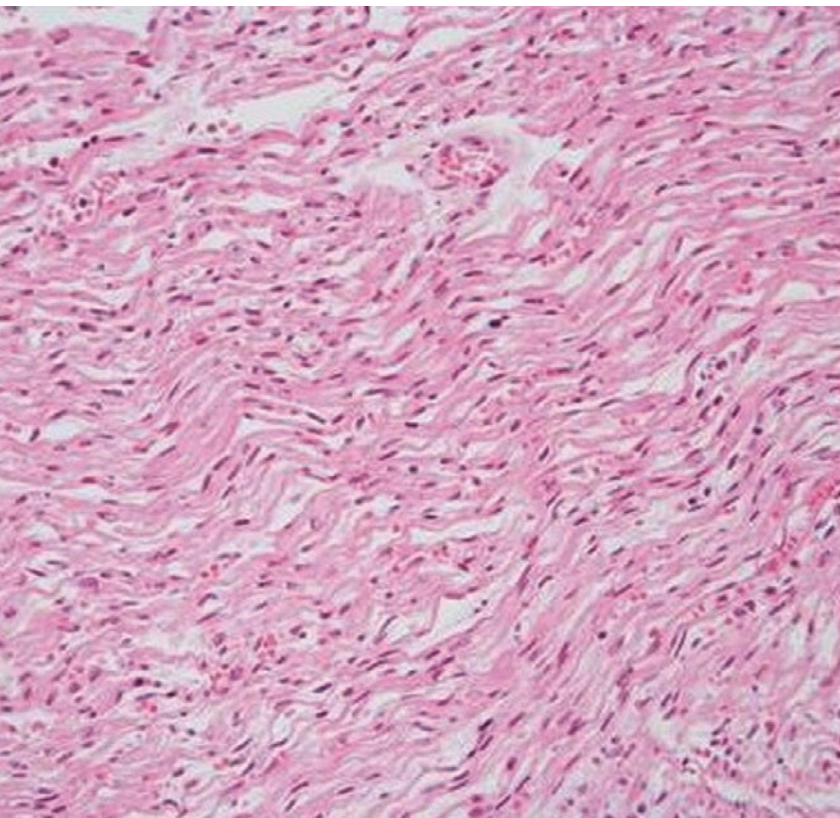


Patent ductus arteriosus,
bottle-meal, and fatal
myocardial ischemia

July 2009



Patent ductus arteriosus (PDA) is a frequent finding in premature infants; the frequency in infants weighting 501 to 1500 g is approximately 30%. Substantial left-to-right shunting through the ductus arteriosus is associated with increased risks for several complications: intraventricular hemorrhage, necrotizing enterocolitis, decreased renal function, bronchopulmonary dysplasia and death (1); fatal myocardial ischemia, however, is not a known complication of PDA.

This 1110 g twin boy was delivered by caesarean section at 27 1/7 weeks of gestation after preterm contractions and suspected chorioamnionitis. No antenatal corticosteroids had been administered. Apgar scores were 1, 3 and 5 at 1, 5 and 10 minutes, respectively. The infant was intubated in the delivery room and surfactant was administered. Chest x-ray showed grade III hyaline membrane disease (Fig. 1). He received amoxicillin and netilmicin for 7 days for suspected sepsis. Blood cultures remained negative. On day 5 of life, he was extubated and put on nasal CPAP for another 23 days. After cessation of CPAP therapy the FiO₂ remained at 0.21. Apnea of prematurity was successfully treated with caffeine citrate.

At one month of life, a grade 4 systolic murmur with radiation to the back was detected. On echocardiography, there was a PDA with a diameter of 2-3 mm and relevant left to right shunting (Fig. 2) but no evidence of

left ventricular hypertrophy. There were no signs of cardiovascular decompensation: renal function (creatinine 48 $\mu\text{mol/l}$, normal < 66 $\mu\text{mol/l}$) and digestion were normal; respiration was stable (respiratory rate 60/min, SpO₂ 95% in room air). Blood pressure was 50/28 (36) mmHg and heart rate was 150 bpm. Chest x-ray showed mild cardiomegaly and some evidence of pulmonary hypercirculation (Fig. 3). Cerebral ultrasound and Doppler examination revealed normal morphology and an elevated RI (0.98) with decreased diastolic flow velocity (Fig. 4) (2). A decision was taken not to attempt to close the PDA.

In the 6th week of life, at a corrected gestational age of 32 6/7 weeks, the boy was offered a meal from the bottle. At this time he was on an 8-meal-regimen with 30 ml of human milk per meal (150ml/kg/day). Forty-five minutes after the second bottle meal he abruptly developed signs of respiratory distress with tachypnea, retractions, flaring, grunting and an oxygen requirement of up to 30% in order to maintain SpO₂ > 94%. Oscillometric measured blood pressure was 40/22 (26) mmHg. The episode was felt to represent an aspiration event despite the absence of a known gastroesophageal reflux or an acute episode of coughing. The infant's condition first improved, blood pressure normalized and respiratory rate returned to baseline (58 bpm).

Three hours later respiratory distress reappeared followed by bradypnea and clinical signs of shock. He was again hypotensive (blood pressure 34/28 (30) mmHg)

and severe mixed acidosis (pH 6.7, pCO₂ 58 mmHg, base excess -26.9 mmol/l, bicarbonate 7.2 mmol/l) was noted. The patient was now transferred to the neonatal and pediatric intensive care unit (PICU). He was intubated with ketamine and pancuronium and ventilated with a FiO₂ of 0.9 and a peak inspiratory pressure (PIP) starting at 25-26 cmH₂O to obtain tidal volumes of 7.5 ml/kg. Due to persistent hypotension, echocardiography was performed and revealed significant impairment of left ventricular function with an LV ejection fraction of 19%. No pericardial effusion or tamponade were found. Arterial and central venous catheters were placed and dobutamine (15 µg/kg/min) and epinephrine (0.1 µg/kg/min for 1 hour, then 0.2 µg/kg/min for 2 hours, as well as six bolus doses for a total of 190 µg over four hours) were administered with the goal to maintain blood pressure in a low normal range (mean 30 mmHg). In the absence of dehydration and the high suspicion of cardiogenic shock, no fluids were given. With the objective to improve the effectiveness of the inotropes, a total of 5.6 mmol/kg of bicarbonate was administered, but metabolic acidosis did not improve (pH 6.8, pO₂ 150 mmHg, pCO₂ 24 mmHg, base excess -27.6 mmol/l, bicarbonate 3.5 mmol/l, lactate 23.3 mmol/l). Troponin I was 46.9 µg/l (normal < 0.6 µg/l). No ECG was done. Two hours after admission to the PICU, severe bradycardia and hypotension (blood pressure 24/12 (18) mmHg) finally led to chest compressions and bolus doses of epinephrine. The boy died 7 hours after onset of respiratory distress from irreversible, catecholamine refractory cardiogenic shock.

At autopsy, there was a PDA and mild left ventricular hypertrophy. Microscopic examination of the heart revealed acute ischemic changes of the inner third of the myocardium, including subendocardial bands of necrosis (Fig. 5) as well as multiple foci of wavy myocardial fibers (Fig. 6) in both ventricles. There was no evidence of myocarditis. The coronary arteries were inconspicuous. The lungs and abdominal organs appeared consolidated, reflecting peripheral congestion. There were no signs of pulmonary aspiration.



Fig. 1

Chest X-ray on the first day of life compatible with grade III HMD.

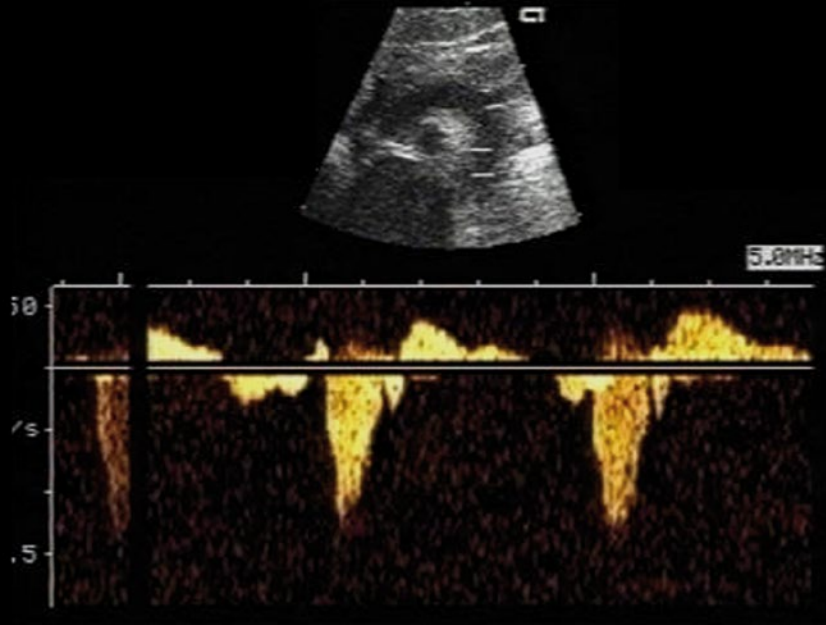


Fig. 2

Doppler echocardiography at 1 month of life demonstrating retrograde diastolic flow in the descending aorta due to ductal steal.

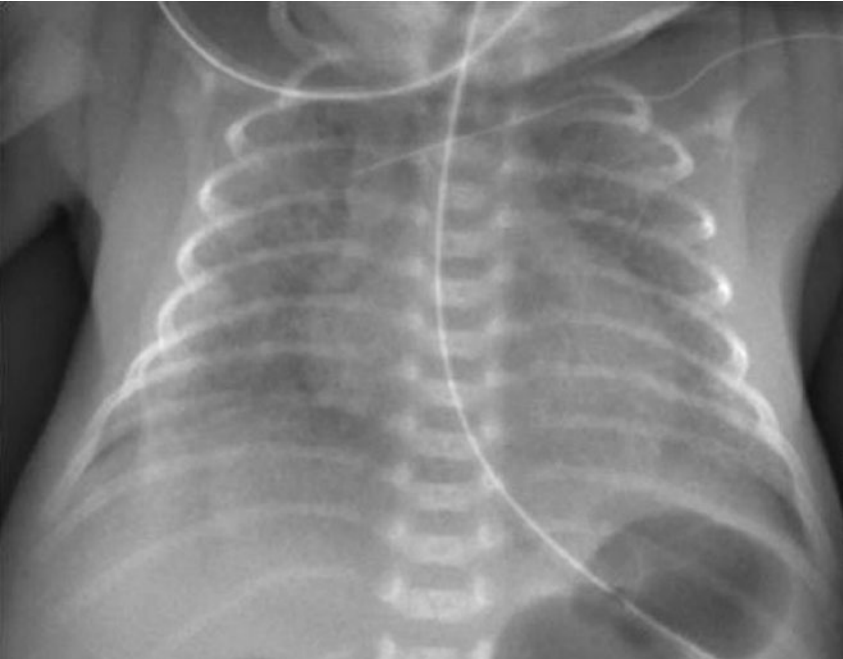


Fig. 3

Chest X-ray at 1 month of life showing cardiomegaly and some evidence of pulmonary hypercirculation.

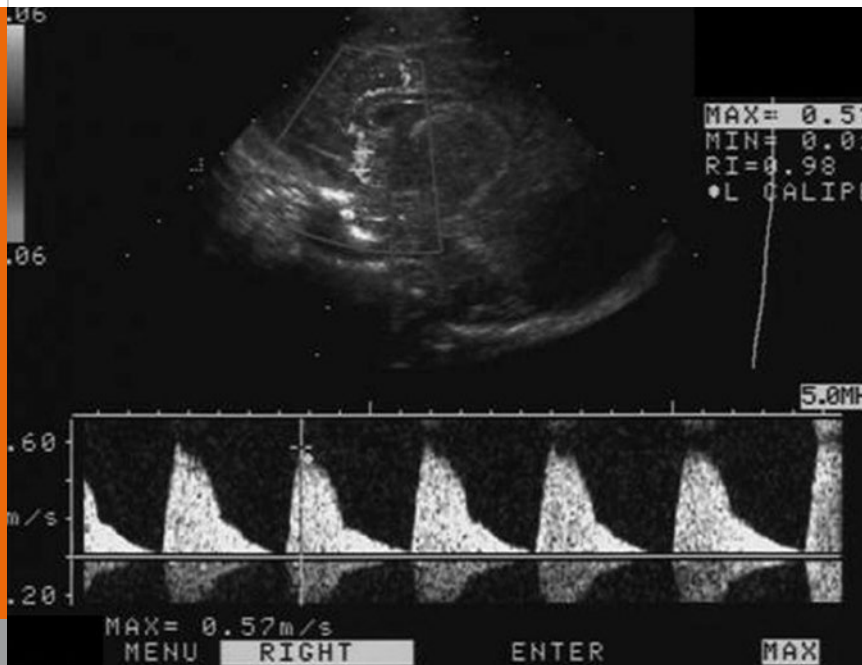


Fig. 4

Cerebral ultrasound with Doppler study showing an elevated resistive index (RI) of 0.98 consistent with a ductal steal phenomenon.

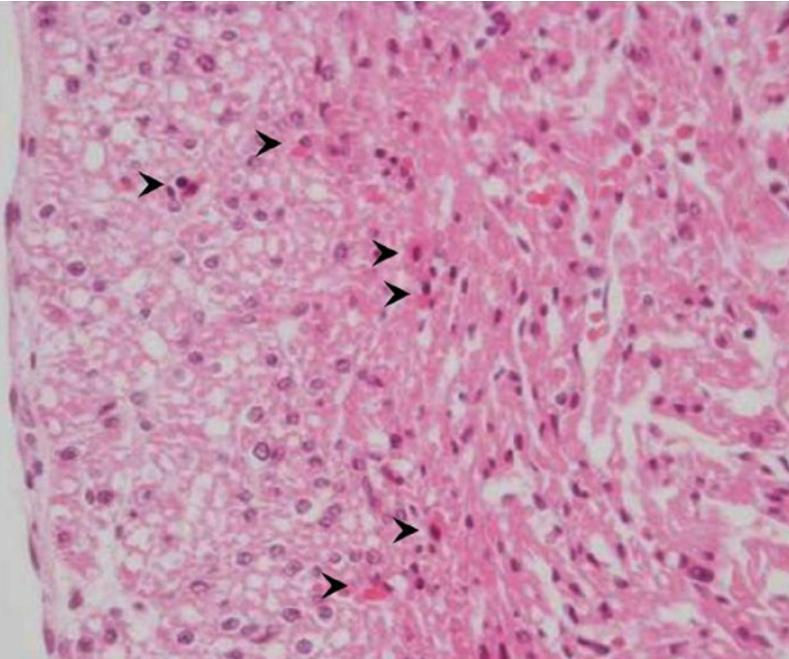


Fig. 5

Autopsy findings: subendocardial band of myocyte necrosis (asterisk) with hyper eosinophilia and pycnotic nuclei (HE-stain).

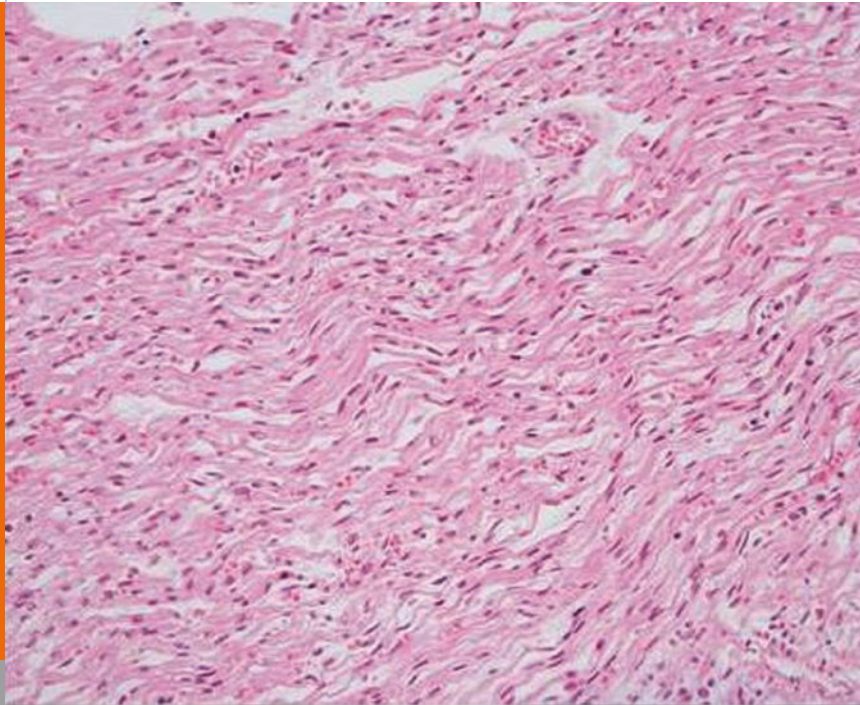


Fig. 6

Autopsy findings: wavy myocardial muscle fibers.

Fatal myocardial ischemia in the newborn is extremely rare (3). Most often it is seen in association with congenital heart disease, specifically, obstructive lesions (i.e. aortic stenosis), anomalous origin of the left coronary artery (Bland-White-Garland syndrome), and tricuspid valve abnormalities. Another cause of neonatal myocardial infarction are embolic injuries: amniotic fluid, air embolism secondary to the placement of an umbilical venous catheter and thrombus formation in the ductus venosus or in the umbilical vein followed by paradoxical thromboembolization. Coronary thrombosis with focal intimal thickening and coronary spasm in stressed newborns have also been reported. Impaired coronary perfusion because of increased work demands created by unusually brisk pulmonary vasoconstriction in newborns with pulmonary hypoxia have been described (4). Epinephrine administration in neonatal resuscitation is a known cause of myocardial ischemia secondary to elevated oxygen consumption (5). In contrast, ductal steal phenomenon secondary to PDA has not been described so far as a cause for fatal myocardial ischemia. However, a recent transthoracic Doppler echocardiography study showed decreased left anterior descending coronary artery blood flow as a result of PDA; coronary perfusion improved after coil closure of the PDA (6). In another study ST depressions on EKG suggesting ischemia were found in a group of neonates with PDA and respiratory distress syndrome; ST-depressions disappeared after surgical PDA ligation (7).

In our patient, there were no pulmonary impairment, metabolic disturbance or infectious disease. Respiratory distress was the first sign of cardiac decompensation. Blood pressure could be maintained within low normal ranges with exception of the last two hours of life but high-dose epinephrine administration were required and may have worsened myocardial damage. The fact that acute ischemic changes were found predominantly in the inner layer of the myocardium supports the diagnosis of myocardial ischemia as the result of ductal steal phenomenon secondary to a PDA because the inner third of the myocardium is typically perfused during diastole. Ductal steal phenomenon results in reduced diastolic blood pressure and therefore compromises coronary artery perfusion.

Bottle feeding represents an important physical effort in every neonate. Very low birth weight newborn cannot increase their resting metabolic rate more than 15% for physical activity (8). Bottle-feeding significantly increases respiratory rate and can decrease oxygen saturation (9). Cardiac output and myocardial oxygen consumption are increased. In our patient, a PDA-associated ductal steal phenomenon probably lead to myocardial ischemia and cardiogenic shock. Acute decompensation may have been triggered by physical strain associated with bottle feeding.

We speculate that newborn infants with hemodynamically significant PDA and extremely low diastolic blood pressure may be at increased risk for myocardial infarction secondary to a coronary steal phenomenon. Such infants may benefit from a very cautious and slow enteral feeding regimen with extended feeding by gastric tubes. They may additionally require indomethacin or PDA ligation even in absence of endorgan dysfunction. Finally, when evaluating a newborn infant with a hemodynamically significant PDA and acute onset of distress, the possibility of myocardial ischemia or infarction should be considered and cardiac isoenzymes and an EKG should be obtained.

CONCLUSION

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