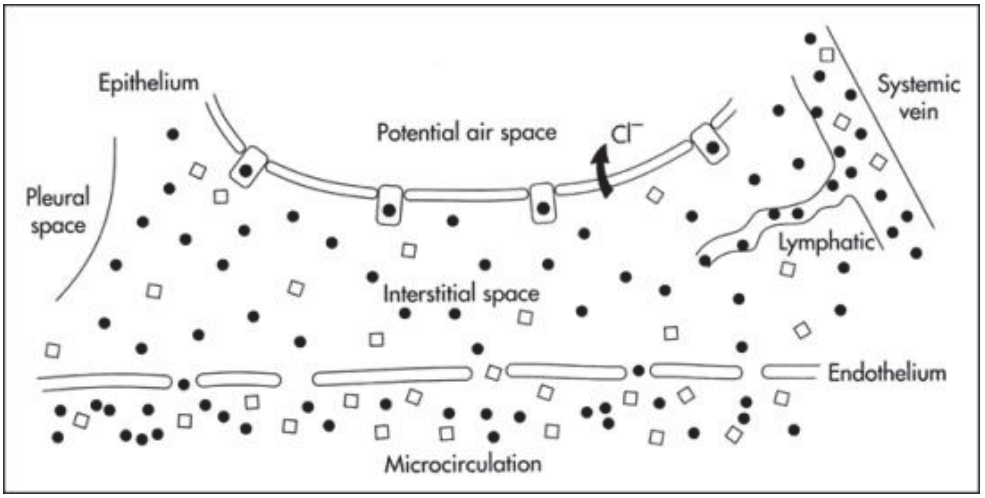
The infant in the vignette was well from the time of birth until the second week when he developed dyspnea aggravated by sweating with feeding. Physical examination findings included a new heart murmur and rales. Rales are caused by the popping open of small airways that have been filled with intraluminal fluid. His chest radiograph (Figure 1) shows an enlarged heart and pulmonary congestion/edema. These signs are consistent with congestive heart failure. Echocardiography (**Figure 3**) demonstrates a large left-to-right shunt through a ventricular septal defect (VSD).

Figure 3: Echocardiogram showing a large left-to-right shunt coursing through a ventricular septal defect (arrows). (Courtesy of Jon Love, MD, University of New Mexico.)

The infant had two early physical examinations that did not detect his congenital heart disease. This happens frequently with large VSDs. Pulmonary vascular resistance is high in utero and at birth. In the normal infant, pulmonary vascular resistance begins to fall shortly after air breathing is initiated. As the pulmonary resistance falls in the infant with a VSD, a left-to-right shunt across the defect starts increasing the blood volume of the pulmonary vascular circuit. This increased volume tends to increase pulmonary arterial pressure and reduce the blood flow across the defect. Eventually, the increased pulmonary vascular volume results in increases in pulmonary venous and capillary pressure. Increased capillary pressure facilitates excess leakage of fluid into airway spaces, resulting in the pulmonary edema seen in the chest radiograph.

Pulmonary air spaces are lined with a thin layer of fluid at low surface tension resulting from the normal production of surfactant. Tight junctions between epithelial cells do not normally allow proteins from the interstitial space to leak into alveoli. The alveolar capillary endothelium does allow a portion of circulating albumin but less circulating globulin to pass through (**Figure 4**).

Figure 4: Schematic diagram of the fluid compartments in the fetal lung, showing the tight epithelial barrier to protein and the more permeable vascular endothelium, which restricts passage of globulins (open squares) more than it restricts albumin (solid circles). (Reprinted with permission from Bland [2003].)



The net flow of fluid out of the alveolar capillary is regulated by the differences in oncotic pressure and in the hydrostatic pressure on either side of the endothelium. Net flow of fluid from the alveolar space depends on the ability of the alveolar epithelium to pump the fluid to the interstitium and the oncotic and hydrostatic pressures within the interstitium.

Gram-negative bacterial sepsis also can cause pulmonary edema. These bacteria release lipopolysaccharide (endotoxin), which disrupts tight junctions directly or through the activities of cytokines. This disruption leads to excess protein leakage across capillary endothelium and alveolar epithelium, resulting in massive fluid loss and tissue edema, including pulmonary edema and shock. The infant in this vignette had a normal blood pressure and moderate respiratory distress as well as an enlarged heart, all inconsistent with gram-negative bacterial sepsis.

Hypoplastic left heart syndrome (HLHS) usually presents with the sudden onset of shock when the patent ductus arteriosus closes, usually within the first 1 to 2 days after birth. These infants appear well before they turn pale and refuse to feed. The chest radiograph may be similar to that seen in this vignette, but low blood pressure and poor perfusion are likely. Moreover, the infant in this vignette did not get sick until the second week after birth, which would be unusual for an infant with HLHS. In HLHS, echocardiography usually shows a small left ventricle, large hypertrophied right ventricle, and abnormal mitral and aortic valves. The aortic root is also hypoplastic. Shunt(s) are seen at the atrial level but not the ventricular level.

The most common variation of obstructed pulmonary veins is total anomalous pulmonary venous return with obstruction. The obstruction can occur above or below the diaphragm. These infants have increasing cyanosis from pulmonary hypertension and decreased pulmonary blood flow. A heart murmur is usually not heard. The infants have increasing pulmonary edema early in the first week after birth from elevated pulmonary venous pressure resulting from increased pulmonary vascular volume. The chest radiograph may be similar to that in this vignette. The echocardiography would show right atrial and right ventricular enlargement and right-to-left shunting through the atrial septum (usually through a patent foramen ovale).

The respiratory symptoms seen in the infant in this vignette could possibly result from pneumonia. The diffuse nature of the pulmonary density on chest radiograph is not the picture of aspiration pneumonia, but it could be consistent with a viral pneumonia. However, no prodromal symptoms, such as fever or cough, were noted. Pneumonia would not have explained the murmur, sweating with feeding, or cardiomegaly.

Other possible causes of pulmonary edema in newborn infants include overhydration

(intravenous or oral), patent ductus arteriosus (in the premature infant), coarctation of the aorta, and peripheral arteriovenous shunt (in brain or liver).

References:

Bland RD. Lung fluid balance during development. *NeoReviews.* 2003;6:e255-e266

Kay JD, Colan SD, Graham TP Jr. Congestive heart failure in paediatric patients. *Am Heart J.* 2001;142:923-928

Rao PS, Turner DR, Forbes TJ. Hypoplastic left heart syndrome. Available at: http://emedicine.medscape.com/article/890196-overview. Accessed January 28, 2010

Wilson AD. Total anomalous pulmonary venous connection. Available at: http://emedicine.medscape.com/article/899491-overview. Accessed January 28, 2010

American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the causes of pulmonary edema and its effects on lung function

03_Cardiovascular: Recognize the clinical features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Recognize the laboratory, imaging, and other diagnostic features of a neonate with a left-to-right shunt lesion

03_Cardiovascular: Formulate a differential diagnosis for a neonate with a left-to-right shunt lesion

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ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **1** Correct Answers: **0**

Question 1

A 5-day-old infant with respiratory distress syndrome is receiving venoarterial (VA) extracorporeal membrane oxygenation (ECMO) because of neonatal hypoxemic respiratory failure refractory to medical management. The infant had received assisted ventilation with high-frequency oscillation, inhaled nitric oxide (INO), sedation, and blood pressure support with infusions of dopamine and dobutamine. The infant had also received four doses of intratracheal surfactant before ECMO was considered. Chest radiograph obtained before initiation of ECMO is shown in **Figure 1**. After initiation of VA-ECMO, a chest radiograph is obtained (**Figure 2**).

Figure 1: Before extracorporeal membrane oxygenation

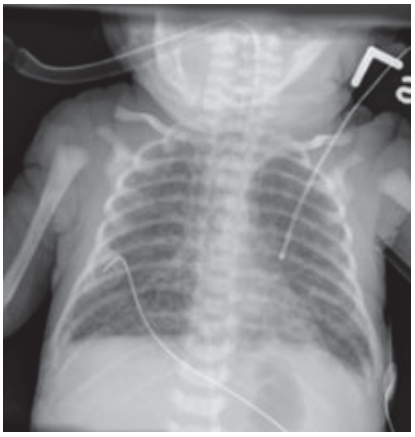
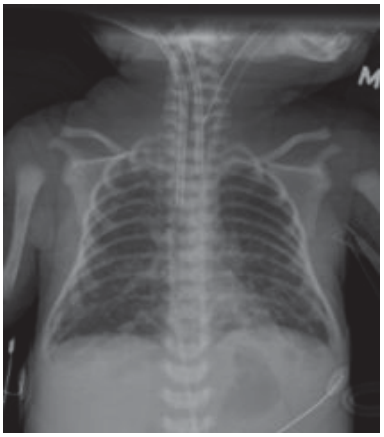


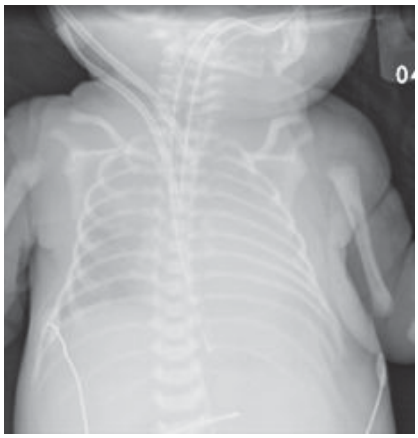
Figure 2: After extracorporeal membrane oxygenation cannulation



INO is discontinued and the pressors weaned off in 4 hours. While receiving ECMO, the infant

receives pressure limited ventilation at settings of fraction of inspired oxygen of 21%, positive inspiratory pressure of 25 cm H_2O, positive end-expiratory pressure of 6 cm H_2O, respiratory rate of 15 breaths per minute. Three days later, with ECMO support, the infant is hemodynamically stable and peripheral perfusion is maintained. The umbilical arterial blood gas shows a pH of 7.39, partial pressure of oxygen of 135 mm Hg, partial pressure of carbon dioxide of 39 mm Hg, and saturation of 95%. The mixed venous oxygen saturation is 75%. A complete blood count shows a total white blood cell count of 9,000µL (9.0×10^9/L), hematocrit of 45% (0.45), and platelet count of 80×10^3/µL (80×10^9/L). No evidence of bleeding from the umbilicus, intravenous access, or other sites is noted. A routine chest radiograph is obtained (**Figure 3**).

Figure 3: Three days after extracorporeal membrane oxygenation



Of the following, on the basis of the chest radiograph in Figure 3, the MOST appropriate next step at this time is:

- **A.** chest ultrasonography
- **B.** echocardiography
- **C.** intratracheal epinephrine
- **D.** routine pulmonary care
- **E.** surfactant administration

Incorrect:

Correct Answer: D

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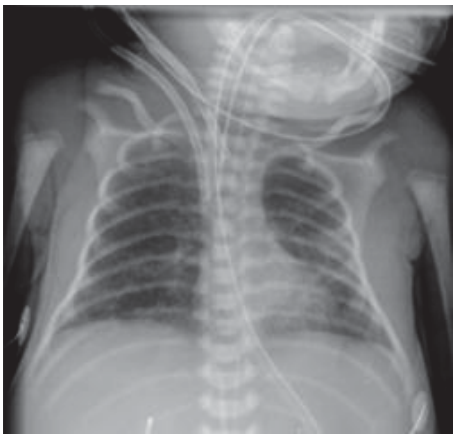
In the infant in the vignette, the chest radiograph taken before extracorporeal membrane oxygenation (ECMO; Figure 1) shows diffuse haziness of the lung fields consistent with a diagnosis of respiratory distress syndrome. In addition, the domes of the diaphragm are flattened and the cardiac silhouette appears small, both of which reflect increased intrathoracic pressure as a result of positive-pressure ventilation. The chest radiograph (CXR) in Figure 2 shows the ECMO cannulae with other findings being essentially unchanged from those seen in Figure 1. The CXR obtained 3 days later (Figure 3) shows the classic bilateral "white-out" appearance attributed to the diffuse pulmonary atelectasis and edema that has been described after ECMO initiation. Typically, as the primary lung disease resolves, dramatic improvement would be expected (**Figure 4**). Therefore, the most appropriate clinical response is the provision of routine pulmonary care.

Figure 4: Five days after extracorporeal membrane oxygenation



During extracorporeal circulation, blood and individual blood components are continuously exposed to the nonbiologic synthetic surfaces of the extracorporeal circuit. As a result, an activated systemic inflammatory reaction is believed to be responsible for the "postperfusion" or "postpump" syndrome noted primarily in the form of acute lung injury. This commonly manifests as opacification of the lung fields after ECMO is initiated. Ultimately, the cycle of inflammatory response associated with ECMO is interrupted because of a number of factors:

- restoration of tissue perfusion and reversal of hypoxia
- "passivation" of the foreign surface in ECMO circuit, ie, adherence of plasma proteins (especially fibrinogen and albumin) to the ECMO biomaterial surface, preventing the ongoing inflammatory response
- anti-inflammatory properties of heparin
- the body's intrinsic regulation to limit inflammatory responses

As the inflammatory response subsides, the lung fields gradually clear.

Following initiation of ECMO, pulmonary care may be provided by endotracheal and oropharyngeal suctioning as needed and gentle chest percussion or vibration. Arterial blood gases, along with circuit pre- and postoxygenator blood gases, are monitored periodically. Pulmonary evaluation of an infant receiving ECMO includes assessment of breath sounds and pulmonary graphics. Periodic CXRs are obtained to confirm line, catheter, and tube positions; assess lung volume changes and areas of significant atelectasis or collapse; and evaluate for free air.

During the first few days of ECMO support, the patient's pulmonary status often worsens, as evidenced by opacification of the lung fields on CXR (Figure 3) and decreased pulmonary compliance. As the infant's compliance improves, the aeration returns, ventilation improves, and chest movement is seen with lesser amounts of inspiratory pressure. Resolution of atelectasis and low lung volume on CXR and lung compliance improvements correlate well with the ability to wean the patient off ECMO support.

Pulmonary improvement in an infant receiving ECMO may be hindered by the interval development of a pneumothorax, hemothorax, pulmonary hemorrhage, pulmonary edema, pleural fluid, surfactant insufficiency, patent ductus arteriosus, or secondary infection. Hemothorax, pulmonary hemorrhage, pulmonary edema, and infection may present with focal or diffuse lung opacification. Cardiac tamponade appears as an enlarged cardiac silhouette on CXR. However, in the presence of diffuse white-out of the lung fields in the ECMO-related systemic inflammatory response, it may be difficult to differentiate these conditions.

Pericardial tamponade and tension hemothorax both result in increased intrathoracic pressure and decreased venous return. The associated decreases in pulmonary blood flow and native cardiac output yield an increase in the relative contribution of the extracorporeal circuit to peripheral perfusion. The peripheral partial pressure of oxygen (Pao_2) may increase while the patient may exhibit decreased perfusion with a narrowed pulse pressure with a decrease in oxygen delivery evidenced by a drop on mixed venous oxygen saturation. The triad of increased Pao_2, poor peripheral perfusion, and decreased venous return with progressive hemodynamic deterioration is associated with tension hemothorax and pericardial tamponade. In the infant in the vignette, all these signs are absent, making hemothorax and cardiac tamponade unlikely. Thus, chest ultrasonography and/or

Feedback

echocardiography would not be necessary for the care of the infant in the vignette at the present time.

Pulmonary hemorrhage may present with bilateral opacification of the lung fields and blood-tinged secretions. The infant in the vignette has no deterioration of hemodynamic variables or evidence of bleeding, making the possibility of pulmonary hemorrhage less likely than the postperfusion syndrome. Therefore, intratracheal administration of epinephrine would not be an appropriate next step for the infant.

The administration of surfactant has proven beneficial in neonates undergoing ECMO when atelectasis is persistent. The infant in the vignette does not have enough evidence to suggest persistent atelectasis, so surfactant administration would not be the best next choice. Notably, a CXR obtained 2 days later showed dramatic improvement in aeration (Figure 4). Although surfactant has not been shown to improve lung mechanics once atelectasis occurs, some clinicians administer surfactant immediately after starting ECMO and use higher positive end-expiratory pressures in an attempt to prevent postpump syndrome.

Right-to-left shunting across a patent ductus arteriosus (PDA) is frequently seen with neonatal hypoxemic respiratory failure. Following ECMO, the pulmonary hypertension resolves, flow through the PDA reverses (left-to-right), and the PDA usually closes within 24 hours; rarely, a PDA does not close spontaneously. For the infant in the vignette, findings are not suggestive of a persistent PDA, and there is no need at the present time to obtain an echocardiogram.

References:

DeBerry BB, Lynch J, Chung DH, Zwischenberger JB. Emergencies during ECLS and Their Management. In: Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization. 2005:133-156

Hopper AO, Pageau J. Management of the neonate on ECMO. In: Van Meurs K, ed. *ECMO Specialist Training Manual.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 1999:123-140

Lewis FC, Reynolds M, Arensman RM. Extracorporeal membrane oxygenation. In Goldsmith JP, Karotkin E, eds. *Assisted Ventilation of the Neonate.* Philadelphia, Pa: WB Saunders; 2003:261-277

Radhakrishnan RS, Cox CS. ECLS and the Systemic Inflammatory Response. In Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:59-83

Van Meurs K, Hintz SR, Sheehan AM. ECMO for Neonatal Respiratory Failure. In Van Meurs K, Lally KP, Peek G, Zwischenberger JB, eds. *ECMO Extracorporeal Cardiopulmonary Support in Critical Care.* Ann Arbor, Mich: Extracorporeal Life Support Organization; 2005:273-295

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Bartlett RH. Historical perspectives: extracorporeal membrane oxygenation (ECMO). *NeoReviews.* 2005;6:e251-e254. Available at: http://neoreviews.aappublications.org/cgi/content/full/6/6/e251? Accessed May 19, 2010

Carriedo H, Deming D. Therapeutic techniques: neonatal ECMO. *NeoReviews.* 2003;4:212-214. Available at: http://neoreviews.aappublications.org/cgi/content/full/4/8/e212? Accessed May 19, 2010

American Board of Pediatrics Content Specification(s):

04_Respiratory: Know the indications, techniques, effects, and risks of extra- corporeal membrane oxygenation (ECMO)

04_Respiratory: Know the management of persistent pulmonary hypertension including assisted ventilation, pharmacologic approaches, and ECMO

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Assessment History

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **4** Correct Answers: **0**

Question: 4

A pregnant woman with diabetes mellitus type I has an appointment with a pediatric cardiologist at 24 weeks' gestation. Fetal echocardiography reveals a structurally normal heart with appropriate function and a normal heart rate and rhythm. The woman is interested in understanding how the fetus' circulation is different from her own. The cardiologist draws her pictures of her fetus' circulation.

Of the following, in fetal circulation:

- A. approximately 25% of total intrauterine blood volume goes to fetal lungs
- B. blood shunts across patent ductus arteriosus from left-to-right
- C. the left side of fetal heart has higher oxygen saturation than the right side
- D. the left ventricle supplies more intrauterine cardiac output than the right ventricle
- E. the vessel with the lowest oxygen saturation in the fetus is the umbilical vein

Incorrect

Correct Answer: C

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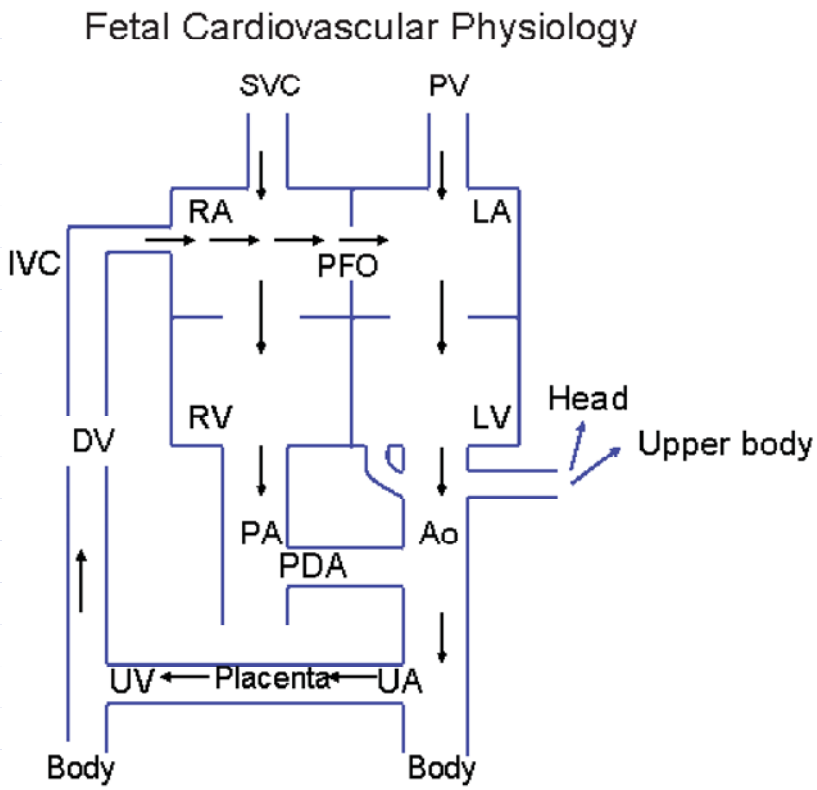
A schematic of the fetal cardiovascular circulation is shown in **Figure 1**. Oxygenated blood from the placenta travels within the umbilical vein; it then crosses into the ductus venosus and enters the inferior vena cava. Because of the angle at which blood enters the right atrium from the inferior vena cava, approximately one third of the inferior vena caval blood is shunted directly through the foramen ovale into the left atrium. The remaining right atrial blood enters the right ventricle, and most of the blood then bypasses the lungs by passing through the patent ductus arteriosus into the postductal aorta. Blood from the left atrium is transported into the left ventricle and then to the aorta. Fetal blood returns to the placenta via the two umbilical arteries for reoxygenation and waste elimination.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

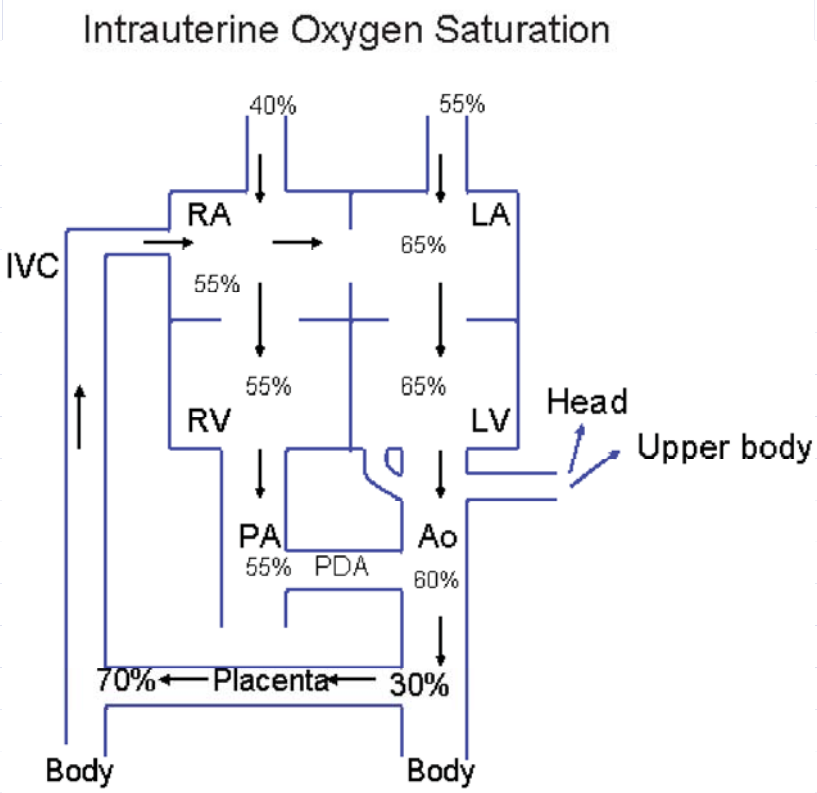
Figure 1: This schematic illustrates the intrauterine circulation. SVC=superior vena cava, PV=pulmonary veins, IVC=inferior vena cava, RA=right atrium, LA=left atrium, PFO=patent foramen ovale, RV=right ventricle, LV=left ventricle, DV=ductus venosus, PA=pulmonary artery, Ao=aorta, PDA=patent ductus arteriosus (Adapted from Keane and colleagues [2006].)



Studies examining the circulation of fetal lambs provide insight into the oxygenation of the vasculature in human fetuses (**Figure 2**). Blood in the umbilical vein has an oxygen saturation of 70%. Upon entering the right atrium, this mixes with blood from the superior vena cava, which has an oxygen saturation of 40%, creating a combined right atrial saturation of approximately 55%. Because blood in the left atrium contains a large amount of highly saturated blood directly from the inferior vena cava via the foramen ovale (oxygen saturation=70%) and mixes with a small amount of blood from the pulmonary veins (oxygen saturation=55%), the left atrial oxygen saturation is approximately 65%. Thus, the left side of the fetal heart has higher oxygen saturation than the right side of the fetal heart. This differential oxygenation enables the preductal aortic vessels supplied by the left ventricle to provide the brain and coronary vessels with higher oxygen saturation blood.

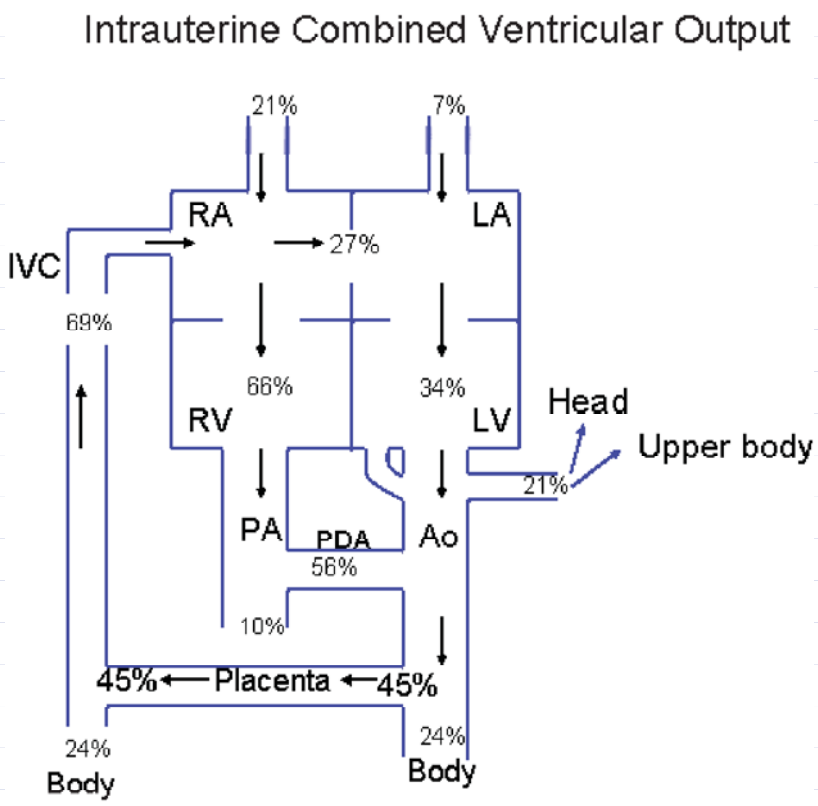
Figure 2: This schematic illustrates the oxygen saturation of vessels during late gestation. The oxygen saturation in the fetus is highest in the umbilical vein (oxygen saturation=70%), representing blood supplied by the placenta. The saturation of the blood in the heart is slightly higher on the left side (oxygen saturation=65%) than on the right side (oxygen saturation=55%) as a result of inferior vena caval blood being shunted across the foramen ovale to the left side of the heart. The umbilical arterial oxygen saturation is approximately 30% while the umbilical venous oxygen saturation is 70%. IVC=inferior vena cava, RA=right atrium, LA=left atrium, RV=right ventricle, LV=left ventricle, PA=pulmonary artery, Ao=aorta, PDA=patent ductus arteriosus. (Adapted from Keane and colleagues [2006].)

Feedback



In adult circulation, 100% of the total blood flow goes through the right side of the circulation and then the entire flow passes through the left side. In contrast, fetal circulation works in parallel and each side of the circulation has distinct roles (**Figure 3**). While the right ventricle supplies most of its output to the lower body, the left ventricle provides output to the heart, brain, and upper body. These parallel forms of circulation are not completely separate because the right and left sides of the fetal circulation combine at the levels of the foramen ovale and patent ductus arteriosus. As a result of these shunts, only 5% to 15% of the total blood flow perfuses the lungs. Both of these shunts are described as *right-to-left* because blood is shunted from the right to the left side of the heart. Across the patent ductus arteriosus, blood shunts from the right-sided pulmonary artery to the left-sided aorta, avoiding the pulmonary circulation, while blood shunts across the foramen ovale from the right atrium to the left atrium.

Figure 3: This schematic illustrates the percentage of combined ventricular output during late gestation. While the intrauterine left ventricle supplies 34% of the ventricular output, the right ventricle supplies a larger amount of cardiac output, with approximately 56% of the total blood flow supplied to the body and 5% to 15% of the total blood flow to the lungs. IVC=inferior vena cava, RA=right atrium, LA=left atrium, RV=right ventricle, LV=left ventricle, PA=pulmonary artery, Ao=aorta, PDA=patent ductus arteriosus (Adapted from Keane and colleagues [2006].)



Because most of the right ventricular blood flow is shunted in utero across the patent ductus arteriosus to supply the cardiac output, the intrauterine right ventricle supplies approximately 59% of the total blood flow to the body and 5% to 15% of the total blood flow to the lungs. As a result of the large amount of cardiac output supplied by the right ventricle and the high distal vascular resistance of the pulmonary vascular bed, the intrauterine right ventricle wall undergoes hypertrophy. While the left ventricle receives some of the shunted blood from the foramen ovale, there is very little pulmonary circulation that feeds back to the left side of the heart. Indeed, the left ventricle supplies 34% of the total intrauterine blood flow, which is less than the right ventricular output. Thus, if there is a left-sided cardiac structural abnormality such as a hypoplastic left ventricle, the fetus will be minimally affected because the right ventricle compensates for the inadequate left ventricular function and supplies a large amount of the cardiac output.

After branches of the aorta perfuse fetal tissues, blood returning to the placenta to be oxygenated is transported through the umbilical arteries. The umbilical arterial blood has a low oxygen saturation of approximately 30%. In contrast, the umbilical vein is providing blood directly from the placenta and is well-oxygenated, with an estimated oxygen saturation of 70%. This umbilical arterial-venous unit is unique because the arterial blood has a lower oxygen content than the corresponding venous blood.

References

Fetal and Neonatal Physiology, 3rd ed. Philadelphia: WB Saunders Co; 2006

Nadas' Pediatric Cardiology, 2nd ed. Philadelphia: WB Saunders; 2006

Brodsky D, Martin C. *Neonatology Review, 2nd ed*. Philadelphia: Elsevier; 2010

American Board of Pediatrics Content Specification(s)

Cardiovascular: Know the factors affecting and regulating myocardial performance and function in the fetus and newborn infant and during the transitional period

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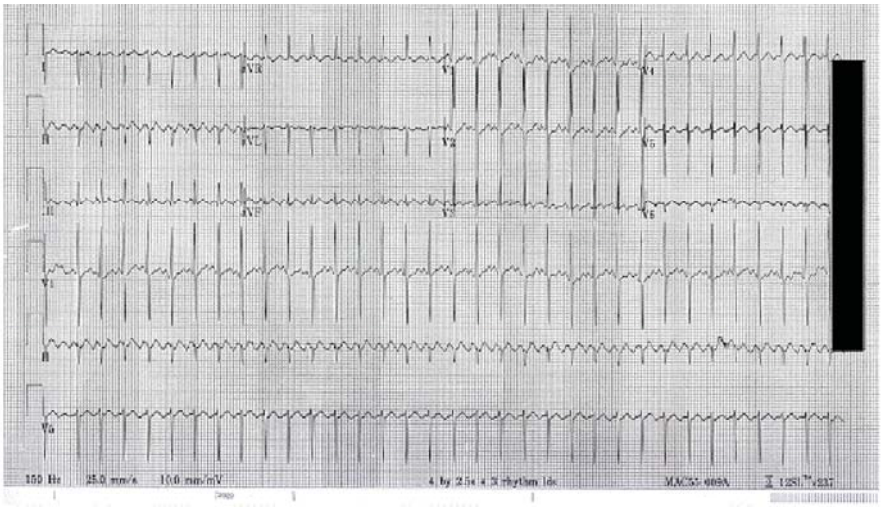
ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **6** Correct Answers: **0**

Question: 6

A full-term infant is admitted to the newborn nursery after an uncomplicated pregnancy and spontaneous vaginal delivery. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. Tachycardia is noted and he is transferred to the neonatal intensive care unit for cardiorespiratory monitoring and evaluation. His heart rate is 205 beats per minute and without variability. On physical examination, he is appropriately grown, afebrile, and without respiratory distress or cyanosis. Perfusion is adequate, peripheral pulses are palpable, and a liver edge is appreciated 0.5 cm below the right costal margin. No cardiac murmurs are auscultated. There is no maternal history of illicit substance use or medications during labor, with the exception of local anesthesia through an epidural catheter. An electrocardiogram is obtained (**Figure**).

Figure: Electrocardiogram



Of the following, the treatment MOST likely to terminate this infant's tachycardia is:

- A. cardioversion
- B. ice to the face
- C. intravenous adenosine
- D. intravenous digoxin
- E. intravenous fluid bolus

Incorrect

Correct Answer: A

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Feedback

The infant in the vignette has a narrow complex tachycardia consistent with atrial flutter, and exhibits typical electrocardiographic (ECG) findings of an undulating, saw-tooth pattern of P waves and 2:1 atrial to ventricular conduction (**Figure**).

Arrhythmias occur in up to 5% of newborn infants during the first 10 days after birth. Premature atrial contractions and premature ventricular contractions are most common, followed by supraventricular tachycardia (SVT), occurring with an estimated incidence of 1 in 250 neonates. Tachyarrhythmias must be differentiated from sinus tachycardia, which is caused by conditions such as fever, infection, dehydration, hypovolemia, pain and anemia, as well as hyperthyroidism and medications including beta-adrenergic agonists and theophylline. Sinus tachycardia resolves with treatment of the underlying condition.

Described in 1892 as “paroxysmal hurry of the heart,” SVT is the most common symptomatic arrhythmia in the neonatal period. These arrhythmias originate proximal to the bundle of His and typically occur with heart rates greater than 230 beats per minute. Atrioventricular re-entrant tachycardia (AVRT) represents 50% to 70% of neonatal SVTs. The arrhythmia circuit in AVRT involves normal impulse conduction over the atrioventricular (AV) node and retrograde conduction from the ventricle to the atrium over an accessory pathway (orthodromic re-entry). In Wolff-Parkinson-White syndrome, anterograde conduction over the accessory pathway occurs during sinus rhythm, avoiding usual AV node delay, and resulting in a shortened P-R interval on ECG. In addition, fusion of ventricular complexes, the result of conduction through both the accessory pathway and the normal pathway, create the characteristic delta wave on ECG. Up to 56% of AVRTs are caused by Wolff-Parkinson-White syndrome. AV nodal re-entry tachycardia (AVNRT) causes approximately 13% of SVTs and similarly involves dual pathways situated within or near the AV node. Usually a premature atrial or ventricular contraction or a junctional escape beat initiates AVRT or AVNRT, and the typical AV conduction relationship is 1:1.

Atrial flutter (AF) is an uncommon type of SVT in the neonate (estimated 14% of SVT cases) and often presents with asymptomatic tachycardia. The mechanism for this atrial tachycardia is a re-entry circuit in the atrial muscle that can be associated with an accessory pathway. The flutter wave rate ranges from 300 to 600 beats per minute and conduction of the atrial impulse through the AV node, which is not part of the re-entry circuit, dictates the ventricular rate. The ventricular rate can be as high as the atrial rate, but more often AV conduction is 2:1 (75% of cases) or slower, distinguishing AF from AVRT and AVNRT. Characteristic ECG findings include regular, rapid, saw-toothed flutter waves seen best in leads II, III, and aVF. Nonconducted P waves additionally distinguish AF from typical SVT. In infants, AF usually occurs in structurally normal hearts, but has been associated with congenital heart disease such as atrioventricular septal defect and hypoplastic left heart. AF has been associated with maternal cocaine and/or opiate use during pregnancy.

Cardiac failure develops in approximately 20% of cases of SVT after 36 hours and 50% after 48 hours, and prompt restoration of normal sinus rhythm is imperative in the unstable infant. Development of symptoms is most associated with duration of the tachyarrhythmia and not the atrial or ventricular rate. Spontaneous conversion to sinus rhythm may occur and with well-tolerated tachyarrhythmias such as AF, a waiting period may be considered before intervention.

Atrial flutter can be terminated most reliably with direct current cardioversion or transesophageal pacing. Vagal maneuvers, such as ice to the face, terminate certain SVTs by transiently blocking the AV node. Because the re-entry circuit in AF does not involve the AV node, such maneuvers are typically ineffective. Similarly, results are variable with the use of adenosine, which also acts by blocking conduction at the AV node. However, slowing conduction at the AV node may elucidate flutter waves on ECG and assist with diagnosis. Similarly, digoxin acts by decreasing conduction through the AV node, and is ineffective for acute termination of AF. In infants, AF typically does not recur and treatment after initial conversion is unnecessary, particularly in the absence of congenital heart disease or additional arrhythmias. When indicated, digoxin is usually the first-line drug for chronic treatment. An intravenous fluid bolus may improve sinus tachycardia related to hypovolemia, but would not terminate tachyarrhythmias such as SVT or AF.

References

Killen S, Fish FA. Fetal and neonatal arrhythmias. *NeoReviews*. 2008;9:e242-252

Lisowski LA, Verheijen PM, Benatar AA, et al. Atrial flutter in the perinatal age group: diagnosis, management and outcome. *J Am Coll Cardiol*. 2000;35:771-777

Singh HR, Garekar S, Epstein ML, L'Ecuyer T. Neonatal supraventricular tachycardia (SVT). *NeoReviews*. 2005;6:e339-350

Texter KM, Kertesz NJ, Friedman RA, Fenrich AL. Atrial flutter in infants. *Pediatr Cardiol*. 2006;48:1040-1046

Wren C. Cardiac arrhythmias in the fetus and newborn. *Semin Fetal Neonatal Med*. 2006;11:182-190

American Board of Pediatrics Content Specification(s)

Cardiovascular: Differentiate normal from common abnormal electrocardiographic patterns and rhythms in

the fetus and newborn infant.

Cardiovascular: Know the physiologic consequences of a dysrhythmia in a fetus or newborn infant.

Cardiovascular: Know appropriate management of common dysrhythmias in the fetus and newborn infant, and understand the potential complications or adverse effects of approaches and drugs used.

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Assessment History

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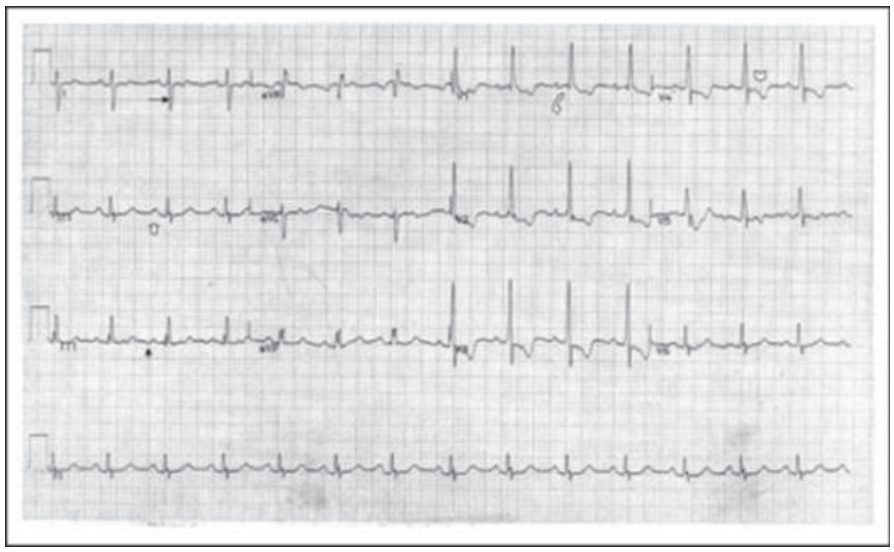
Question: 1

An infant born at 25 weeks' gestation is now near his initially estimated due date. Despite prenatal steroid treatment, surfactant at birth, early extubation to nasal continuous positive airway pressure, and subsequent treatment with vitamin A and caffeine, he suffers from bronchopulmonary dysplasia. Over the last week he has tired more with his feedings and now is not receiving anything by mouth. His oxygen requirements, to maintain oxygen saturation above 85%, have increased to 100% and he now requires mechanical ventilation. Electrocardiographic findings suggest cor pulmonale (**Figure**).

Figure: Electrocardiography demonstrating 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) (adapted from Rothstein and colleagues [2009].)



Echocardiography estimates a pulmonary artery systolic pressure that is almost equal to the systemic systolic pressure with evidence of right heart failure. You discuss treatment options with the cardiologist, including those that are yet unproven.

Of the following, the agent MOST likely to reverse the acute pulmonary hypertensive crisis in this infant is:

- ○ **A.** bosentan
- ○ **B.** chlorothiazide
- ✗ **C.** iloprost
- ○ **D.** nitric oxide
- ○ **E.** sildenafil

✗ **Incorrect**

Correct Answer: D

Bronchopulmonary dysplasia (BPD) develops in the lungs of premature infants in association with a number of factors (**Table 1**). The observed pathology includes impaired alveolarization and dysregulated angiogenesis, causing fewer alveoli, abnormal small-airway architecture, and dysmorphic pulmonary vasculature. **Table 2** lists some abnormalities of pulmonary function observed in infants with BPD.

Table 1: Factors Involved in the Development of Bronchopulmonary Dysplasia
Prematurity
Hyperoxia
Volutrauma
Inflammation
Sepsis
Pneumonia
Aspiration
Maternal chorioamnionitis
Pulmonary hypoplasia
Congenital heart disease
Persistent pulmonary hypertension

Table 2: Pulmonary Function Abnormalities seen with Bronchopulmonary Dysplasia
Increased airway resistance
Increased airway obstruction
Increased airway reactivity
Decreased lung compliance
Ventilation/perfusion mismatch [/]
Increased thoracic gas volume
Decreased tidal volume
Increased respiratory rate
Increased work of breathing

Prevention of BPD ideally involves prevention of prematurity, an elusive goal. The role of antenatal steroids in preventing BPD is disputed.

Some measures can be taken in the first week after birth to prevent BPD, including ventilatory, pharmacologic, and nutritional strategies (**Table 3**). Some measures may be effective in preventing BPD, but lack sufficient proof for widespread use, such as nitric oxide, inositol, or recombinant human Clara cell protein.

Table 3: Some Early Measures to Prevent the Development of Bronchopulmonary Dysplasia*
Ventilatory
Avoidance of intubation
Early surfactant with extubation
Low tidal volumes
Oxygen saturation <95%
Pharmacologic
Caffeine
Vitamin A
Nutritional strategies
Increased energy intake
Restrictive fluid intake

* Adapted from Bhandari and Bhandari (2009).

When BPD evolves and becomes established, several treatments have been found to provide short-term improvement, including corticosteroids, diuretics, and β-agonists. A lack of long-term benefits and the chance of complications have tempered the chronic use of these agents.

Feedback

In established BPD, dysregulated angiogenesis can lead to dysmorphic pulmonary vasculature, pulmonary hypertension, and cor pulmonale, as in the vignette. There are no screening guidelines for pulmonary hypertension in infants with BPD, so a high clinical index of suspicion is needed for detection.

Signs consistent with pulmonary hypertension initially are nonspecific, such as failure to thrive or tiring with feeding. Later signs can include peripheral edema, ascites, and hepatomegaly. Electrocardiographic findings (Figure) may include right ventricular hypertrophy, right axis deviation, right atrial enlargement, or incomplete right bundle branch block.

Some of the increased pulmonary vascular resistance in BPD is caused by irreversible fibrosis and dysplastic vascular branching. Another portion is caused by reversible vasoconstriction. Treatment of pulmonary

hypertension aims at relaxation of pulmonary vasoconstriction, until pulmonary growth can provide a more lasting remedy. Agents used to reverse vasoconstriction include oxygen (maintaining an oxygen saturation over 95%), inhaled nitric oxide (when intubated and receiving mechanical ventilation), sildenafil, and iloprost or bosentan (in adults). Inhaled oxygen dilates the pulmonary vasculature by also activating guanylyl cyclase via endothelium-derived nitric oxide. Of the agents listed, inhaled nitric oxide is most likely to reverse the pulmonary hypertensive crisis in the infant in the vignette.

Inhaled nitric oxide works to relax pulmonary vascular smooth muscle cells by activating the enzyme guanylyl cyclase. This produces more cyclic guanosine monophosphate (cGMP), which enhances protein kinase and intracellular calcium sequestration, resulting in relaxation. Side effects, rarely seen, can include potentially injurious concentrations of nitrogen dioxide, peroxynitrite, and methemoglobin.

Sildenafil acts in the pulmonary vascular smooth muscle cell by inhibiting phosphodiesterase type 5, an enzyme that degrades cGMP. The results are more intracellular cGMP and relaxation of the smooth muscle. Adverse effects in older children and adults may include systemic hypotension, nausea, vomiting, hearing impairment, and priapism. No adverse effects have been reported in human neonates, based on small studies, although there are concerns about its effects on retinopathy. Animal studies suggest the potential for adverse effects on the developing nervous system. The use of sildenafil for pulmonary hypertension associated with BPD requires further study. The use of sildenafil in persistent pulmonary hypertension of the neonate, a different condition, may be promising, but also requires additional study.

Bosentan, a competitive inhibitor of the vasoconstrictor endothelin-1, is used in adults with primary pulmonary hypertension. Data are not available regarding its use in neonates. Side effects in adults may include edema, anemia, and hepatic damage.

Iloprost, a synthetic form of prostacyclin, is used as an inhalant to treat adult primary pulmonary hypertension. Data are lacking for its use in neonates. Iloprost promotes smooth muscle relaxation by stimulating production of cyclic adenosine monophosphate and of protein kinase. Side effects may include congestive heart failure, supraventricular tachycardia, edema, dyspnea, and renal failure.

Diuretics such as chlorothiazide are used in pulmonary hypertension as adjunctive agents to reduce preload to the burdened right ventricle. Chlorothiazide acts at the distal convoluted tubule of the kidney, where it inhibits sodium and chloride reabsorption. Side effects may include hypokalemia, hypercalcemia, hyperuricemia, hyperglycemia, tachycardia, intrahepatic cholestasis, pancreatitis, and a hypersensitivity reaction.

References

Baraldi E, Filippone M. Chronic lung disease after premature birth. *N Engl J Med*. 2007;357:1946-1955

Bhandari A, Bhandari V. Pitfalls, problems, and progress in bronchopulmonary dysplasia. *Pediatrics*. 2009;123:1562-1573

Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics*. 2007;120:1260-1269

Ramanathan R. Bronchopulmonary dysplasia and diuretics. *NeoReviews*. 2008;9:e260-e267

Rothstein R, Paris Y, Quizon A. Pulmonary hypertension. *Pediatr Rev*. 2009;30:39-64

Shaffer TH, Cullen AB, Wolfson MR. Clinical assessment of airway function in health and disease. *NeoReviews*. 2002;3:131-136. Accessed February 12, 2010 at: http://neoreviews.aappublications.org/cgi/content/full/3/7/e131

Truog WE. Chronic lung disease and randomized interventional trials: status in 2005. *NeoReviews*. 2005;6:e278-e288. Accessed February 12, 2010 at: http://neoreviews.aappublications.org/cgi/content/full/6/6/e278

American Board of Pediatrics Content Specification(s)

Respiratory: Know the management of bronchopulmonary dysplasia/chronic lung disease

Respiratory: Know the pathogenesis, pathophysiology, and pathologic features of bronchopulmonary dysplasia/chronic lung disease

Cardiovascular: Know the mechanisms of action, therapeutic indications for, and toxicity of vascular afterload-reducing drugs

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Question: 9

You are consulted by a pediatrician who observes a 1-hour old full-term infant develop cyanosis while crying. The infant has normal findings on physical examination. His vital signs are stable except for pre- and postductal oxygen saturation of 75% while crying, with equal oxygen saturation rates of 100% at rest. Echocardiography reveals elevated pulmonary vascular pressures and bilateral shunting across the patent ductus arteriosus.

Of the following, the MOST likely additional echocardiographic finding in this infant is:

- **A.** anomalous origin of the left coronary artery from the pulmonary artery
- **B.** D-transposition of the great arteries with an intact ventricular septum
- **C.** tetralogy of Fallot with severe pulmonary valvar stenosis
- **D.** tricuspid atresia with a small ventricular septal defect
- **E.** ventricular septal defect

Incorrect

Correct Answer: E

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It is common for pulmonary vascular resistance in neonates to be elevated during the first few hours to days after birth. Clinical symptoms will depend on the severity of elevation in the pulmonary vascular resistance and the cardiac anatomy. Neonates with severe pulmonary hypertension will manifest severe cyanosis at rest as a result of shunting across the patent ductus arteriosus (PDA) from the right-sided pulmonary artery to the left-sided aorta, shunting blood away from the pulmonary circulation. Infants with milder forms of pulmonary hypertension may have less consistent right-to-left shunting across the PDA and may have normal oxygen saturation at baseline with episodic cyanosis when the pulmonary vascular resistance is further elevated, such as with crying. Regardless of whether the right-to-left ductal shunting is persistent or transient, during periods of cyanosis, infants will have higher preductal oxygen saturation than their postductal oxygen saturation. However, if an infant with elevated pulmonary vascular resistance has right-to-left ductal shunting with significant intracardiac shunting across a ventricular septal defect (VSD), atrial septal defect, or persistent foramen ovale, the pre- and postductal oxygen saturation will be similar. Thus, an echocardiogram in the infant in this vignette most likely will also reveal a large VSD.

Anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) is a rare vascular abnormality in which the left main coronary artery originates abnormally from the pulmonary artery. During the early neonatal period, neonates with ALCAPA are typically asymptomatic because the elevated pulmonary vascular resistance drives blood from the pulmonary artery to the anomalous left coronary artery, and myocardial ischemia does not occur. As the pulmonary vascular resistance decreases during the first few weeks after birth, the pulmonary arterial pressure is no longer sufficient to force blood into the anomalous left coronary artery. During this stage, flow to the left coronary arterial system relies on collateral oxygenated flow from the right coronary arterial system. Infants with inadequate collaterals and low pulmonary vascular resistance have blood flow from the high resistance left coronary arterial system into the

Feedback

low resistance pulmonary artery. This reversal of flow, also known as the *pulmonary-coronary steal*, leads to left ventricular myocardial ischemia and possibly infarction.

The clinical findings in patients with ALCAPA depend on the degree of pulmonary vascular resistance, presence or absence of collateral vessels between the right and left coronary arterial systems, and degree of myocardial ischemia and/or infarction. Symptoms usually occur in early infancy at approximately 2 to 3 months of age when the pulmonary vascular resistance is lowest. An infant with ALCAPA will present with respiratory distress, feeding intolerance, and/or failure to thrive. Transient ischemia may lead to periods of pallor, paroxysmal crying, diaphoresis with feeding, and severe agitation. If the infant's disease progresses to an anterolateral myocardial infarction, the electrocardiographic findings show abnormal Q waves in leads I, aVL, V4, V5, and V6 with ST segment elevations in leads V4 through V6. Because infants with ALCAPA are not typically symptomatic while the pulmonary vascular resistance is elevated, the infant in this vignette is unlikely to have ALCAPA. Furthermore, symptomatic infants with ALCAPA usually present with congestive heart failure instead of episodic cyanosis.

D-Transposition of the great arteries (TGA) is the most common cyanotic heart defect presenting in the first week after birth. If the aortic valve is anterior to, inferior to, or to the right of, the pulmonary valve, the great arteries are in the dextro (D) position. Because the aorta and pulmonary arteries are transposed, two parallel patterns of circulation are created. The affected infant's degree of cyanosis and survival depend on the amount of mixing between these parallel patterns of circulation. Possible communications include a patent foramen ovale, atrial septal defect, VSD (most common), PDA, systemic collateral arteries, or any combination of these. Affected infants with an intact ventricular septum have severe cyanosis, and may survive if there is left-to-right flow through a dilated foramen ovale and a large PDA with aorta-to-pulmonary artery flow, cumulatively creating significant flow into the pulmonary circulation. In this scenario, infants will have equal but low pre- and postductal oxygen saturation. If infants have an elevated pulmonary vascular resistance, ductal flow may be directed from the pulmonary artery to the aorta evident by reversed differential cyanosis with postductal oxygen saturation being higher than preductal saturation. The infant in this vignette cannot have D-TGA with an intact ventricular septum because an infant with this lesion should have significant cyanosis at rest.

Infants with tetralogy of Fallot (TOF) have a tetrad of cardiac findings: an overriding aorta, a subaortic large VSD, right ventricular hypertrophy, and varying degrees of right ventricular outflow tract obstruction (ie, pulmonary valvar stenosis [PS]). In infants with TOF, the direction of blood flow across the VSD and the degree of cyanosis are directly related to the severity of the right ventricular outflow obstruction. When the pulmonary valvar region is severely stenotic, most of the right ventricular output exits through the VSD, leading to significant cyanosis at rest. In contrast, when the right ventricular outflow tract obstruction is mild, infants have little or no right-to-left shunting across the VSD and normal systemic arterial oxygen saturation, often called "pink tetralogy." If the pulmonary vascular resistance is low, some of these infants with mild outflow tract obstruction may even have left-to-right intraventricular shunting leading to pulmonary overcirculation and congestive heart failure, similar to infants with an isolated VSD.

Superimposed on the fixed anatomic right ventricular outflow tract obstruction, dynamic factors can increase the right-to-left ventricular shunting, worsening the degree of cyanosis in infants with TOF. These factors include spasm of the subpulmonary muscular infundibulum, an increase in pulmonary vascular resistance as occurs with crying, or a decrease in systemic vascular resistance as occurs during exercise. Because infants with TOF and severe pulmonary valvar stenosis typically exhibit severe cyanosis at rest, as a result of inadequate pulmonary blood flow, the acyanotic infant in this vignette is unlikely to have this defect. Although the additive presence of a large PDA with persistent left-to-right shunting might decrease the degree of cyanosis, this would still not be associated with an oxygen saturation of 100%. An infant with TOF and a mild outflow tract obstruction may exhibit similar clinical findings as the infant in this vignette, with normal oxygen saturation at rest and lower pre- and postductal oxygen saturation when the pulmonary vascular resistance is increased, such as occurs with crying.

Infants with tricuspid atresia have an obligatory right-to-left shunt at the atrial level and a hypoplastic right ventricle because there is no direct communication between the right atrium and right ventricle. Most patients also have an associated VSD, creating a left-to-right shunt at the ventricular level to augment pulmonary blood flow. A large PDA with left-to-right shunting will further increase pulmonary blood flow. While infants with a large VSD will have sufficient intrauterine flow to the right ventricle and lungs, in infants with a small VSD, the right ventricular outflow will be limited, increasing the infant's degree of cyanosis. If an infant has elevated pulmonary vascular resistance, this will further induce right-to-left intraventricular shunting and attenuate left-to-right ductal shunting, causing further cyanosis. Similar to the infant in this vignette, an infant with tricuspid atresia may have significant cyanosis while crying, with equal pre- and postductal oxygen saturation. However, in contrast to the infant in the vignette, the inadequate pulmonary blood flow associated with this defect will also lead to cyanosis at rest.

References

Nadas' Pediatric Cardiology. 2nd ed. Philadelphia, PA: WB Saunders Co; 2006

Lee AC, Foster E, Yeghiazarians Y. Anomalous origin of the left coronary artery from the pulmonary artery: a case series and brief review. *Congenit Heart Dis*. 2006;1:11-15. Abstractat: http://www.ncbi.nlm.nih.gov/pubmed/18377554

American Board of Pediatrics Content Specification(s)

Cardiovascular: Recognize the clinical features of a cyanotic neonate

Cardiovascular: Formulate a differential diagnosis for a cyanotic neonate

Cardiovascular: Recognize the clinical features of a neonate with a right-sided cardiac lesion

Cardiovascular: Formulate a differential diagnosis for a neonate with a right-sided cardiac lesion

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ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **5** Correct Answers: **2**

Question: 5

You have just admitted a 1-week-old term infant to the neonatal intensive care unit with severe coarctation of the aorta. The infant was born at your hospital, and a review of the chart shows normal examination findings recorded by both house officers and attending staff. You consider the reasons underlying a missed or delayed diagnosis of severe congenital heart disease.

Of the following, a delay in diagnosis of significant congenital heart disease in the newborn period is MOST often attributable to:

- A. early hospital discharge
- B. failure to detect cardiac murmur
- C. lack of a second (discharge) physical examination
- D. patency of the ductus arteriosus
- E. undetected clinical cyanosis

Incorrect

Correct Answer: D

Congenital heart disease (CHD) is responsible for more infant mortality than any other form of congenital malformation. CHD occurs at a rate of about 9 per 1,000 births, and 25% of affected infants have a condition requiring catheter or surgical intervention in the first year after birth, defined as *critical congenital heart disease* (CCHD). In spite of these numbers, approximately 25% of infants with CCHD are not diagnosed until sometime after hospital discharge (median age at diagnosis, 6 weeks) and, in the United States, delayed or missed diagnosis of CCHD is estimated to occur in over 7 cases per 100,000 live births.

Delayed diagnosis is associated with severity of illness at the time of diagnosis and long-term morbidities related to shock and/or hypoxemia-ischemia. Delayed diagnosis of CCHD is estimated to account for 0.4 to 2.0 deaths per 10,000 live births, a significant fraction of overall infant mortality. Missed diagnosis of CCHD is associated with potentially preventable mortality: in one series, 6.6% died at home and 44.7% died in the hospital emergency department. Two thirds of these patients had either coarctation of the aorta or hypoplastic left heart syndrome. Many of the remainder had conditions for which treatment options are available.

Critical congenital heart disease is shown to be associated with an increased risk of acute brain injury. Periventricular leukomalacia has been found in 39% of infants with CCHD before surgical intervention. Long-term neurodevelopmental impairments of motor, language, visual, and executive functions are more frequent in children having CCHD. Although not yet documented in controlled studies, prompt and accurate diagnosis, combined with earlier intervention before shock and/or hypoxemia lead to deterioration, may reduce the morbidity associated with CCHD.

Most of the deaths resulting from delayed diagnosis of CCHD are associated with ductal-dependent conditions such as coarctation of the aorta (including aortic atresia) and hypoplastic left heart syndrome. In most cases, the most significant feature underlying the difficulty in diagnosing CCHD before hospital discharge is ductal dependency. Often the ductus arteriosus remains open through the time of discharge and obscures the diagnostic clinical features of the condition. Ductal dependency is a major component of several forms of CHD (**Table 1**).

Table 1: Hypoxemia and Ductal Dependency in Selected forms of Congenital heart Disease

Lesion	Incidence, %	Hypoxemia Associated	SPO_2 <95%, %	DA Dependent
Tetralogy of Fallot	6.1	Most	69	Uncommon
D-transposition	4.0	All	100	Uncommon
Double outlet R ventricle	1.7	Some	100	Some
Total anomalous pulmonary venous connection	1.2	All	85.7	None
Ebstein anomaly of tricuspid valve	0.6	Some	NA	Some
Tricuspid atresia	0.5	All	100	Some
Pulmonary valve atresia, intact ventricular septum	0.8	All	100	All
Pulmonary stenosis	6.3	Some	33	Some
Hypoplastic left heart	3.3	All	100	All
Coarctation of the aorta	4.7	Some	53	Some
Aortic atresia or hypoplasia	1.0	Some	75	All

DA = Ductus arteriosus; SPO_2 = oxygen saturation.

* Adapted from Mahle (2009).

Feedback

The standard practice of clinical examination of newborns, with emphasis on the cardiovascular examination, has been shown to miss half of the infants with CCHD. Even examining a newborn twice was not effective in resolving this problem. On the other hand, infants discharged in the first 2 or 3 days after birth may be helped by re-examination within the following week. For infants suspected of having CHD, this return visit has been shown to detect a significant number of defects. In addition to close attention to feeding success and jaundice, early-discharged infants may benefit from more detailed cardiovascular examination, especially if a ductal-dependent lesion is present.

Cardiac murmurs in the immediate neonatal period most often reflect changes in the transitional circulation; only a small fraction of patients with cardiac murmurs have CHD or CCHD. Hypoplastic left heart often has no murmur and the shunting across a wide open ductus arteriosus often cannot be heard. Other lesions may have murmurs that only will be heard after pressure gradients are established as the pulmonary vascular resistance diminishes. Failure to detect a significant murmur is not a reason for delayed diagnosis of CCHD.

When associated with 4 to 5 g/dL (40 to 50 g/L) of deoxygenated hemoglobin in the blood, hypoxemia will create clinical cyanosis. Ability to detect clinical cyanosis varies greatly among observers and is affected by lighting, skin pigmentation, jaundice, hemoglobin level, and the oxygen content of the hemoglobin. Studies have demonstrated that after 24 hours after birth, median oxygen saturation in normal term infants is 97.8% and remains constant for the remainder of the first week. Among infants with CCHD, 81% were noted to have saturation values less than 95% (lower extremity). Although hypoxemia is regularly associated with many of the most common forms of CHD, screening results may not always be positive (Table 1). In most cases, the saturation level associated with the condition likely would not lead to clinically evident or detectable cyanosis, making it a less likely contributor to missed diagnosis of CCHD. The potential to identify subtle hypoxemia did spur interest in the use of oximetry to screen for CHD in the newborn (**Table 2**).

Table 2: Pulse Oximetry to Screen for Congenital Heart Disease in Neonates*

Age at Test	False Positive (n)	True Positive (n)	False Negative (n)	True Negative (n)	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity
24 h	18	16	7	51,063	47%	99.9%	69.6%	99.9%

* Adapted from Mahle and Associates (2009).

Because of concerns regarding low positive predictive value and sensitivity, technical issues, interpretation, and costs, routine use of pulse oximetry to screen for CHD is being evaluated at some centers, while others await results from ongoing trials.

Early hospital discharge of healthy term infants was introduced over 15 years ago, yet studies show a decrease in undiagnosed CCHD over the decade 1989 to 1999, with no change from 2000 to 2004. Thus, early discharge is unlikely to be the root cause of delayed diagnosis of CCHD.

References

Chang RK, Gurvitz M, Rodriguez S. Missed diagnosis of critical congenital heart disease. *Arch Pediatr Adolesc Med*. 2008;162:969-974. Accessed November 4, 2010 at: http://archpedi.ama-assn.org/cgi/content/full/162/10/969

Kaplan JH, Ades AM, Rychik J. Effect of prenatal diagnosis on outcome in patients with congenital heart disease. *NeoReviews*. 2005;6:e326-e331. DOI: 10.1542/neo.6-7-e326. Accessed November 4, 2010 at: http://neoreviews.aappublications.org/cgi/content/extract/6/7/e326?

Mahle WT, Newberger JW, Matherne GP, et al. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the AHA and AAP. *Pediatrics*. 2009;124:823-836. DOI: 10.1542/peds.2009-1397. Accessed November 4, 2010 at: http://pediatrics.aappublications.org/cgi/content/full/124/2/823

Padula MA, Ades AM. Neurodevelopmental implications of congenital heart disease. *NeoReviews*. 2006;7:e363-e369. DOI: 10.1542/neo.7-7-e363. Accessed November 4, 2010 at: http://neoreviews.aappublications.org/cgi/content/extract/7/7/e363?

American Board of Pediatrics Content Specification(s)

Cardiovascular: Know the pathophysiology (including genetics) of a cyanotic neonate

Cardiovascular: Recognize the clinical features of a cyanotic neonate

Cardiovascular: Recognize the clinical features of a neonate with a right-sided cardiac lesion

Cardiovascular: Recognize the clinical features of a neonate with a left-sided cardiac obstructive lesion

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Assessment History

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Question: 3

A male infant was born via vaginal delivery at 32 weeks' gestation after his mother presented with preterm labor presumed secondary to chorioamnionitis. She had a fever and severe abdominal pain on the day of delivery. After birth, the infant was noted to have respiratory distress, which prompted endotracheal intubation, surfactant administration, and mechanical ventilation. His initial vital signs included a heart rate of 180 beats per minute, respiratory rate of 60 breaths per minute, blood pressure of 30/12 mm Hg, and oxygen saturation of 88%, while receiving supplemental oxygen of 80%. His initial physical examination findings included the following: decreased activity, normal heart sounds without murmur, clear breath sounds with moderate intercostal retractions, warm skin with excellent perfusion, and bounding peripheral pulses. Laboratory serum data revealed the following:

Laboratory Data	Patient Result (SI Values)
White blood cell count, ($\times 10^3$/μL ($\times 10^9$/L)	2 (2)
• Polysegmented neutrophils, %	20
• Lymphocytes, %	77
Hemoglobin, g/dL (mmol/L)	17 (10.5)
Hematocrit, %	52 (0.52)
Platelet count, $\times 10^3$/μL ($\times 10^9$/L)	80 (80)
Arterial blood gas	
• pH	7.17
• $Paco_2$ mm Hg (kPa)	65 (8.6)
• Pao_2 mm Hg (kPa)	49 (6.5)
Base excess, mEq/L (mmol/L)	-6 (-6)

Echocardiography revealed a structurally normal heart with slightly decreased left ventricular function.

Of the following, the type of shock MOST consistent with this infant's clinical condition is:

- A. cardiogenic
- B. dissociative
- C. distributive
- D. flow restrictive
- E. hypovolemic

✗ **Incorrect**

Correct Answer: C

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Inadequate tissue perfusion and/or oxygen delivery to one or multiple organs lead to shock. Shock can be explained by three possible mechanisms:

- decreased cardiac output
- abnormal vasomotor tone
- insufficient oxygen delivery to tissues

In the neonate, decreased cardiac output is most commonly attributable to a low heart rate. An extremely high heart rate may also contribute to poor cardiac output by attenuating the ventricular filling time, resulting in lowered end-diastolic volume and decreased preload. A lower stroke volume as a result of poor cardiac contractility, decreased preload, and/or increased afterload, will also lead to a decrease in cardiac output. Vascular, tissue, and neurohormonal factors may affect central vasoregulation and/or local autoregulation. In the latter, if local autoregulation is unable to maintain blood flow to local tissues, flow becomes pressure passive, leading to possible ischemia or hemorrhage. Finally, decreased oxygen tissue delivery can result from poor oxygen delivery to alveoli, decreased lung perfusion, low oxygen-carrying capacity, and/or poor oxygen extraction by tissues.

Shock occurs in three progressive phases (**Figure**). Clinical delineation of the infant's specific phase may be difficult. In the initial phase, blood flow is distributed to the brain, heart, and adrenal glands at the expense of nonvital organ perfusion. During this *compensated phase* of shock, decreased stimulation of baroreceptors in the aortic arch and carotid sinus and an increased chemoreceptor response induces vasoconstriction. The renin-angiotensin system also helps to maintain blood pressure by means of angiotensin II–induced vasoconstriction and elevated aldosterone concentrations, which increase water reabsorption in the kidney and decrease urine volume. The neonate's heart rate and cardiac contractility are elevated as a result of an initial catecholamine surge. Finally, reabsorption of interstitial fluid temporarily increases intravascular volume. These compensatory mechanisms help to maintain normal blood pressures during the initial phase of shock without altering serum bicarbonate or lactate concentrations.

If shock progresses, the amount of blood flow to all organs decreases and the amount of oxygen and nutrients to tissues is insufficient to meet tissue demand. A cascade of metabolic changes, including release of histamine, cytokines, and, in the case of septic shock, bacterial toxins, further decreases tissue perfusion. Because this phase is still reversible, it is often denoted as the *uncompensated, reversible* phase of shock. The infant's heart rate remains elevated but the blood pressure is now low. Correspondingly, bicarbonate concentrations decrease and lactate concentrations increase. Further advancement of shock leads to irreversible cellular damage. During this *uncompensated, irreversible* phase, the blood pressure continues to decline further, the heart rate drops precipitously, and bicarbonate and lactate concentrations become more abnormal. Neonatal shock arising from all five causes (cardiogenic, dissociative, distributive, flow restrictive, and hypovolemic, see **Table**) may progress through the three phases and the goal of management is to avoid reaching the final phase.

The infant in this vignette has an elevated heart rate, low blood pressure, and mild-moderate metabolic acidosis, which corresponds with the uncompensated, reversible phase of shock. Because of the finding of neutropenia and thrombocytopenia, in the setting of a maternal fever and probable chorioamnionitis, sepsis is the most likely contributor to this infant's state of shock. Sepsis can be associated with distributive shock by causing abnormalities in the vascular system, hypovolemic shock because of the excessive fluid losses associated with an inadequate endothelial barrier, and cardiogenic shock because of the decreased contractility that may occur.

Feedback

The infant in this vignette most likely has distributive shock because of his warm, well-perfused skin with bounding pulses and a wide pulse pressure, often described as *warm shock*. Less common causes of distributive shock in the neonate include excessive amounts of a vasodilator agent and adrenal insufficiency. Anaphylactic and neurogenic shock are also associated with distributive shock but these are uncommon in the neonate. Pharmacotherapy is aimed at increasing systemic vascular resistance and avoiding vasodilator agents.

Cardiogenic shock occurs when the cardiac muscle itself is depressed. Decreased contractility leads to a lower stroke volume as a result of both poor ventricular filling and emptying. This lower stroke volume causes cardiac output, and ultimately blood pressure, to decrease. In the neonate, this decreased contractility can be attributed to cardiomyopathy, heart failure, and arrhythmias. In addition, severe perinatal depression can lead to global myocardial ischemia, reducing myocardial contractility and causing papillary muscle dysfunction with secondary tricuspid valvular insufficiency. Because acidosis suppresses cardiac contractility and is associated with the last two phases of all types of shock, cardiogenic shock may be superimposed on any type of shock. Typically, affected infants show signs of congestive heart failure evident by hepatomegaly, gallop rhythm, and pulmonary edema with radiographic findings of an enlarged heart. Pharmacotherapy includes inotropic agents that induce some peripheral vasodilation and avoidance of excessive volume expansion.

Dissociative shock is an uncommon cause of neonatal shock. It is attributable to profound anemia, excessive carbon monoxide, or methemoglobinemia. Although tissue perfusion is sufficient during these abnormalities, oxygen released to tissues is inadequate.

Flow restrictive or obstructive shock is caused by a tension pneumothorax, cardiac tamponade, or left-sided obstructive cardiac disease, including severe aortic stenosis, hypoplastic left ventricle, and coarctation of the aorta without adequate right-to-left ductal shunting. Affected infants have inadequate cardiac output despite sufficient preload. While cardiac contractility is initially normal, inotropic ability may decline as the flow restriction continues, thereby leading to congestive heart failure.

Hypovolemic shock is caused by a large and acute blood and/or fluid loss leading to a decrease in preload. This lower preload decreases stroke volume and cardiac output. Hypovolemic shock is the most common type of shock in the neonate. Clinical signs of hypovolemic shock correlate with the degree of intravascular depletion, estimated to be 25% in compensated shock, 25% to 40% in uncompensated shock, and more than 40% in irreversible shock. Treatment of infants with hypovolemic shock involves volume resuscitation using fluids that remain intravascular, such as a colloid solution or whole or reconstituted blood.

References

Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008;34:17-60

Gupta A, Sinha SK, Donn SM. Shock and hypotension in the newborn. *eMedicine.com Web site*. . Accessed October 5, 2010 at: http://www.emedicine.medscape.com

Noori S, Seri I. Pathophysiology of newborn hypotension outside the transitional period. *Early Hum Dev*. 2005;81:399-404

Schmaltz C. Hypotension and shock in the preterm neonate. *Adv Neonatal Care*. 2009;9:156-162

American Board of Pediatrics Content Specification(s)

Cardiovascular: Formulate a differential diagnosis for an infant with systemic hypotension

Cardiovascular: Know the pathophysiology of a term or preterm infant with a condition affecting the systemic blood pressure, such as hypotension

Cardiovascular: Recognize the clinical features of an infant with systemic hypotension

Cardiovascular: Know the management of an infant with systemic hypotension and the adverse effects of such management

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Question: 1

A female infant who was born at 28-weeks' gestation with a birthweight of 930 g had respiratory distress, apnea and bradycardia, hyperbilirubinemia, and anemia early in her hospital course. In addition, she received medical treatment for necrotizing enterocolitis. At 7 weeks of age, when she weighed 1,800 g, her mean oscillometric blood pressure measured in the right arm twice daily began to vary from 68 mm Hg to 76 mm Hg.

Of the following, a TRUE statement about blood pressure estimation in the premature infant is that:

- A. arterial catheter pressures are lower than cuff pressures
- B. cuff pressures are higher in the arm than in the leg
- C. normal mean pressures increase with birthweight and postnatal age
- D. pressures are higher in the prone position than supine
- E. the last of three pressures measured serially is often the highest

Incorrect

Correct Answer: C

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The infant in the vignette has systemic hypertension if the pressures reported are accurate, but the information in the vignette is not sufficient to make that assessment or to begin an investigation into the cause. Historically, measuring blood pressure in neonates and defining the limits of normal have been difficult. Normal values for systolic, diastolic, and mean blood pressure increase with the birthweight and postnatal age of neonates making reference to appropriate graphs indispensable. Reference values for infants of various sizes and ages are provided in the articles in the reference list.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Many factors influence the blood pressure measurement in neonates. For instance, intra-arterial blood pressure measurements tend to be higher than those measured using cuff oscillometry. However, for practical purposes, the two methods correlate well. Blood pressures measured when the infant is hungry or irritable are often higher than those obtained when the infant is resting. When blood pressures are measured three times in a row at 2-minute intervals using the same limb and method, the first measure tends to be higher statistically but minimally higher in absolute terms than the second and third. The latter two measurements are considered more representative of the infant's resting blood pressure.

Cuff size is also an important variable in the measurement of blood pressure. Ideally, the cuff width should be two thirds the length of the limb segment and three fourths of the limb circumference. Cuff widths that are too large or too small will yield pressures that underestimate or overestimate the intra-arterial blood pressure, respectively. Cuff leg pressures tend to be higher than arm pressures because of the greater muscle mass in the leg. If the cuff leg pressure is not higher, aortic coarctation should be considered. Furthermore, blood pressures obtained in the prone position are significantly, but only slightly, lower than those taken in the supine position.

Given these known causes of variation, it is recommended that in convalescent infants suspected of having

Feedback

systemic hypertension, the measurement should be made with the infant in the supine position long enough after the placement of an appropriate sized cuff to establish a return to a quiet (resting) state. Pressures persistently above the 95th percentile for size and age indicate systemic hypertension. However, borderline measurements are confusing. Finding concentric left ventricular hypertrophy on echocardiography can clear up the ambiguity and suggests the need for treatment. Subsequently, resolution of the hypertrophy can be used to demonstrate the effectiveness of the treatment. If cardiac hypertrophy is not present, expectant management with additional blood pressure monitoring could be justified.

Systemic hypertension has been reported in 0.08% to 2% of infants in neonatal intensive care unit populations. The most common causes of systemic hypertension in the newborn include renal disease, renovascular disorders, coarctation of the aorta, and bronchopulmonary dysplasia. Among the renal diseases are congenital malformations such as polycystic kidney disease, multicystic-dysplastic kidney, and urinary obstructions. Acute tubular necrosis and hemolytic-uremic syndrome also can cause systemic hypertension.The renovascular disorders that cause systemic hypertension most frequently are thromboembolism, renal artery or vein thrombosis, and renal artery compression (eg, from a tumor).

Systemic hypertension has been reported in 13% to 43% of infants with bronchopulmonary dysplasia. The underlying mechanism is not fully understood, but hypoventilation and hypoxemia have been associated with systemic hypertension in other situations such as in Guillain-Barré syndrome.

Neurologic causes of systemic hypertension include pain, intracranial hypertension, seizures, and drug withdrawal. Endocrine causes such as salt-retaining adrenal hyperplasia, pseudohyperaldosteronism type II, adrenal hemorrhage, and hypercalcemia are less frequently encountered. Systemic hypertension may also complicate venoarterial extracorporeal life support because of acute aortic distention and reduced arterial pulsatility.

Finally, but importantly, medications administered to the infant might be the cause of systemic hypertension. Such medications include corticosteroids, methylxanthines, α-adrenal receptor agonists (eg, phenylephrine), and muscle relaxants like vecuronium bromide.

References

Ettinger LM, Flynn JT. Hypertension in the neonate. *NeoReviews*. 2002;3:e151-e156. Accessed November 2, 2010 at: http://neoreviews.aappublications.org/cgi/content/full/3/8/e151?

Kent AL, Meskell S, Falk MC, Shadbolt B. Normative blood pressure data in non-ventilated premature neonates from 28-36 weeks gestation. *Pediatr Nephrol*. 2009;24:141-146. Abstractat: http://www.ncbi.nlm.nih.gov/pubmed/18612658

Nwanko MU, Lorenz JM, Gardiner JC. A standard protocol for blood pressure measurement in the newborn. *Pediatrics*. 1997;99:e10. Accessed November 2, 2010 at: http://pediatrics.aappublications.org/cgi/content/full/99/6/e10?

Zubrow AB, Hulman S, Kushner H, Falkner B. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. *J Perinatol*. 1995;15:470-479. Abstractat: http://www.ncbi.nlm.nih.gov/pubmed/8648456

American Board of Pediatrics Content Specification(s)

Water/Salt/Renal: Formulate a differential diagnosis for an infant with systemic hypertension in early infancy

Water/Salt/Renal: Know the clinical and diagnostic features of an infant with systemic hypertension, including laboratory and imaging studies

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Question: 9

A 5-day-old child who was born at 25 weeks' gestation has a hemodynamically significant patent ductus arteriosus. You and the pediatric cardiologist discuss the potential for some drugs commonly used in neonates to interfere with the closure of the ductus arteriosus.

Of the following, the medication MOST likely to interfere with the closure of a patent ductus arteriosus is:

○	**A.**	caffeine
○	**B.**	cimetidine
✓	**C.**	furosemide
○	**D.**	gentamicin
○	**E.**	heparin

Correct

PC

Factors that have been established to increase the risk for patent ductus arteriosus (PDA) in neonates are listed in the **Table**. The ductus arteriosus normally constricts soon after birth because of exposure to oxygen (**Figure 1**) and a decrease in placental prostaglandins. Final closure and remodeling occur with the aid of platelets (**Figure 2**) and hypoxia-inducible growth factors.

CONTENT SPECIFICATIONS ADDRESSED ABP American Board of Pediatrics

Each medication listed in the vignette has general vasodilatory effects in human studies or

animal models. The medication with the most clinical evidence of a vasodilatory effect on the human ductus arteriosus is furosemide, primarily because of its stimulation of prostaglandin synthesis.

Sepsis, inflammation, thrombocytopenia, or reactive oxygen species interfere with platelet action in final ductus closure. Interestingly, although prostaglandin synthesis blockers might be expected to interfere with platelets and their role in the final closure of the ductus arteriosus, this is not always so. Aspirin does interfere with platelet aggregation by inhibiting the action of cyclooxygenase-I, preventing the formation of thromboxane A2, a potent platelet-clumping factor. Indomethacin and ibuprofen also interfere with thromboxane synthesis, but only over a matter of hours, whereas aspirin will inhibit thromboxane synthesis for days. Clinically, indomethacin and ibuprofen promote platelet plug formation after endothelial damage or constriction of the ductus arteriosus.

Furosemide interferes with ductus closure by stimulating prostaglandin E2 synthesis in the thick ascending limb of the loop of Henle. Clinically, the diuretic effect encouraging ductal closure is overpowered by the prostaglandin effect, thereby encouraging patency. Higher rates of treatment failure result.

Caffeine does not have a vasodilatory effect on the ductus arteriosus, and does not interfere with the actions of oxygen or indomethacin. One clinical study found caffeine use in neonates was associated with fewer medical or surgical PDA treatments, but this was not considered a direct effect of the drug on the ductus arteriosus.

Gentamicin is a myocardial depressant and a neuromuscular blocker, but clinical evidence is lacking for a direct effect on the human ductus arteriosus. Gentamicin does dilate the surgically isolated ductus arteriosus of fetal and newborn mice, but at 100 to 1,000 times the usual in vivo concentrations seen clinically. The mechanism of ductal dilation is thought to involve alterations in intracellular calcium flux.

Cimetidine has been associated with PDA in a randomized trial of its use to prevent lung disease. The hope was that cimetidine's inhibition of the cytochrome P450 system would prevent formation of reactive oxygen species and so would reduce the resultant lung injury. This was not the case. Post hoc analysis found a decrease in PDA incidence in the treatment group. As with gentamicin, concentrations of cimetidine at 100 to 1000 times those seen clinically through an isolated murine ductus showed significant ductus dilation. Famotidine, another H2 blocker, has little effect on the cytochrome P450 system in a murine model.

Heparin has vasodilatory and antihypertensive properties that are based on a number of mechanisms, including calcium sequestration, histamine increases, renin-angiotensin inhibition, and impairment of the blood-flow shear-sensing mechanism. Clinically, these effects are well-known in association with cardiopulmonary bypass, but have not been directly seen with the neonatal PDA. Indirectly, a review of a change in practice from continuous heparin infusion to intermittent flushes found a reduction in the incidence of PDA treatment failure.

Suggested Readings

Clyman RL. Mechanisms regulating closure of the ductus arteriosus. *Fetal and Neonatal Physiology. 3rd ed*. Polin RA, Fox WW, Abman SH, ed. Philadelphia, Pa: Elsevier Saunders; 2004:743-748.

Hamrick SE, Hansmann G. Patent ductus arteriosus of the preterm infant. *Pediatrics*. 2010;125:1020-1030. DOI: 10.1542/peds.2009-3506. Accessed October 7, 2010 at: http://pediatrics.aappublications.org/cgi/content/full/125/5/1020?

Reese J, Veldman A, Shah L, Vucovich M, Cotton RB. Inadvertent relaxation of the ductus arteriosus by pharmacologic agents that are commonly used in the neonatal period. *Semin*

Perinatol. 2010;34:222-230. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/20494739

American Board of Pediatrics Content Specification(s)

Cardiovascular: Know the physiology of the ductus arteriosus

Print

Table: Risk factors for Patent Ductus Arteriosus*

- Early gestational age
- Low birth weight
- Lack of antenatal betamethasone†
- Maternal diabetes
- High-altitude birth
- Sepsis
- Congenital rubella
- Hypothyroidism
- Excess fluid administration

* Adapted from Reese and colleagues (2010).

† Animal studies suggest lack of other antenatal corticosteroids may also increase the risk of a patent ductus arteriosus.

Print

Figure 1: Mechanisms for oxygen-induced ductus arteriosus smooth muscle cell contraction. Oxygen exposure induces contraction via reactive oxygen species (ROS), endothelin-1 production, and potassium-channel (Kv) sensitization. (From Hamrick [2010].) DASMC = ductus arteriosus smooth muscle contraction

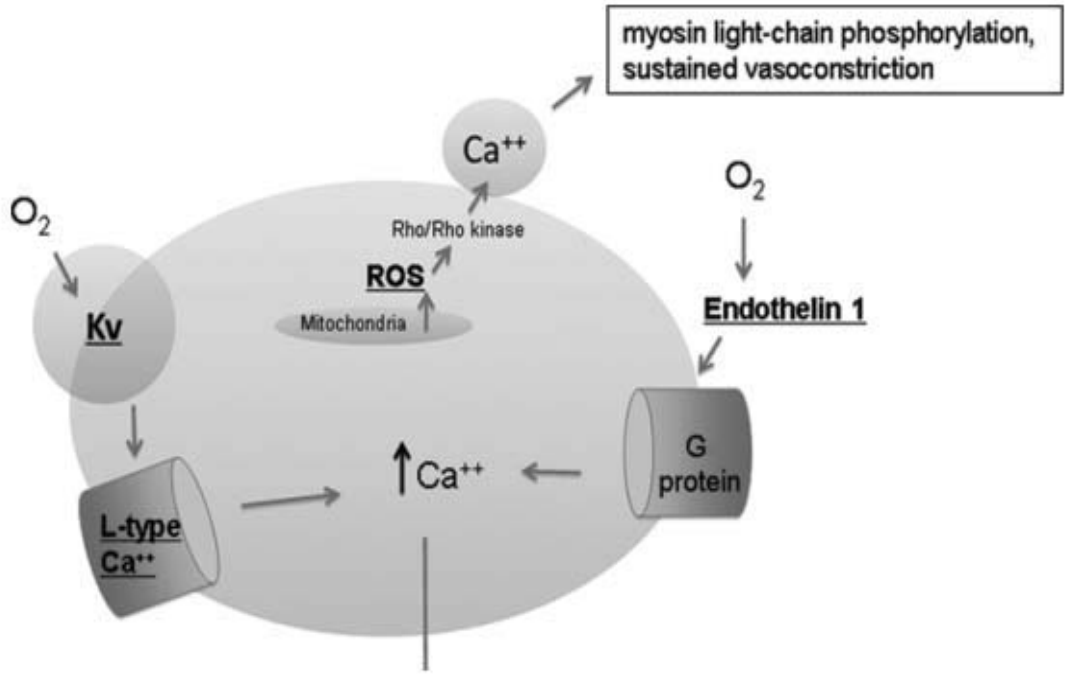

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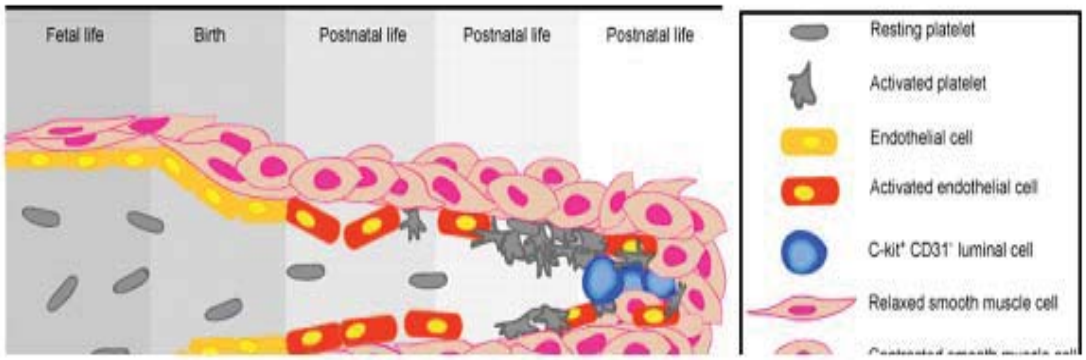
Figure 2: The role of platelets for sealing of the contracted ductus arteriosus (DA). The scheme delineates the proposed sequence of events that contribute to postnatal DA occlusion. (Adapted with permission from Echtler K, Stark K, Lorenz M, et al. *Nat Med.* 2010;16[1]:75-82; supplementary Figure 9.)



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June

Question View: All (10)

Page 1 of 11

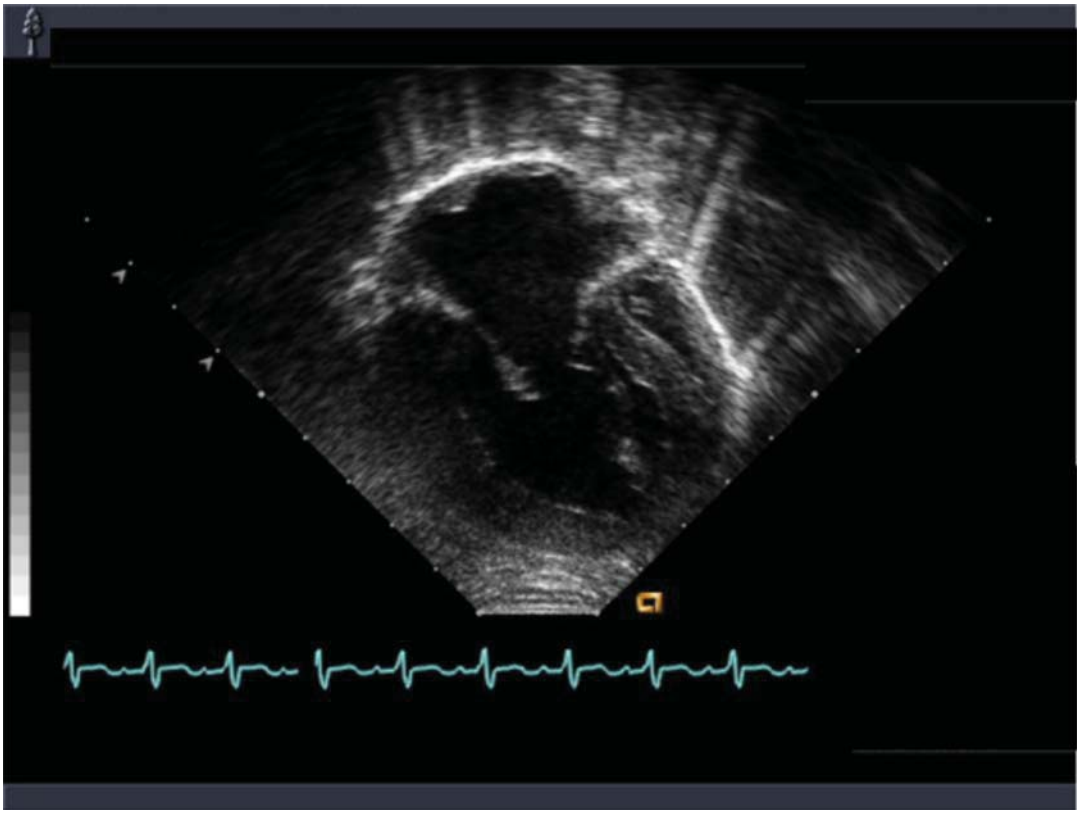
Mode:	Learner [ ]	Exam

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 1

An infant with cyanosis and respiratory distress beginning 6 hours after birth is stabilized and transferred for additional treatment. An echocardiogram is obtained (**Figure 1**). You are discussing the surgical steps in the treatment of the infant with the nursing staff.

Figure 1: Four-chamber echocardiographic view of the heart. (Courtesy of T. Cordes, MD and R. Caldwell, MD, Indiana University School of Medicine.)



Of the following, the first step of the traditional INITIAL surgical treatment of this infant includes

a (an):

○	**A.**	atrial septectomy
○	**B.**	ductus arteriosus stent
○	**C.**	interatrial septum stent
✗	**D.**	left ventricle to pulmonary artery conduit
○	**E.**	pulmonary artery band

Incorrect

Correct Answer: A

PBLI

The echocardiogram of the infant in the vignette shows hypoplastic left ventricle (**Figure 2**). The Norwood procedure for hypoplastic left heart syndrome revolutionized the care of these infants (**Figure 3** and **Figure 4**). Before the 1980s, this congenital heart defect was fatal, often within days of birth. The Norwood procedure was developed to provide an unobstructed systemic circulation using the right ventricle and balancing the flow to the pulmonary circulation (ie, avoiding pulmonary overcirculation). The steps of the Norwood procedure include:

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- *Performing an atrial septectomy* to ensure pulmonary venous return to the circulation by bypassing the obstructive hypoplastic left ventricle.
- *Reconstructing the aortic arch* to remove obstruction caused by aortic arch hypoplasia or coarctation of the aorta. A neoaorta is constructed by joining the hypoplastic arch with the pulmonary artery using a homograft patch. The right ventricle becomes a single ventricle providing blood flow to the systemic and pulmonary circulations.
- *Placing a Blalock-Taussig shunt*, or *right* ventricle to pulmonary artery shunt, providing right ventricular output to the pulmonary circulation. The size of this shunt helps limit overcirculation of blood flow through the lung.

A functional univentricular circulation results from the Norwood procedure, ideally with a 1 to 1 ratio of pulmonary-to-systemic blood flow (Figure 4). Achieving such a balance helps provide adequate oxygen delivery without a volume overload of the pulmonary circulation.

The Norwood procedure is one of the most complex pediatric cardiac interventions. It is the first step in a series of three surgical interventions for hypoplastic left heart syndrome. The Norwood procedure is often performed within several days of birth. Survival to 30 days after surgery is about 82%. A number of different factors contribute to poor survival and more complications:

- Low birthweight
- Intact or restrictive atrial septal defect
- Small aortic size (<2 mm diameter)
- Other congenital anomalies
- Unbalanced atrioventricular septal defect

Other factors, with lesser impact on survival, include weak ventricular function,

preoperative mechanical ventilation, tricuspid regurgitation, prematurity, age at surgery, cardiopulmonary bypass time (especially deep hypothermic circulatory arrest versus continuous low-flow antegrade cerebral perfusion), aortic or mitral atresia (versus stenosis), and operator experience. Among Norwood procedure survivors, 4% to 15% die before the second stage operation. Infants with a small ascending aorta are at particularly high risk, presumably because of flow limitation to the coronary arteries. These interstage deaths are likely the result of various complications such as:

- residual aortic arch (10% of cases) or interatrial obstruction
- pulmonary hyperperfusion and systemic hypoperfusion
- coronary ischemia from diastolic runoff into the Blalock-Taussig shunt or right ventricular to pulmonary artery conduit
- shunt stenosis or thrombosis
- right ventricular volume overload and failure

A second approach to the initial stage of repair for hypoplastic left heart syndrome is called the *hybrid procedure* (**Figure 5**). The procedure combines cardiac catheterization techniques (interatrial balloon septostomy or stenting; ductus arteriosus stenting) with surgery (bilateral pulmonary artery banding). Cardiopulmonary bypass is avoided with the hybrid procedure. Because of this advantage, the hybrid procedure usually is reserved for high-risk patients, such as those with low birthweight, poor ventricular function, or unstable cardiopulmonary status. Survival is 80% to 85%; interstage mortality is 15% to 20%. The hybrid procedure is still being investigated; excellent results with the Norwood procedure have slowed adoption of the hybrid procedure and focused implementation on high-risk infants who are poor candidates for cardiopulmonary bypass or those with a small ascending aorta and/or transverse arch. Additional concerns include difficulties with placing pulmonary artery bands on small branch pulmonary arteries and inserting a ductal stent in the presence of a small aortic arch. A partially misplaced or migrated ductal stent may obstruct retrograde flow into the ascending and transverse arch and coronary circulation. Stage 2 is a more complex and challenging procedure after the hybrid procedure than after the Norwood procedure and carries a higher mortality (10%-15% versus 3%-4% after the Norwood procedure).

The second step of the repair sequence for hypoplastic left heart syndrome involves joining the superior vena cava to the pulmonary artery and taking down the original right ventricle to pulmonary artery shunt (bidirectional Glenn shunt or cavopulmonary shunt) (**Figure 6**). The volume load to the right ventricle is significantly reduced and generally results in improved mechanical efficiency. The second procedure usually takes place at 4 to 6 months of age; survival is 96% or higher. Interstage mortality between stages 2 and 3 is 3% to 4%.

The third step in the series of interventions for hypoplastic left heart involves directing the inferior cava blood flow to the pulmonary arteries (Fontan procedure, **Figure 7**). This procedure separates the systemic and pulmonary circulations and the child is no longer cyanotic. Unlike two-ventricle physiology, the Fontan procedure requires the right ventricle to provide the power to move blood through *both* the systemic and pulmonary circulations. Although dependent on clinical status, the third step, called *total cavopulmonary connection* or the *Fontan procedure*, is usually performed around 4 years of age. Mortality after the Fontan procedure is 3% to 4%. Of note, the Fontan circulation is the final common intervention for most univentricular cardiac defects.

Suggested Readings

Barron DJ, Kilby MD, Davies B, et al. Hypoplastic left heart syndrome. *Lancet*. 2009;374:551-564. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/19683641

Fricker FJ. Hypoplastic left heart syndrome: diagnosis and early management. *NeoReviews*. 2008;9:e253-e259. DOI: 10.1542/neo.9-6-e253. Available at: http://neoreviews.aappublications.org/cgi/content/full/9/6/e253?

Stumper O. Hypoplastic left heart syndrome. *Postgrad Med J*. 2010;86:183-188.

American Board of Pediatrics Content Specification(s)

Cardiovascular: Know the evaluation and management plans (medical and/or surgical) and associated potential complications or adverse effects of such management for a neonate with a left-sided cardiac obstructive lesion

Print

Figure 2: Hypoplastic left heart

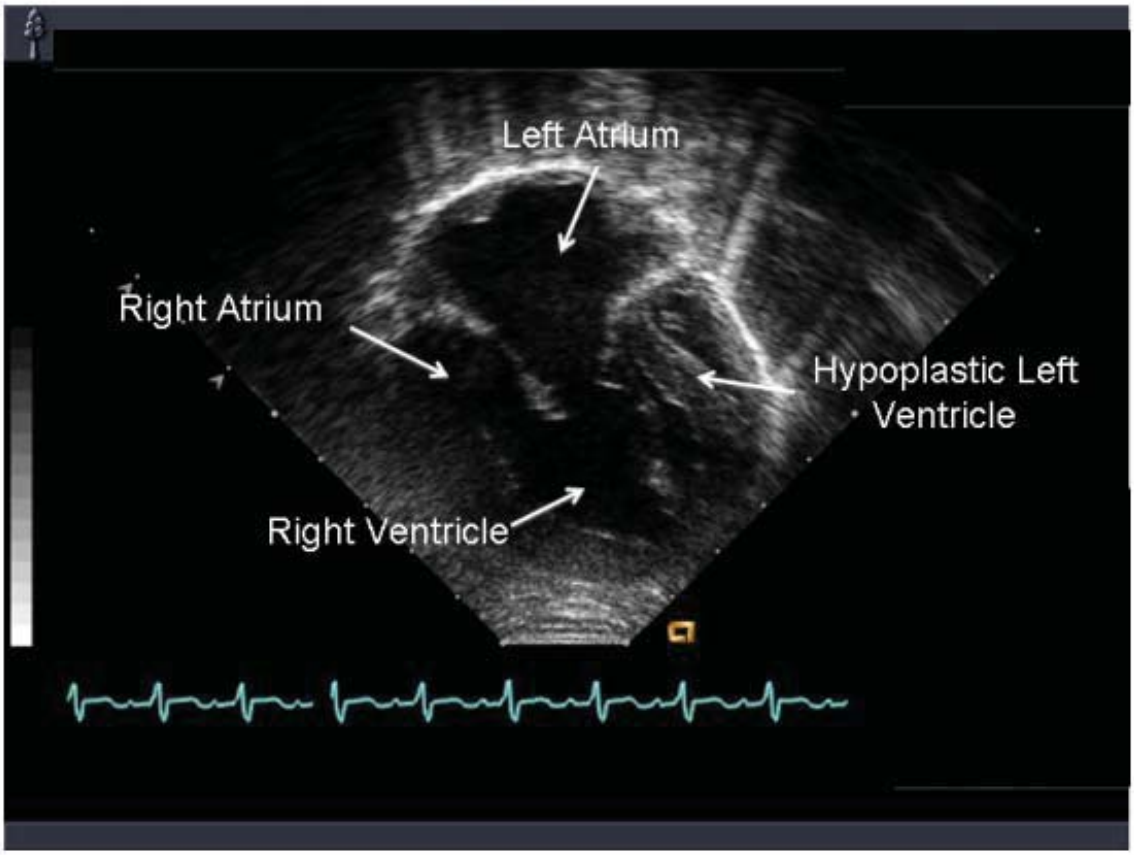

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Figure 3: Schematic representation of hypoplastic left heart syndrome. Blue arrows represent systemic venous (deoxygenated) blood; the red arrow, oxygenated blood returning from the lungs; and purple arrows, mixed blood. Ao = aorta; IVC = inferior vena cava; LPA = left pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve. (Reprinted with permission from Barron DJ et al. *Lancet.* 2009;374:551-564, © Elsevier.)

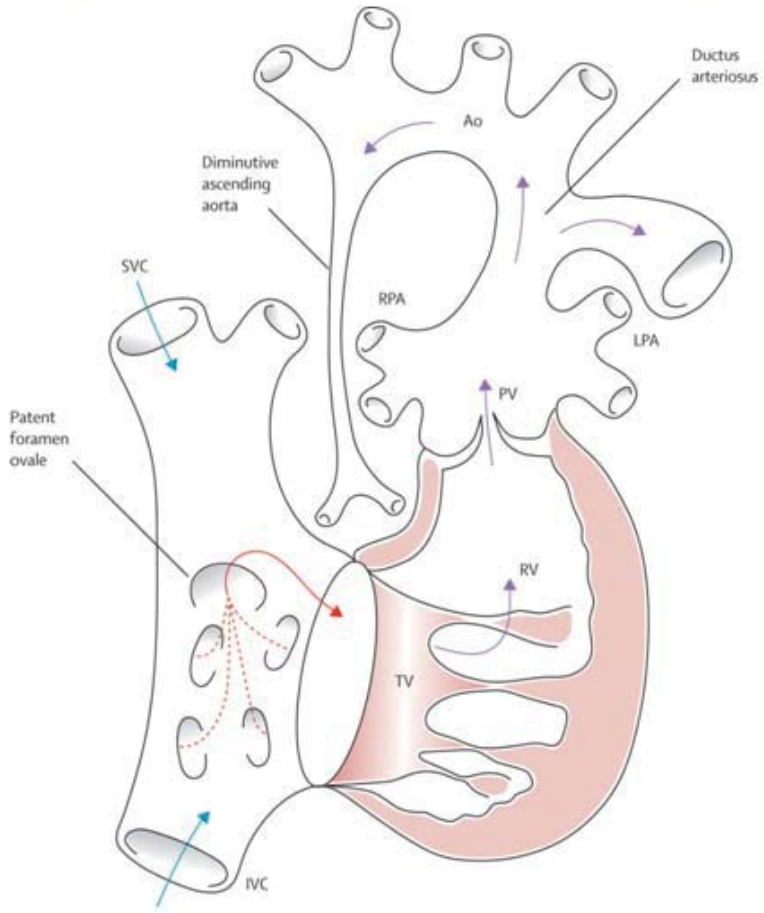

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Figure 4: The Norwood procedure for hypoplastic left heart syndrome. The figure shows the two variants in surgical technique according to the way in which pulmonary blood flow is established. A, The classic procedure with a systemic pulmonary artery shunt (Blalock-Taussig). B, Modification with a right ventricle–pulmonary artery conduit. Ao = aorta; IVC = inferior vena cava; LPA = left pulmonary artery; PA = pulmonary artery; PV = pulmonary valve; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve. (Reprinted with permission from Barron DJ et al. *Lancet.* 2009;374:551-564, © Elsevier.)

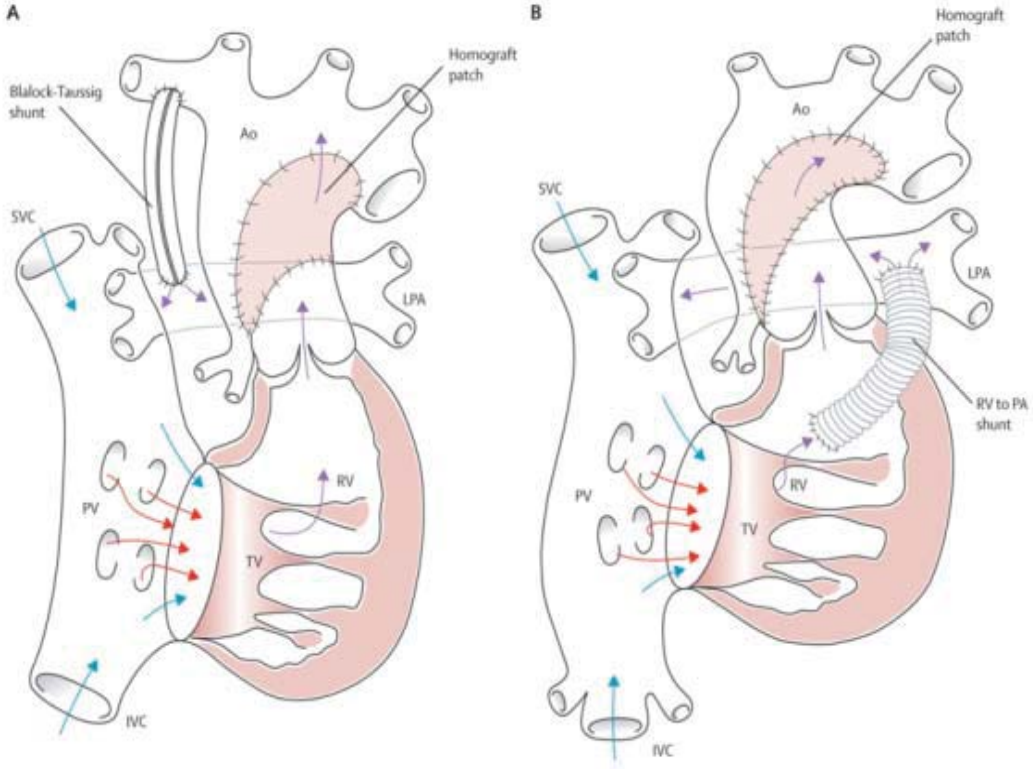

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Figure 5: The hybrid procedure: an alternative approach to the Norwood procedure. The hybrid procedure uses bilateral pulmonary artery bands to limit pulmonary blood flow and places a stent in the ductus arteriosus to hold it open. A balloon atrial septostomy is also done. (Reprinted with permission from Barron DJ et al. *Lancet.* 2009;374:551-564, © Elsevier.)

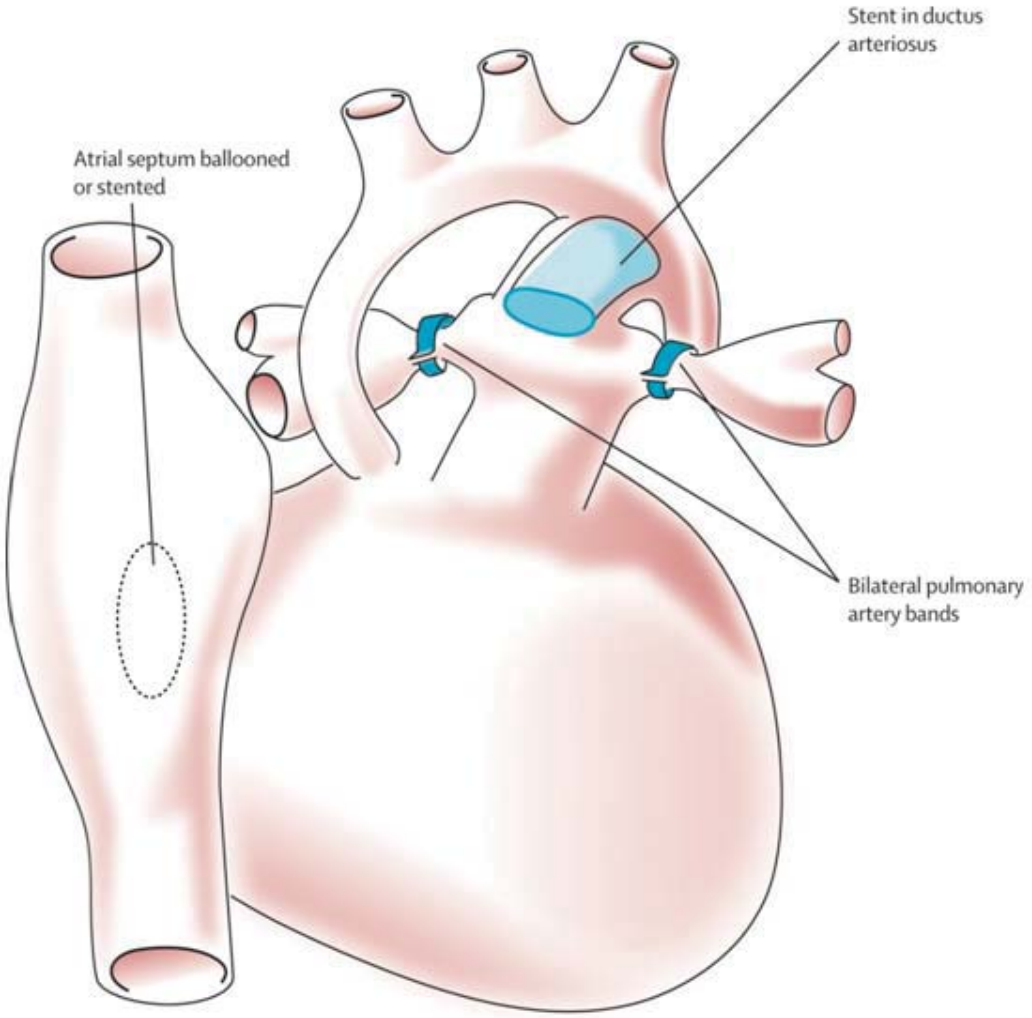

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Figure 6: The stage II procedure: the cavopulmonary shunt. Ao = aorta; IVC = inferior vena cava; LPA = left pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve. (Reprinted with permission from Barron DJ et al. *Lancet*. 2009;374:551-564, © Elsevier.)

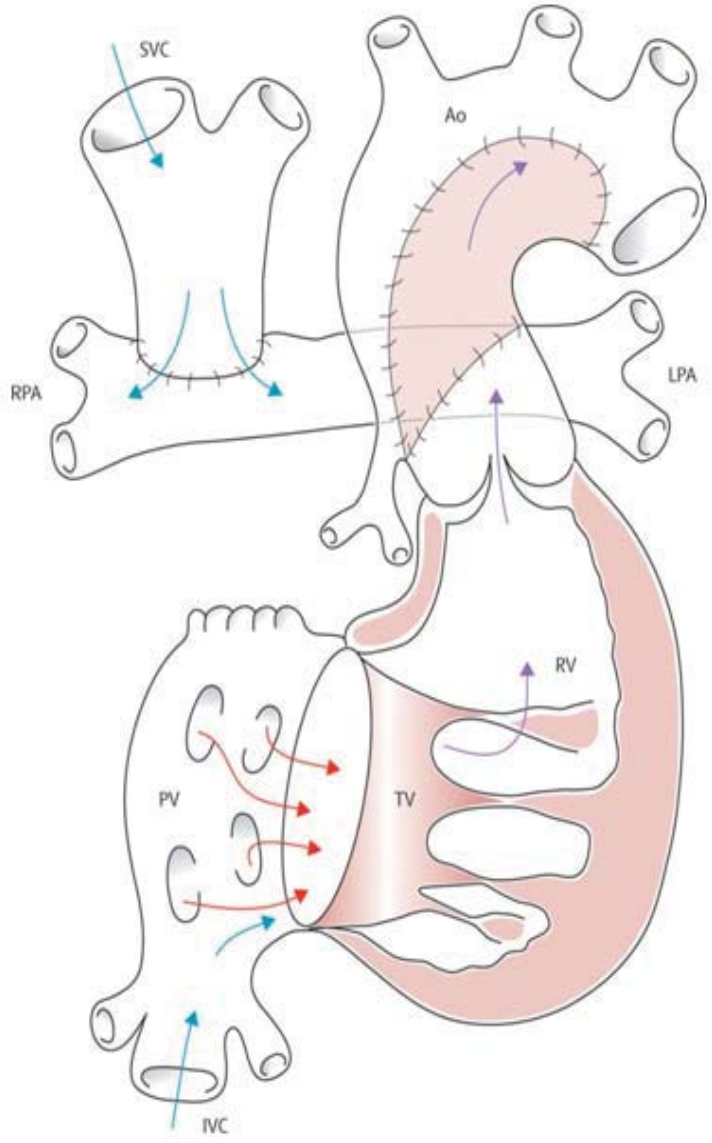

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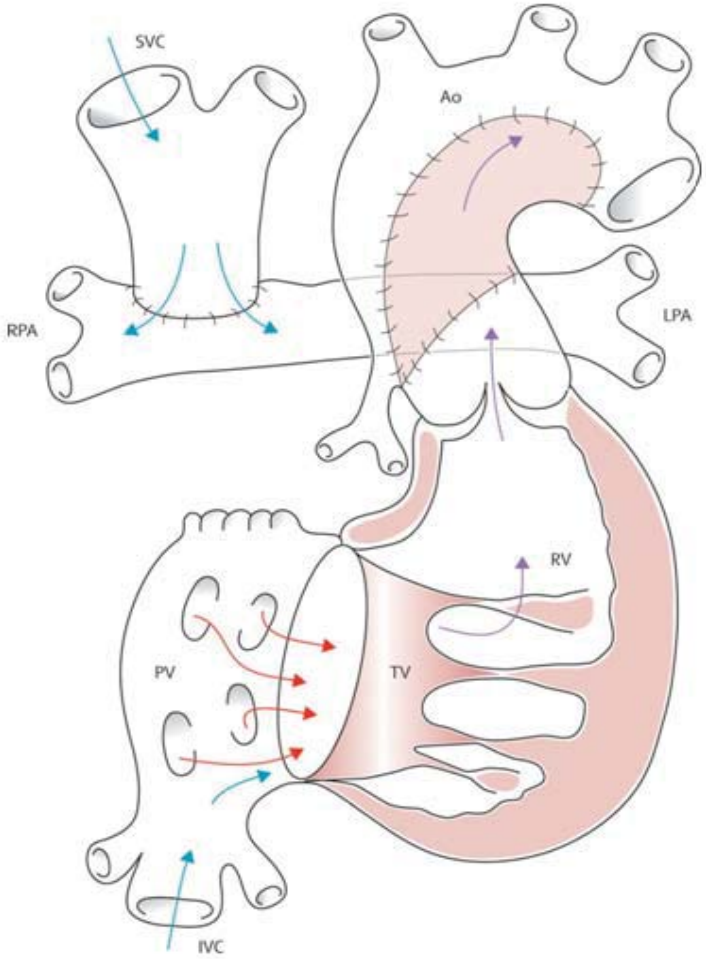
Figure 6: The stage II procedure: the cavopulmonary shunt. Ao = aorta; IVC = inferior vena cava; LPA = left pulmonary artery; PV = pulmonary valve; RPA = right pulmonary artery; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve. (Reprinted with permission from Barron DJ et al. *Lancet.* 2009;374:551-564, © Elsevier.)



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July

Question View: All (10)

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **8**

Question: 5

A 12-week-old male infant, whose birthweight was 910 g and estimated gestational age at birth 27 weeks, has systolic blood pressures ranging from 98 to 124 mm Hg, diastolic blood pressures from 46 to 62 mm Hg, and mean blood pressures from 59 to 81 mm Hg. These measurements were obtained with the oscillometric method, using the right arm and appropriately sized blood pressure cuff, and while the infant was asleep.

Neonatal history is significant for prolonged mechanical ventilation, brief umbilical artery catheterization, caffeine and furosemide administration, and two courses of antibiotic treatment for airway infection. Currently, the infant is receiving full enteral feeds of fortified human milk, is maintaining normal oxygen saturations on a nasal cannula at a fraction of inspired oxygen of 0.3, has normal physical examination findings, and is receiving no medications other than supplemental vitamins and iron.

Laboratory data reveal normal blood counts, calcium and electrolytes, renal function test results, and metabolic studies including thyroid hormone and cortisol. Chest radiography shows chronic changes of bronchopulmonary dysplasia. Findings on cranial ultrasonography and echocardiography are normal. Aortic and renal ultrasonography, including Doppler blood flow imaging, reveal a partially nonocclusive thrombus adjacent to the origin of the right renal artery.

You decide to start treatment with an oral antihypertensive drug.

Of the following, the medication with mechanism of action MOST applicable to this infant's hypertension is:

○	**A.**	amlodipine
✓	**B.**	captopril
○	**C.**	hydralazine
○	**D.**	phenoxybenzamine
○	**E.**	propranolol

Correct

The infant in this vignette has systemic hypertension, which is defined as systolic and/or diastolic blood pressure equal to or greater than the 95th percentile adjusted for postmenstrual age. Among the causes of neonatal hypertension, summarized using a mnemonic (**Table**), the most likely cause of systemic hypertension in this infant is renovascular disease.

Much of the information on drugs used in the treatment of neonatal systemic hypertension is derived from observational studies, case series, and small randomized trials. However, in the absence of large, statistically powered, randomized trials and pharmacokinetic studies, the safety and efficacy of these drugs in neonates remain unconfirmed. Thus, currently the use of a specific antihypertensive drug in neonates is influenced largely by personal preference of the physician, anecdotal experiences of safety and efficacy, extrapolation from studies in adults and older children, and availability of pediatric formulations.

Antihypertensive drugs are classified into four categories based on their principal mode of action.

- Diuretics
  - thiazide diuretics (eg, hydrochlorothiazide)
  - loop diuretics (furosemide)
  - potassium-sparing diuretics (spironolactone)
- Vasodilators
  - calcium-channel blockers (amlodipine)
  - potassium-channel openers (hydralazine)
  - Renin-angiotensin system blockers
  - angiotensin-converting-enzyme inhibitors (captopril)
  - angiotensin receptor blockers (losartan)
- Sympatholytics
  - β-adrenergic receptor blockers (propranolol)
  - mixed α/β-adrenergic receptor blockers (labetalol)
  - α-adrenergic receptor blockers (phenoxybenzamine)
  - central nervous system sympathetic outflow blockers (clonidine)
  - ganglionic blockers (hexamethonium)
  - postganglionic adrenergic nerve terminal blockers (reserpine)

Among these drugs, the most frequently used drug in the treatment of hypertension in neonatal renovascular disease is captopril.

Renovascular hypertension often is associated with elevated serum concentrations of renin. Renin promotes the conversion of angiotensinogen to angiotensin I. As an angiotensin-converting-enzyme (ACE) inhibitor, captopril prevents the ACE-mediated conversion of angiotensin I to angiotensin II. This leads to decreased circulating concentrations of angiotensin II and aldosterone. By decreasing the concentration of the vasoconstrictor angiotensin II, the ACE inhibitor decreases peripheral vascular resistance. By decreasing the concentration of aldosterone, the ACE inhibitor promotes natriuresis, and consequently reduces intravascular volume. Furthermore, the ACE inhibitor decreases bradykinin breakdown, and the resultant increase in circulating concentration of bradykinin causes further vasodilation.

Captopril is rapidly absorbed after oral administration; its oral bioavailability in children ranges from 60% to 75%. Its onset of action is within 15 minutes, with peak effect in 30 to 90 minutes; its duration of action varies between 2 and 6 hours, occasionally longer. It is metabolized primarily in the kidney and secondarily in the liver. A recommended starting dose is 0.01 mg/kg per dose administered orally every 12 hours; the dose and the dosing interval are adjusted based on the response. The potential side effects of captopril are dose-dependent and include oliguria from renal hypoperfusion, seizures and apnea from cerebral hypoperfusion, and hyperkalemia from decreased aldosterone. Some patients may develop a chronic cough.

Amlodipine is a calcium-channel blocker. It decreases the flux of calcium into smooth muscle cells of the vasculature, leading to vasodilation and decreased peripheral vascular resistance. Secondarily, amlodipine as a dihydropyridine class of calcium-channel blocker, can decrease the flux of calcium into smooth muscle cells of the heart, leading to decreased myocardial contractility (negative inotropic effect) and decreased heart rate from slowed impulse conduction (negative chronotropic effect). Amlodipine is rapidly absorbed after oral administration; its oral bioavailability in children ranges from 64% to 90%. Its onset of action is within 3 hours, with peak effect in 6 to 12 hours; its duration of action may be as long as 24 hours. It is metabolized primarily in the liver, and a developmentally regulated cytochrome, P450 enzyme (CYP3A4), is the major enzyme involved in its metabolism. A recommended starting dose is 0.1 mg/kg per dose administered orally every 24 hours; the dose and the dosing interval are adjusted based on the response. The potential side effects of amlodipine are dose-dependent and include hypotension, oxygen desaturation, and neurologic deterioration.

Hydralazine is a potassium-channel opener. It hyperpolarizes vascular smooth muscle cells, leading to generalized arteriolar vasodilation. The absorption of hydralazine after oral administration is highly variable, based on its inactivation by acetylation in the gastrointestinal mucosa. It is metabolized primarily in the liver by acetylation. A suggested starting dose is 0.25 mg/kg per dose administered orally every 8 hours; the dose and the dosing interval are adjusted based on the response. The potential side effects of hydralazine are dose-dependent and include gastrointestinal intolerance, hypotension, tachycardia, agranulocytosis, lupuslike syndrome, and tachyphylaxis to the drug.

Propranolol is a β-adrenergic receptor blocker. It attenuates sympathetic stimulation through competitive antagonism of epinephrine and norepinephrine, leading to decreased myocardial contractility (negative inotropic effect) and decreased heart rate from slowed impulse conduction (negative chronotropic effect). In addition, it blocks the β-adrenergic receptors in the kidney, leading to decreased secretion of renin, and resultant decreased production of the vasoconstrictor angiotensin II.

Propranolol is rapidly absorbed after oral administration; its oral bioavailability in children ranges from 25% to 40%. Its onset of action is within 30 minutes, with peak effect in 1 to 2 hours. Its duration of action is variable, based on its metabolism in the liver by cytochrome P450 enzyme (CYP2D6). The recommended starting dose is 0.25 mg/kg per dose administered orally every 6 hours; the dose and the dosing interval are adjusted based on the response. The potential side effects of propranolol are dose-dependent and include hypotension and bradycardia, hypoglycemia and hypertriglyceridemia, and bronchochoconstriction. Propranolol is a preferred drug in the treatment of supraventricular tachycardia, hypertrophic obstructive cardiomyopathy, and as an adjunct in neonatal thyrotoxicosis.

Phenoxybenzamine is an α-adrenergic receptor blocker. It decreases circulating concentration of catecholamines, leading to vasodilation and decreased peripheral vascular resistance. Its pharmacokinetics and safety/efficacy profile remain unexplored, limiting its use in neonates.

Suggested Readings

Armstrong AW, Myers CW, Yeh DC, Rocco TP. Integrative cardiovascular pharmacology: hypertension, ischemic heart disease, and congestive heart failure. *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*. Golan DE, Tashjian Jr AH, Armstrong EJ, Galanter JM, Armstrong AW, Arnaout RA, Rose HS, ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:375-399.

Ettinger LM, Flynn JT. Hypertension in the neonate. *NeoReviews*. 2002;3:e151-e156. Accessed November 8, 2010 at: http://neoreviews.aappublications.org/cgi/content/full/3/8/e151?

Wells TG, Ilyas M. Antihypertensive drugs. *Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice. 3rd ed*. Yaffe SJ, Aranda JV, ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:678-697.

Young TE, Mangum B. *Neofax 2010. 23rd ed*. Chapel Hill, NC: Thomson Reuters; 2010:148-149, 176-177, 196.

American Board of Pediatrics Content Specification(s)

Cardiovascular: Know the mechanism of action of commonly used autonomic agonist and antagonist drugs

Cardiovascular: Know the therapeutic indications for, and toxicity of, commonly used autonomic agonist and antagonist drugs

Cardiovascular: Know the mechanisms of action, therapeutic indications for, and toxicity of vascular afterload-reducing drugs

Water/Salt/Renal: Formulate a differential diagnosis for an infant with systemic hypertension in early infancy

Water/Salt/Renal: Know the management of an infant with systemic hypertension, including adverse effects of management

Complete Assessment

Print

Table: Causes of Neonatal Hypertension

H	Heart disease (eg, coarctation)
Y	Yet undetermined (idiopathic)
P	Pulmonary disease (bronchopulmonary dysplasia)
E	Endocrine disorder (congenital adrenal hyperplasia, hyperaldosteronism, Cushing disease, hyperthyroidism)
R	Renal disease (renovascular thromboembolism, polycystic/ multicystic/ dysplastic/hypoplastic kidney, obstructive nephropathy, acute tubular necrosis)
T	Total parenteral nutrition (high calcium, high salt)
E	Extracorporeal membrane oxygenation
N	Neoplasm (Wilms tumor, mesoblastic nephroma, neuroblastoma, pheochromocytoma)
S	Surgery (abdominal wall defect repair)
I	Intoxication (dexamethasone, xanthines, adrenergic drugs, phenylephrine eye drops)
O	Opioid withdrawal (withdrawal from any sedation)
N	Neurologic cause (seizures, pain, intracranial hemorrhage, intracranial hypertension)

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July

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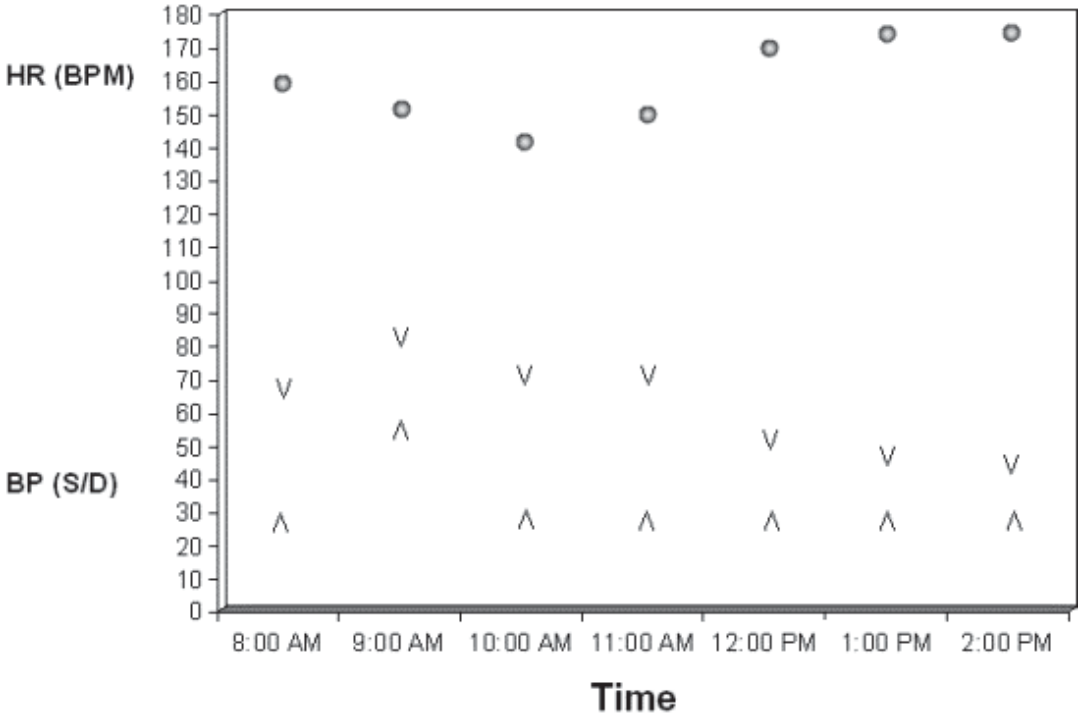
ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **8**

Question: 1

A 25-day-old 890-g male infant with a central venous catheter underwent extubation 12 hours ago to 6 cm of continuous airway pressure. A culture specimen, taken several days ago, of an excoriated lesion of the right naris that is now healed yielded *Staphylococcus aureus*. Because of increased apnea, mechanical ventilation was restarted. A review of his vital signs from the past 12 hours is shown in **Figure 1.** His pulses are weak, heart sounds are muffled, and capillary refill is greater than 4 seconds; he is lethargic and his urine output has dropped to 0.5 mL/kg per hour.

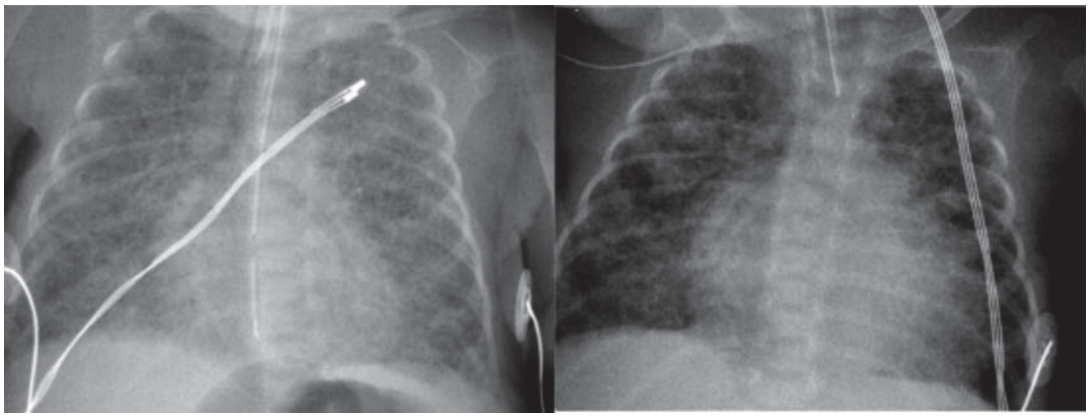
Figure 1: Vital signs over the preceding 12 hours



Capillary blood gas values are as follows: pH 7.08, Pco_2 61 mm Hg, Po_2 40 mm Hg, base excess -12.8 mEq/L (-12.8 mmol/L). His hematocrit value is 30%, platelet count 95,000×10^3/μL (95,000×10^9/L), and white blood cell count is 25×10^3/μL (25×10^9/L). The differential on the

white blood cell count includes 10 bands, 58 segmented neutrophils, and 32 lymphocytes. **Figure 2** shows the findings on chest radiography to assess endotracheal tube placement next to a radiograph taken several days earlier. You discuss the infant's treatment with the resident team.

Figure 2



Of the following, the MOST effective next step in the treatment of this infant would be:

○	**A.**	decreasing end expiratory pressure
○	**B.**	infusing milrinone
✓	**C.**	performing pericardiocentesis
○	**D.**	removing the central venous catheter
○	**E.**	transfusing packed red blood cells

Correct

PC PBLI

The neonate in the vignette has clinical features compatible with shock, an unstable pathophysiologic state characterized by inadequate tissue perfusion. The infant's cardiogenic shock is the result of acute pericarditis. All shock states will eventually involve a decrease in delivery or impaired use of essential cellular substrates resulting in a disruption and loss of cellular metabolism and function. Although the clinical presentation of shock in neonates may vary depending on the type (hypovolemic, cardiogenic, or distributive; **Table**) the infant showed several signs (tachycardia, hypotension, prolonged capillary refill, oliguria and lethargy that are common to most cases of neonatal shock.

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Hypotension is a late finding of shock. Systemic blood flow correlates poorly with blood pressure in neonates and as such individual blood pressure measurements do not reliably detect a decrease in blood flow during the early stages of shock. However, repeated blood pressure measurements with narrowing pulse pressures associated with an increasing heart rate (**Figure 1**) are suggestive of developing shock.

Initial evaluation of neonatal shock includes rapid recognition of the circulatory compromise

as well as determining the cause of the shock to guide treatment. Physical examination findings and diagnostic evaluations are often indicative of the cause for shock. In the infant in the vignette, the narrowing of pulse pressure, weak peripheral pulses, and muffled heart sounds combined with a large cardiac silhouette on chest radiograph and deteriorating condition indicate pericardial tamponade. Pericardiocentesis is emergently needed for both diagnostic and treatment reasons. If pericardial tamponade is not relieved by a pericardiocentesis, resuscitative measures likely will be unsuccessful.

Pericarditis is inflammation of the pericardium and proximal aspects of the great vessels. The pericardium consists of two layers, an inner visceral layer that is continuous with the outer surface of the myocardium and the outer parietal pericardium which lines the surrounding mediastinal structures. Inflammation of the pericardium leads to an influx of fibrin, polymorphonuclear and mononuclear cells, and exudation of fluid into the potential space between the two pericardial layers. Small increases in fluid will be clinically insignificant as they are readily reabsorbed. However, large or rapid increases in pericardial fluid that exceed resorptive capacity will result in significant cardiac dysfunction. When resorptive capacity is exceeded, even small incremental fluid accumulation will result in increased intracardiac pressure that interferes with cardiac filling, resulting in a decrease in stroke volume and cardiac output.

The cause of pericarditis can be infectious or noninfectious, and may be the sole manifestation of a disease or part of a multisystem disorder. Although a number of organisms may be responsible for purulent pericarditis, *Staphylococcus aureus* is most often implicated. *Escherichia coli*, *Klebsiella,* and *Pseudomonas aeruginosa* have all been reported to cause purulent pericarditis. Virtually all infants with purulent pericarditis, including the neonate in the vignette, have an associated infected focus, most commonly pneumonitis or multiple pulmonary abscesses. In fact, the presence of an infectious process elsewhere is frequent enough to consider pericarditis in any infant who develops cardiogenic shock or a sudden increase in the size of the cardiac silhouette during the course of a purulent infection. The pericardium can be involved through direct extension from an adjoining lung infection or a hematogenous spread of bacteria. Other causes of neonatal pericardial effusions include viral pericarditis, maternal lupus, intrapericardial teratoma, fetal hydrops, congenital diaphragmatic defects, chylopericardium, and central venous catheter perforation.

Purulent pericarditis is a medical and surgical emergency. Treatment is directed at relief of the cardiac tamponade through pericardial drainage and antibiotic treatment of the underlying infection. Care must be taken when aspirating pericardial fluid so that cardiac puncture or lacerations do not occur. The aspirating needle position usually can be monitored by using echocardiographic imaging or attaching an electrode of an electrocardiograph to the needle and monitoring for electrocardiographic signs of myocardial contact. Because of the occurrence of loculations of pus, especially with staphylococcal infections, an open surgical pericardiotomy may be required for adequate drainage of purulent pericarditis.

Depending on the clinical circumstances, positive expiratory pressure may increase, decrease, or have little effect on the cardiac output. Excessive positive end expiratory pressure in neonates with minimal lung disease is likely to diminish right ventricular volume and right ventricular output. However reducing positive expiratory pressure will do little to improve cardiac output in a neonate with a cardiac tamponade.

Milrinone, a phosphodiesterase III inhibitor increases intracellular cyclic adenosine monophosphate and calcium. Milrinone improves cardiac output by improving contractility, enhancing myocardial diastolic relaxation, and decreasing vascular resistance. It would not be indicated as an initial treatment for pericardial tamponade.

Cardiac tamponade can occur after the migration of a percutaneously placed central venous catheter from the right atrium into the pericardium. The neonate's central venous catheter

was positioned well outside the right atrium in both radiographs and was an unlikely cause of the pericardial fluid.

Initial treatment of cardiac tamponade often includes volume expansion while preparing for a pericardiocentesis. Increasing preload may temporarily increase right ventricular volume and cardiac output. However, any volume expander, including packed red blood cells, will only temporarily improve cardiac output. Draining the pericardial effusion is the definitive treatment for the infant's condition.

Suggested Readings

Evans N, Seri I. Cardiovascular compromise in the newborn infant. *Avery's Diseases of the Newborn. 8th ed*. Taeusch HW, Ballard RA, Gleason CA, ed. Philadelphia, PA: Elsevier; 2005:398.

Hilinski JA. Pericarditis. *Principles and Practice of Pediatric Infectious Diseases. 3rd ed*. Long SS, ed. Philadelphia, PA: Elsevier; 2008. Accessed August 10, 2010 at: http://www.mdconsult.com/das/book/body/214035361-2/0/1679/45.html?tocnode=55240989

Jain A, Daum RS. Staphylococcal infections in children: Part 1. *Pediatr Rev*. 1999;20:183-191. Accessed August 10, 2010 at: http://neoreviews.aappublications.org/cgi/content/full/pedsinreview;20/6/183

Overturf G, Marcy SM. Pericarditis. *Infectious Diseases of the Fetus and Newborn Infant. 6th ed*. Remington JS, Klein JO, Wilson CB, Baker CJ, ed. Philadelphia, PA: Elsevier Saunders; 2006:364-365.

Quak JM, Szatmari A, van den Anker JN. Cardiac tamponade in a preterm neonate secondary to a chest tube. *Acta Pædiatr*. 1993;82:490-491. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/8518529

Wetzel RC. Shock. *Textbook of Pediatric Intensive Care*. Rogers MC, ed. Baltimore, MD: Williams & Wilkins; 1987:483-524.

American Board of Pediatrics Content Specification(s)

Cardiovascular: Recognize the clinical features in an infant with a condition affecting myocardial performance

Cardiovascular: Recognize the laboratory, imaging, and other diagnostic features of an infant with a condition affecting myocardial performance

Cardiovascular: Formulate a differential diagnosis of an infant with a condition affecting myocardial performance

Cardiovascular: Know the evaluation and management plans and associated potential complications or adverse effects of such management for an infant with a condition affecting myocardial performance

Cardiovascular: Know the pathophysiology of a term or preterm infant with a condition affecting the systemic blood pressure, such as hypotension

Cardiovascular: Recognize the clinical features of an infant with systemic hypotension

Cardiovascular: Recognize the laboratory and imaging features of an infant with systemic hypotension

Cardiovascular: Formulate a differential diagnosis for an infant with systemic hypotension

Cardiovascular: Know the management of an infant with systemic hypotension and the adverse effects of such management

Complete Assessment

Print

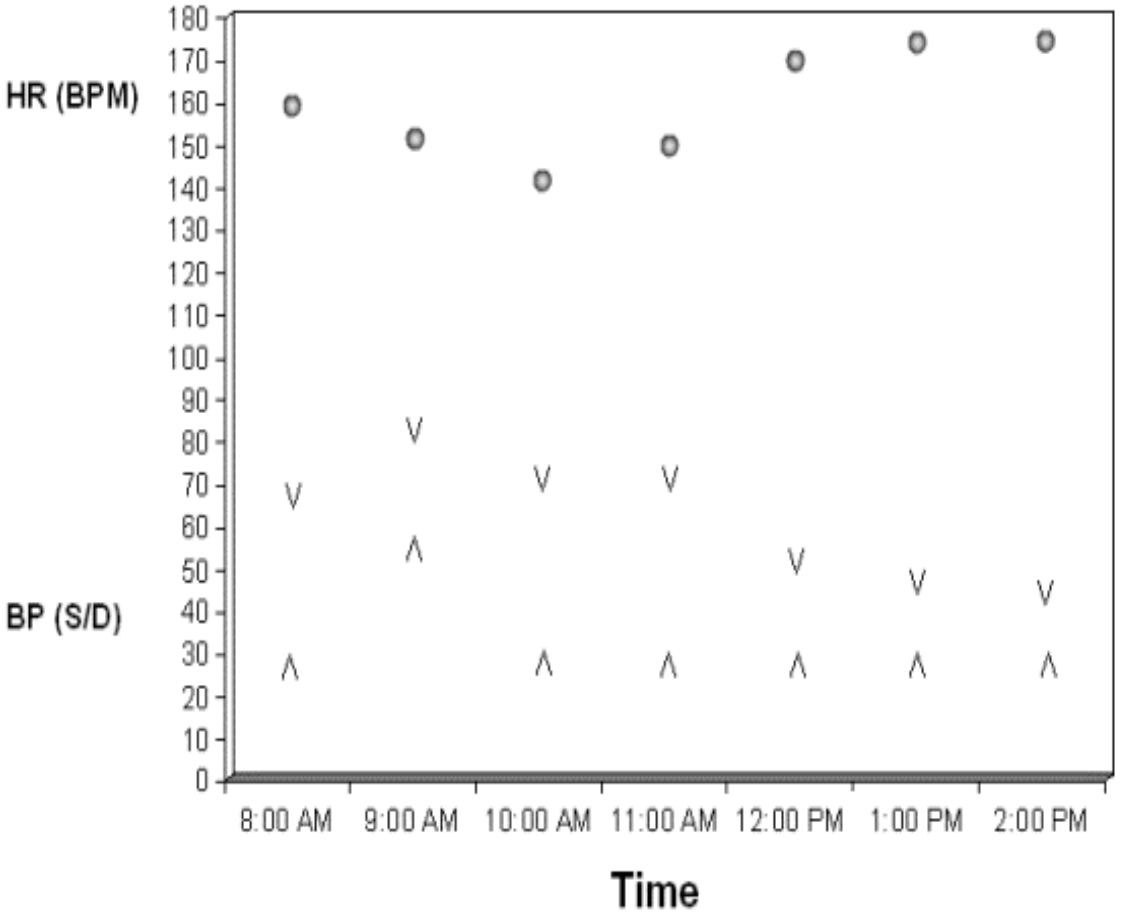
Table: Classification of Shock in Neonates*

Hypovolemic • Dehydration • Hemorrhage
Distributive • Anaphylaxis • Neurogenic • Drug toxicity
Cardiogenic • Congenital heart disease • Ischemic heart disease • Traumatic • Infectious cardiomyopathies • Drug toxicity • Tamponade
Septic shock
Miscellaneous • Air emboli • Drug overdose

* Adapted from Wetzel (1987).

Print

Figure 1: Vital signs over the preceding 12 hours



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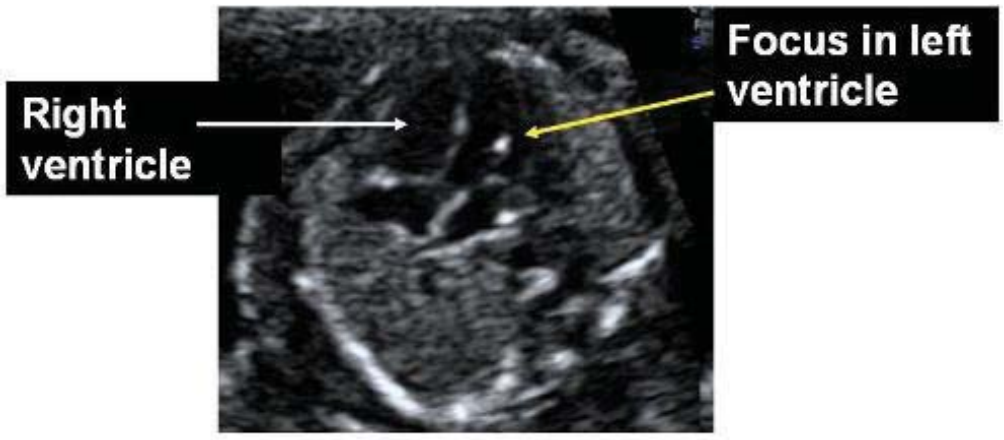
Question View: All (10)

ASSESSMENT PROGRESS: Total Questions: **10** Questions Answered: **10** Correct Answers: **9**

Question: 10

A 40-year old woman undergoes routine ultrasonography at 18 weeks' gestation which shows one intracardiac echogenic focus in the left ventricle (**Figure**). The obstetrician discusses the significance of this finding.

Figure



Of the following, the MOST likely cause of the intracardiac echogenic focus in the fetus in this vignette is:

○	**A.**	arteriovenous shunting in the ventricular wall
○	**B.**	increased velocity of intraventricular blood flow
○	**C.**	hypertrophy of the left ventricle
○	**D.**	microcalcification of the papillary muscle
✗	**E.**	structural heart disease

Incorrect

Correct Answer: D

Intracardiac echogenic foci (ICEF) are ultrasonographically detected in 0.5% to 20% of pregnancies, with the mean incidence occurring in approximately 5% of evaluated fetuses. The prevalence of ICEF may be higher among Asian women compared with other races. Foci can be observed using transvaginal ultrasonography as early as 11 weeks' gestation. The ability to detect ICEF varies based on angle of insonation, fetal position, gestational age, and maternal habitus. In addition, different ultrasound equipment, instrument settings, and sonographer experience may affect the ability to recognize foci. As ultrasound equipment and technology improve, the rate of ICEF identification may increase. A grading system that quantifies the size and number of foci may be useful for standardizing assessment but has not yet been established.

The ultrasonographic finding in the vignette, fetal ICEF, was first described in 1987. These intracardiac structures are small and discrete and are seen in the vicinity of the papillary muscles or chordae tendinae. They usually measure 1 to 4 mm in diameter, but can be as large as 18 mm. The brightness of these foci as seen on ultrasonography is equivalent to that of bone. The ICEF are typically observed in the cardiac ventricle and are most commonly located in the left ventricle (88%); right ventricular foci occur in 5% of affected fetuses and 7% have foci in both the left and right ventricles. While most fetuses with this finding have a single intracardiac focus, multiple foci in one or both ventricles have been observed in 2.4% to 25%. Foci in the atria have been described but are extremely rare: a recent study found right atrial ICEF in 3 of 15,076 fetuses.

Intracardiac echogenic foci appear to move in synchrony with the mitral or tricuspid valvular leaflets during the cardiac cycle. Initially ICEF were thought to be attributable to bulbous thickening of the chordae tendinae as a result of incomplete fenestration. However, histologic studies have shown that ICEF represent microcalcification and fibrosis of the papillary muscle or chordae. The reason for these mineralizations is unknown. The other possible explanations of ICEF listed in this vignette, including arteriovenous shunting in the ventricular wall, increased velocity of intraventricular blood flow, and ventricular hypertrophy, are not associated with ICEF. The finding of ICEF in a chromosomally normal fetus does not increase the risk of congenital heart disease or cardiac dysfunction.

The precise clinical significance of ICEF is uncertain but most likely depends on underlying aneuploidy risk and presence or absence of ultrasonographic abnormalities. The risk of a chromosomal abnormality seems to be low for fetuses with isolated ICEF in a low-risk population (eg, young pregnant woman with normal serum screening results), but more data are needed. Intracardiac foci may be markers for autosomal trisomies and other chromosomal abnormalities if the low-risk fetus has additional ultrasonographic findings. These abnormalities include the following: thickened nuchal fold, cystic hygroma, central nervous system anomaly, congenital heart disease, hyperechoic bowel, and renal pyelectasis. At present, low-risk women with ICEF undergo further testing for chromosomal anomalies only if additional markers of aneuploidy are present.

If the fetus is at high risk for chromosomal abnormalities (eg, maternal age $\geq$35 years, increased trisomy 18 or 21 risk by maternal serum screening, prior affected offspring), independent of additional ultrasonographic abnormalities, ICEF has been found to be associated with an increase in aneuploidy frequency, especially trisomy 21 and 13. In the largest prospective series examining echogenic foci in high-risk pregnant women, Winter and colleagues found that ICEF was associated with trisomy 21, with a likelihood ratio of 6.6, relative risk of 8.2, and positive-predictive value (PPV) of 9.8% (P<.001). In cases of isolated ICEF, the likelihood ratio of trisomy 21 was 4.3, relative risk was 4.8, and positive predictive value was 3.7. Unfortunately, precise adjusted risk estimates are

not currently available to counsel pregnant women who have ICEF. Moreover, additional studies are needed to determine if laterality, size, number, or degree of echogenicity of the ICEF alters the risk of a fetal chromosomal abnormality.

Suggested Readings

Bromley B, Lieberman E, Shipp TD, et al. Significance of an echogenic intracardiac focus in fetuses at high and low risk for anueploidy. *J Ultrasound Med*. 1998;17:127-131. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/9527573

Shanks AL, Odibo AO, Gray DL. Echogenic intracardiac foci: associated with increased risk for fetal trisomy 21 or not?. *J Ultrasound Med*. 2009;28:1639-1643. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/19933476

Wax JR, Mather J, Steinfeld JD, Ingardia CJ. Fetal intracardiac echogenic foci: current understanding and clinical significance. *Obstet Gynecol Surv*. 2000;55:303-311. Abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/10804537

Winter TC, Anderson AM, Cheng EY, et al. Echogenic intracardiac focus in 2nd-trimester fetuses with trisomy 21: usefulness as a US marker. *Radiology*. 2000;216:450-456. Accessed February 10, 2011 at: http://radiology.rsna.org/content/216/2/450.long

American Board of Pediatrics Content Specification(s)

Maternal-Fetal Medicine: Know the essentials of prenatal care, including risk assessment, perinatal referral, screening, and standard monitoring

Maternal-Fetal Medicine: Know the general principles, applications, and limitations of ultrasonography, including Doppler blood flow measurements, in assessment of fetal conditions and well-being

Complete Assessment