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

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.

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].)
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**


*Nadas’ Pediatric Cardiology, 2nd ed.* Philadelphia: WB Saunders; 2006


**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
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).

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
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 (AVNR) 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
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.
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
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**

<table>
<thead>
<tr>
<th>Factor</th>
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<tbody>
<tr>
<td>Prematurity</td>
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<tr>
<td>Hyperoxia</td>
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<tr>
<td>Volutrauma</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Sepsis</td>
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<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>Maternal chorioamnionitis</td>
</tr>
<tr>
<td>Aspiration</td>
</tr>
<tr>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td>Congenital heart disease</td>
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<tr>
<td>Persistent pulmonary hypertension</td>
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</table>

**Table 2: Pulmonary Function Abnormalities seen with Bronchopulmonary Dysplasia**

<table>
<thead>
<tr>
<th>Abnormality</th>
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<tbody>
<tr>
<td>Increased airway resistance</td>
</tr>
<tr>
<td>Increased airway obstruction</td>
</tr>
<tr>
<td>Increased airway reactivity</td>
</tr>
<tr>
<td>Decreased lung compliance</td>
</tr>
<tr>
<td>Ventilation/perfusion mismatch [ / ]</td>
</tr>
<tr>
<td>Increased thoracic gas volume</td>
</tr>
<tr>
<td>Decreased tidal volume</td>
</tr>
<tr>
<td>Increased respiratory rate</td>
</tr>
<tr>
<td>Increased work of breathing</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Measure</th>
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<tbody>
<tr>
<td>Ventilatory</td>
</tr>
<tr>
<td>Avoidance of intubation</td>
</tr>
<tr>
<td>Early surfactant with extubation</td>
</tr>
<tr>
<td>Low tidal volumes</td>
</tr>
<tr>
<td>Oxygen saturation &lt;95%</td>
</tr>
<tr>
<td>Pharmacologic</td>
</tr>
<tr>
<td>Caffeine</td>
</tr>
<tr>
<td>Vitamin A</td>
</tr>
<tr>
<td>Nutritional strategies</td>
</tr>
<tr>
<td>Increased energy intake</td>
</tr>
<tr>
<td>Restrictive fluid intake</td>
</tr>
</tbody>
</table>

* 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.

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, 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


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