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MORNING REPORT

Cyanosis in a Newborn Immediately after Birth

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Editor

Reason for presentation: cyanosis after birth

Part 1: The Case

A male neonate, weighing 3.9 kg, was delivered via repeat Cesarean section at 39 weeks of gestation at a community hospital. He cried immediately after birth, but his whole body appeared blue and he had low muscle tone that did not improve with suctioning and stimulation. His heart rate was between 70 and 100 beats per minute (a typical neonatal heart rate is >100). Blow-by with 100% oxygen was initiated, and pulse oximetry on his left hand measured 40%. Continuous positive airway pressure (CPAP) of 5 cm of H_2O with 100% oxygen was applied, and he was transferred to the neonatal intensive care unit. Additional information about the maternal history and prenatal course is shown in Box 1.

Box 1: Maternal History and Prenatal Course

Maternal History:

Anxiety treated with sertraline

Hypertension

4 prior pregnancies

Prenatal Course:

The mother had received routine prenatal care, and no anomalies had been noted on prenatal ultrasounds. Maternal prenatal screening laboratory test results for infection (including HIV, hepatitis B, syphilis, chlamydia, and gonorrhea) were negative and showed immunity to rubella. A screening rectal and vaginal culture grew group B *Streptococcus*. Antibiotic treatment was not indicated given the scheduled Cesarean section. There was no maternal fever.

AFTER YOU LEARN THIS INITIAL INFORMATION, WHAT ELSE DO YOU WANT TO KNOW AND WHY?

Q1: Can you describe the patient's chest wall movements during breathing?

Rationale for question: Grunting, nasal flaring, and retractions during breathing are abnormal and provide physical examination evidence of respiratory distress attributable to lung disease, upper airway obstruction, metabolic acidosis, or other stresses on the ventilatory system. If there is no respiratory distress or the patient is tachypneic in the absence of distress, cyanosis may be more likely due to some forms of congenital heart disease. Hypopnea may be suggestive of neurologic causes of disordered breathing leading to cyanosis.

Answer: The infant was tachypneic with mild retractions and nasal flaring, which did not improve with the use of CPAP.

Q2: Did the cyanosis improve with oxygen?

Rationale for question: Cyanosis that improves with oxygen indicates that sufficient blood flow enters the lungs and that oxygenated blood reaches the systemic circulation without mixing with deoxygenated blood. Conversely, cyanosis that does not improve with oxygen may suggest inadequate pulmonary blood flow with right to left shunting of deoxygenated blood (e.g., tetralogy of Fallot), intracardiac mixing of oxygenated and deoxygenated blood (e.g., truncus arteriosus), or that oxygenated blood does not reach the systemic circulation (e.g., dextro-transposition of the great arteries [d-TGA]). Improvement in oxygen saturation in response to oxygen therapy in the first minutes of life may be difficult to interpret because saturations increase from approximately 60% to more than 90% in the first 5 to 10 minutes of life with normal transition from fetal to postnatal circulation.[1]

Answer: After the initiation of CPAP with 100% oxygen, pulse oximetry indicated an increase in hemoglobin saturation to a peak of 72%.

Q3: What were the pre- and postductal saturations?

Rationale for question: Preductal saturations (measured in the right arm) and postductal saturations (measured in either leg) provide a measure of oxygenation in the systemic circulation before and after the insertion of the patent ductus arteriosus (PDA). These measurements can help narrow the differential diagnosis for a cyanotic infant. In a healthy infant, pre- and postductal saturations are equal as pulmonary pressure rapidly falls below systemic pressure after birth. If pre- and postductal saturations are the same, then shunted blood across the PDA is going from the aorta to the pulmonary artery (Fig. 1A). Pre- and postductal saturations that are similar in magnitude can also occur if the PDA has closed or is congenitally absent. Preductal saturation that is higher than postductal saturation suggests shunting of deoxygenated blood from the pulmonary artery through the PDA to the aorta. This is referred to as differential cyanosis and is seen in persistent pulmonary hypertension of the newborn and in some forms of congenital heart disease with left-sided obstruction such as critical coarctation of the aorta (Fig. 1B). Preductal saturation that is lower than postductal saturation is called reverse differential cyanosis and occurs in d-TGA with pulmonary hypertension or rarely in total anomalous pulmonary venous return (Fig. 1C). In d-TGA without pulmonary hypertension or with closed PDA, there will be no differential between the pre- and postductal saturations (Fig. 1D).

Answer: Pre- and postductal saturations were 72% and 74%, respectively.

PHYSICAL EXAMINATION

The patient's vital signs are shown in Box 2.

Box 2: Vital Signs

Axillary temperature: 36.9°C; heart rate: 160 beats per minute; respiratory rate: 54 breaths per minute; blood pressure: 71/25 mm Hg; and O_2 saturation by pulse oximetry: 72% (right arm) and 74% (right leg)

The infant was cyanotic, most prominently in the upper body, with no apparent dysmorphic features. The head was normocephalic with an open anterior fontanelle; conjunctivae were clear with normal eye movements, and the oropharynx was normal with an intact palate. The neck was supple with intact clavicles. The lungs were clear to auscultation, but the infant was tachypneic with mild subcostal retractions. The heart rate and rhythm were normal; there was a normal S1 and single S2 without murmur, rub, or gallop. The precordial impulse was of normal intensity, palpated in the left chest. Peripheral pulses were strong in all extremities. The abdomen was soft and not distended. The patient had male external genitalia with descended testes and a patent anus. He had diffuse hypotonia and decreased movement of the arms and legs.

Part 2: Approaching the Differential Diagnosis: Putting the Case Together Thus Far

The key features of this presentation are immediate and profound hypoxemia after birth and mild respiratory

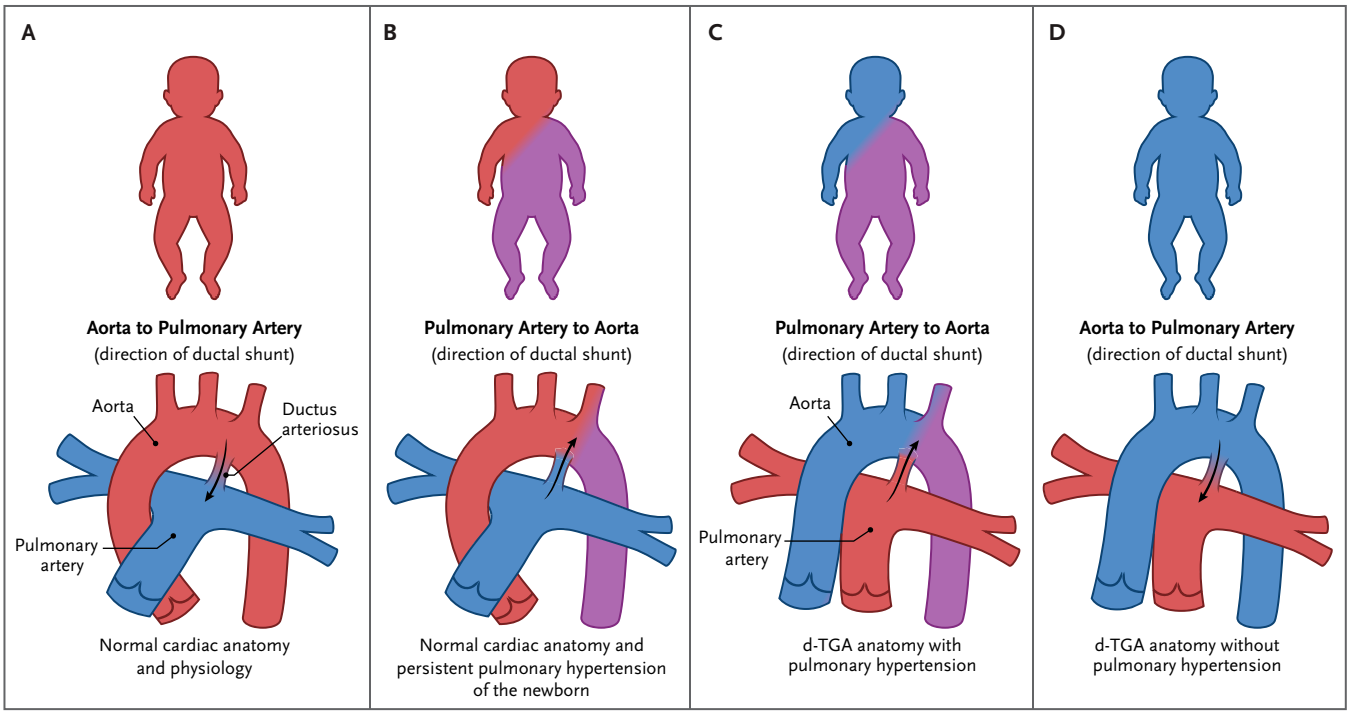

Figure 1. Pre- and Postductal Saturations in Normal and Abnormal Cardiac Anatomy and Physiology.
Oxygenated blood is shown in red, deoxygenated blood in blue, and mixed blood in purple. A) No differential in saturations in normal anatomy with shunt from the aorta to the pulmonary artery via the patent ductus arteriosus. B) differential cyanosis with shunt from the pulmonary artery to aorta. C) reverse differential cyanosis in d-transposition of the great arteries and pulmonary hypertension with shunt from the pulmonary artery to aorta. D) No differential in saturations with d-transposition of the great arteries without pulmonary hypertension with shunt from the aorta to the pulmonary artery.

distress with minimal improvement with oxygen therapy. It is important to differentiate between the terms *cyanosis*, *hypoxemia*, and *hypoxia*. Cyanosis refers to the blue appearance of skin, hypoxemia specifies low oxygen tension in the bloodstream, and hypoxia means low oxygen tension in the tissues. The finding of a low oxygen saturation in this patient rules out nonhypoxemic causes of cyanosis such as polycythemia and acrocyanosis.[2]

Developing an approach to the differential diagnosis for hypoxemia in neonates requires an understanding of how normal oxygen levels in the blood are achieved. A normal oxygen level in the blood is dependent on appropriate neurologic, respiratory, and circulatory function and is achieved with five steps:

1. Inspired oxygen reaches the alveolar-capillary units through adequate ventilation.
2. Deoxygenated blood flows through the pulmonary arteries to alveolar-capillary units.
3. In the alveolus, oxygen diffuses from the airspace into the capillary blood.
4. Oxygen binds to hemoglobin in the red blood cells flowing through the pulmonary capillaries.
5. Oxygenated blood from all regions of the lungs mixes together as it returns to the left side of the heart and is pumped to the systemic circulation.

Considering lesions at each of these steps is one framework for approaching the differential diagnosis, which is outlined in Box 3. This list of diagnoses is not exhaustive but includes representative or common examples from each category. Some diagnoses may cause hypoxemia through multiple mechanisms and therefore fit in multiple categories.

Box 3: Framework for Approaching the Differential Diagnosis

1. Inspired oxygen cannot reach alveolar-capillary units.

(continued)

(Box 3: continued)

a. Inadequate ventilation due to neurologic dysfunction or muscular weakness
Examples: Hypoxic ischemic encephalopathy, exposure to sedating medications during delivery

b. Mechanical obstruction to ventilation
Examples: Micrognathia, choanal atresia

2. Deoxygenated blood cannot reach the lungs and/or shunts to the systemic circulation.

a. Inadequate pulmonary blood flow with right to left shunt due to elevated pulmonary pressures
Example: Persistent pulmonary hypertension of the newborn

b. Inadequate pulmonary blood flow with to right to left shunt due to congenital heart disease
Examples: Tetralogy of Fallot, Ebstein anomaly, total anomalous pulmonary venous return)

c. Congenital heart disease with normal or increased pulmonary blood flow but intracardiac mixing of oxygenated and deoxygenated blood
Examples: truncus arteriosus, hypoplastic left heart syndrome

3. Oxygen that has reached alveolar-capillary units cannot enter the bloodstream.

a. Alveolar or interstitial lung disease
Examples: Meconium aspiration syndrome, pneumonia

b. Extrinsic compression of lungs leading to inadequate ventilation of some alveolar-capillary units
Examples: Pleural effusion, pneumothorax

4. Oxygen cannot bind normally to hemoglobin.
Example: Methemoglobinemia

5. Oxygenated blood cannot reach the systemic circulation.
Example: dextro-Transposition of the great arteries (d-TGA)

WHAT TESTS DO YOU WANT TO DO?

An arterial blood gas would assess the degree of metabolic and respiratory acidosis, and the partial pressure of oxygen (PaO_2). A white blood count and differential would provide guidance to the likelihood of infection, and a blood culture should be obtained before starting antibiotics. A glucose level should be checked as hypoglycemia can cause cyanosis via neurologic dysfunction, apnea, or inadequate activation of the muscles of ventilation.[3]

A chest radiograph would assess lung fields for the presence of abnormal thoracic opacities or pulmonary hypoplasia or may demonstrate an abnormal cardiac silhouette suggestive of heart disease. An echocardiogram should be done to evaluate for congenital heart disease or persistent pulmonary hypertension of the newborn.

TEST RESULTS

Laboratory study results are shown in Box 4.

Box 4: Laboratory Studies

The patient's laboratory results are shown in Figure 2.

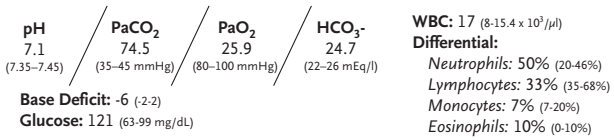

Figure 2. The Patient's Laboratory Results.
Reference ranges are given in parentheses. HCO_3 denotes bicarbonate, $PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, WBC white blood cell.

A chest radiograph demonstrated a normal cardiothymic silhouette and clear lungs without pleural effusion or pneumothorax.

Part 3: Refining the Differential Diagnosis

The patient had chest wall retractions during breathing, profound hypoxemia, respiratory acidosis, and normal appearing lungs and cardiac silhouette on a radiograph. Hypoxemia rules out methemoglobinemia, which is characterized by a normal PaO_2 but falsely low pulse oximetry readings. The severity and time of onset hypoxemia also makes certain types of congenital heart disease less likely. Congenital heart disease with intracardiac mixing, such as truncus arteriosus or hypoplastic left heart syndrome, generally causes only mild hypoxemia with saturations of at least 80%. Congenital heart disease with obstruction to pulmonary blood flow, such as tetralogy of Fallot and pulmonary or tricuspid atresia, generally has mild hypoxemia at birth and does not progress to severe hypoxemia until a few days of life when the PDA closes. The finding here that the pre- and postductal saturations are equal makes persistent pulmonary hypertension of the newborn less

likely, as we would expect differential cyanosis with lower saturations in the legs.

The absence of abnormal opacities on the chest radiograph also helps refine our differential diagnosis. Lung disease is usually high on the differential of a hypoxemic and hypercarbic newborn, but the normal appearance of the lungs makes diagnoses in this category less likely. Severe Ebstein anomaly can present with profound hypoxemia at birth, but patients with this disease have marked cardiomegaly due to right atrial enlargement, which would typically be visible on a chest radiograph. Obstructed total anomalous pulmonary venous return can also present with immediate, severe hypoxemia, but these patients will have marked pulmonary congestion visible on a chest radiograph as a result of obstruction to pulmonary venous egress.

Problems with inspired oxygen reaching the lungs due to either obstruction or inadequate ventilation remain on the differential. However, the patient's normal oropharyngeal examination and lack of stridor make upper airway obstruction less likely.

A problem with oxygenated blood reaching the systemic circulation (e.g., with d-TGA) remains high on the differential. In d-TGA, pulmonary and systemic circulations are in parallel instead of in series. This means that oxygenated blood cycles between the left side of the heart and the pulmonary circulation, and deoxygenated blood cycles between the right side of the heart and the systemic circulation. Therefore, oxygenated blood can only reach the systemic circulation via mixing between the two circulations, which happens primarily at the level of the atrial septum, and less so via the PDA or a ventricular septal defect (if present) (Fig. 3). Patients with d-TGA are considered to have adequate mixing if oxygen saturations are greater than 75%.[4] d-TGA is anatomically and physiologically distinct from the similarly named levo-transposition of the great arteries (l-TGA), which is also known as congenitally corrected transposition of the great arteries. Patients with l-TGA do not present with hypoxemia at birth. This refined differential diagnosis is shown in Box 5.

Box 5: Refining the Differential Diagnosis

1. Inspired oxygen cannot reach alveolar-capillary units.
   a. Inadequate ventilation due to neurologic dysfunction or muscular weakness

(continued)

(Box 5: continued)

   Examples: Hypoxic ischemic encephalopathy, exposure to sedating medications during delivery

   b. Mechanical obstruction to ventilation
   Examples: Micrognathia, choanal atresia

~~2. Deoxygenated blood cannot reach the lungs and/or shunts to the systemic circulation.~~

~~a. Inadequate pulmonary blood flow with right to left shunt due to elevated pulmonary pressures~~
~~Example: Persistent pulmonary hypertension of the newborn~~

~~b. Inadequate pulmonary blood flow with to right to left shunt due to congenital heart disease~~
~~Examples: Tetralogy of Fallot, Ebstein anomaly, total anomalous pulmonary venous return~~

~~c. Congenital heart disease with normal or increased pulmonary blood flow but intracardiac mixing of oxygenated and deoxygenated blood~~
~~Examples: truncus arteriosus, hypoplastic left heart syndrome~~

~~3. Oxygen that has reached alveolar-capillary units cannot enter the bloodstream.~~

~~a. Alveolar or interstitial lung disease~~
~~Examples: Meconium aspiration syndrome, pneumonia~~

~~b. Extrinsic compression of lungs leading to inadequate ventilation of some alveolar-capillary units~~
~~Examples: Pleural effusion, pneumothorax~~

~~4. Oxygen cannot bind normally to hemoglobin.~~
~~Example: Methemoglobinemia~~

5. Oxygenated blood cannot reach the systemic circulation.
   Example: dextro-Transposition of the great arteries (d-TGA)

INTERVAL HISTORY 1

Because of ongoing hypoxemia and respiratory distress, the infant's trachea was intubated and mechanical ventilation with 100% oxygen was instituted. A repeat arterial blood gas showed a pH of 7.34, a $PaCO_2$ of 44 mm Hg, and a PaO_2 of 27 mm Hg. Respiratory compliance was normal, but the patient remained hypoxemic and developed reverse differential cyanosis with preductal saturation of 50% and postductal saturation of 70%. An intravenous infusion of prostaglandin E_1 was started to maintain ductal patency.

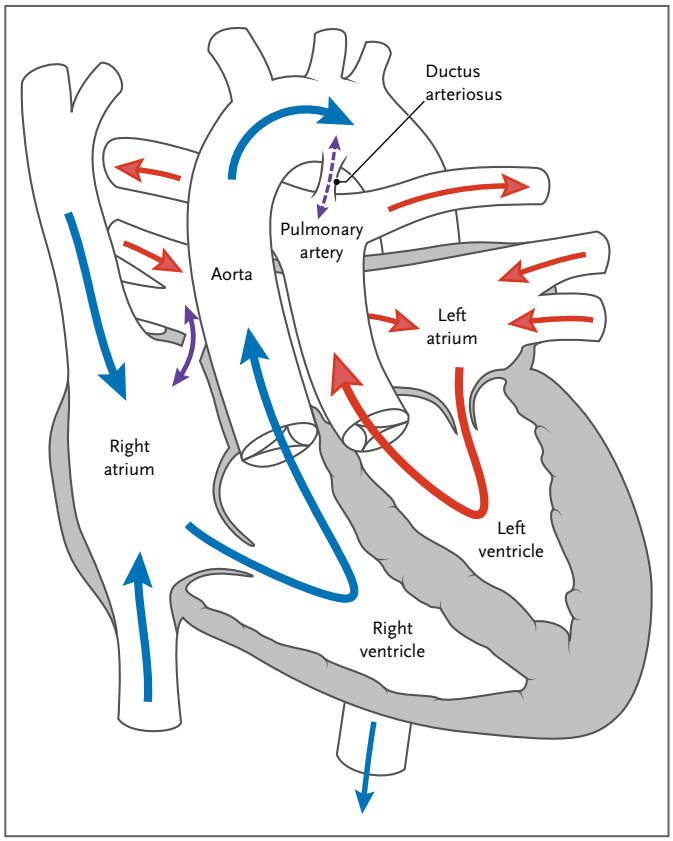

Figure 3. Anatomy and Blood Flow in d-Transposition of the Great Arteries Showing the Pulmonary and Systemic Circulations in Parallel.

Deoxygenated blood (blue arrows) cycles from the right side of the heart to the aorta to the body and back to the right side of the heart. Oxygenated blood (red arrows) cycles from the left side of the heart to the pulmonary artery to the lungs and back to the left side of the heart. Mixing between the circulations occurs primarily at the atrial level via the patent foramen ovale (purple arrow). Mixing also occurs across the patent ductus arteriosus (dashed purple arrow), but the direction of shunt is dependent on whether pulmonary pressures are higher or lower than systemic pressures.

Empiric antibiotics were initiated after a blood culture was obtained. An echocardiogram was completed, but the results were not yet available to the treating clinicians. Given the severity and persistence of hypoxemia, the patient was transferred to a tertiary care center.

HOW DOES THE INTERVAL HISTORY AFFECT YOUR APPROACH TO THE CASE NOW?

The patient has ongoing profound hypoxemia that did not improve with tracheal intubation and mechanical ventilation, and now has a new finding of reverse differential cyanosis. Intubation and mechanical ventilation should fix hypoxemia related to inadequate ventilation, neuromuscular weakness, or upper airway obstruction. Lung disease remains unlikely, given the normalization of ventilation with no improvement in oxygenation after intubation. The finding of reverse differential cyanosis effectively excludes other types of congenital heart disease besides d-TGA (obstructed total anomalous pulmonary venous return has already been ruled out based on the normal chest radiograph). Even without the echocardiography results, we are confident in our diagnosis of d-TGA as shown in Box 6.

Box 6: Making the Diagnosis

~~1. Inspired oxygen cannot reach alveolar capillary units.~~
~~2. Deoxygenated blood cannot reach the lung and/or shunts to the systemic circulation.~~
~~3. Oxygen that has reached alveolar capillary units cannot enter the bloodstream.~~
~~4. Oxygen cannot bind normally to hemoglobin.~~

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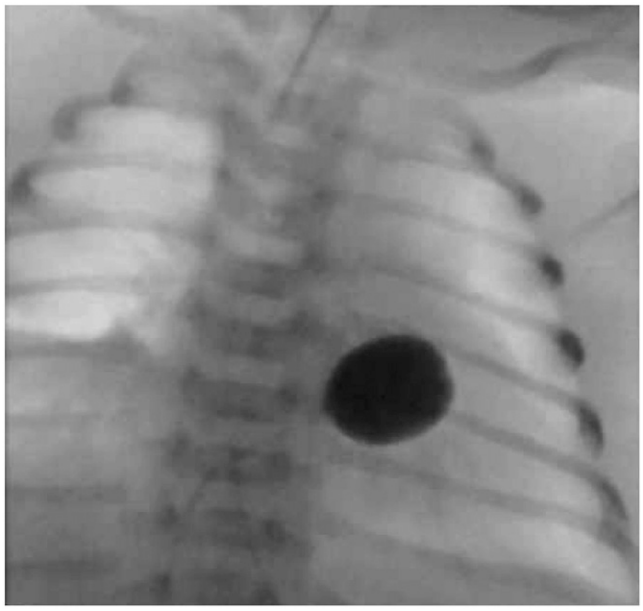

Figure 4. Fluoroscopic Image of a Balloon Atrial Septostomy.

A balloon-tipped catheter is passed across the patent foramen ovale into the left atrium, inflated, and pulled back into the right atrium, enlarging the size of the atrial communication. See video available online.

(Box 6 continued)

5. Oxygenated blood cannot reach the systemic circulation.
   - d-Transposition of the great arteries (d-TGA)

INTERVAL HISTORY 2

Echocardiography confirmed the diagnosis of d-TGA with intact ventricular septum and a small restrictive atrial communication. The infant received treatment with sedation and neuromuscular blockade to limit oxygen demand and to improve mixed venous oxygen saturation. Inhaled nitric oxide was initiated to improve pulmonary blood flow. Volume resuscitation and dopamine were initiated to treat hypotension and improve cardiac output and hypoxemia by optimizing mixed venous saturation and promoting mixing at the atrial septum. Prostaglandin E_1 was continued to maintain ductal patency and promote mixing between the systemic and pulmonary circulations. Despite these interventions, the hypoxemia continued to worsen with preductal saturation below 60% and at times was as low as 20% during transport.

Because of profound ongoing hypoxemia, the patient was transported directly from the ambulance to the cardiac catheterization laboratory to undergo a balloon atrial septostomy. In this procedure, a balloon-tipped catheter is inserted via the femoral or umbilical vein to the right atrium, then advanced through the patent foramen ovale into the left atrium. The balloon is inflated in the left atrium and pulled back into the right atrium, enlarging the atrial communication and allowing for improved mixing of the systemic and pulmonary circulations (Fig. 4 and Video—see video available online). After the procedure, the patient had immediate improvement in preductal saturations measured in the right arm to 75%.

The patient underwent surgical repair with an arterial switch operation on day of life 5. His postoperative course was notable for subclinical seizures and evidence of hypoxic ischemic brain injury on magnetic resonance imaging, likely owing to his profound perinatal hypoxemia and hemodynamic instability. He was discharged home on day of life 41. At 3 months of age, he was growing well on full oral feeds and demonstrating some gross motor delays. He remains at risk for neurodevelopmental delays, given his history of brain injury and congenital heart disease.[5]

TAKE-HOME POINTS

- Congenital heart disease should be suspected in newborns with hypoxemia refractory to oxygen therapy
- Although congenital heart disease may be identified on prenatal screening ultrasounds, many babies with d-TGA are diagnosed after birth.[6,7]
- Balloon atrial septostomy is recommended in patients with d-TGA and profound hypoxemia (saturation less than 60% or PaO_2 less than 25 mm Hg). While preparing for this procedure, medical therapy includes endotracheal intubation and mechanical ventilation with 100% oxygen, inhaled nitric oxide, sedation, paralysis, prostaglandin E_1 infusion, and hemodynamic support with volume resuscitation and inotropic infusion.[4,8]
- Patients with d-TGA who have undergone surgical repair are susceptible to adverse neurodevelopmental outcomes, while the causes are multifactorial, hypoxemia appears to play an important role.[5,9]

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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