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Evaluating the fetus with transposition

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TRANSPOSITION, DEFINED AS CONCORDANT atrioventricular and discordant ventriculo-arterial connections, is a common neonatal congenital cardiac malformation.[1] Repair of this lesion by means of the arterial switch in the neonatal period has progressed such that preoperative factors are playing a larger role in the postoperative outcomes.

The majority of newborns with transposition and an intact ventricular septum are born in the delivery room after an uncomplicated obstetrical course. A subgroup of these may present with severe cyanosis. It is suspected that this sub-set is cyanotic not only because of a restrictive atrial septum, but also because of elevated pulmonary vascular resistance. This decrease in flow of blood to the lungs, seen even with normal ventilation after birth, may have its genesis in the prenatal physiology.

Detection of transposition in the fetus

The role of the perinatal cardiologist is to identify the fetus with cardiac disease, and to improve the outcome. This is another way of saying that the standard of care that exists for the neonate is being translated to the prenatal setting. In the neonate with transposition, the pulmonary trunk arises from the morphologically left ventricle, while the aorta takes its origin from the morphologically right ventricle (Fig. 1). After birth, because of these discordant ventriculo-arterial connections, the oxygenated blood courses through the pulmonary arteries, back to the left atrium and the left ventricle, and is then recirculated to the lungs. The deoxygenated blood passes to the body, is returned by the systemic veins to the right atrium, thence to the right ventricle, and again to the body, producing the severe cyanosis seen in the newborn infant.

Detection of this abnormal anatomy before birth requires suspicion that the arterial trunks are abnormally arranged. On the other hand, prediction of the prognosis of the anatomy after birth requires information about the physiology. This requires information about the likely functional setting after birth. Some of these variables in postnatal physiology, such as the state of the pulmonary vascular bed, the interatrial communication, and ventricular performance, can be surmised from data obtained in the fetus.

The results of modern fetal echocardiography in the second and third trimester have been studied in several settings, and diagnosis of the discordant ventriculo-arterial connections can now be achieved with a high degree of success, with some authors citing 95 percent overall accuracy in detecting cardiac defects on indicated fetal echocardiographic examinations.[2] In order to evaluate the prenatal occurrence of transposition, however, the malformation needs to be detected during fetal life in a non-selected population of pregnant women undergoing prenatal ultrasonic screening. In this setting, the results are quite poor. This reflects the fact that fetuses with transposition lack several of the classical findings of congenital cardiac malformations as usually seen in fetal life. For many years, programmes have been in place with the aim of screening for congenital cardiac disease. They emphasize the typical markers of the congenital cardiac malformations, including disproportion at the level of the atrial and ventricular chambers or the arterial trunks, enlargement of the heart, or an abnormal position of the heart within the chest. In fetuses having transposition with an intact ventricular septum, the four-chamber view is entirely normal, while the heart occupies its normal position. Thus, the lack of any obvious disproportion of the chambers

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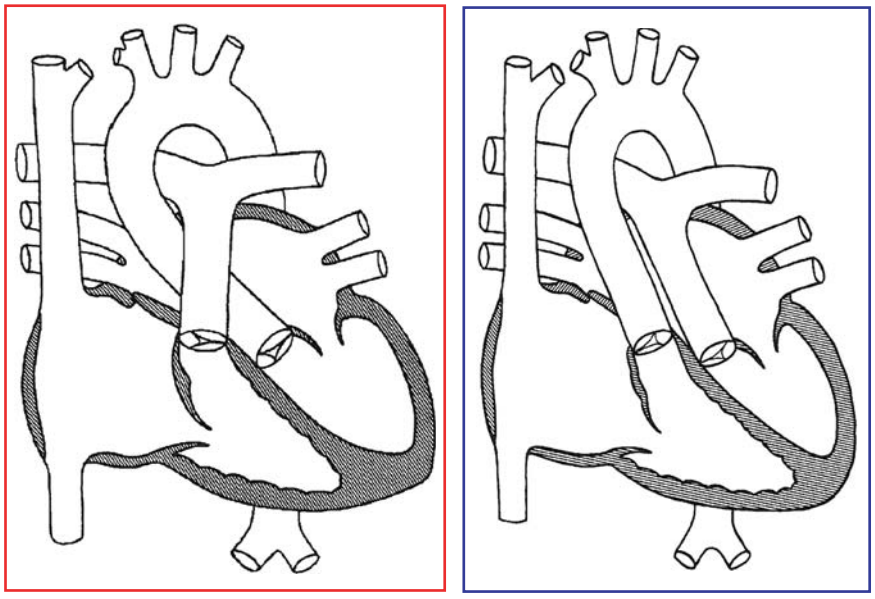

Figure 1.
Cartoon showing the normal postnatal anatomy (left panel) as opposed to the situation in transposition (right panel). Note the spiraling as opposed to the parallel course of the arterial trunks.

and arterial trunks, the low association with chromosomal abnormalities or other non-cardiac congenital anomalies, and the "passive" course of the gestation without signs of fetal congestive heart failure, make detection of transposition a challenge in fetal life. It was only with the advent of emphasis on the outflow tracts in fetal cardiac screening that the characteristic finding of parallel outflow tracts was recognized more frequently (Fig. 2). The parallel course of the arterial duct beneath the aortic arch differentiates the fetus with discordant ventriculo-arterial connections from the normal arrangement, in which there is crossing of the arterial trunks. This lack of spiraling of the great arteries is not usually associated with any discrepancy in size between the aorta and the pulmonary trunk unless there is an associated interventricular communication, pulmonary stenosis, or coarctation of the aorta. Thus, the four-chamber echocardiographic view of the fetus with transposition is essentially normal, with no disproportion at the atrial, ventricular, or arterial levels. The defect is detected because of the abnormal arrangement of the arterial trunks, which fail to cross normally.[2]

Colour and pulsed Doppler

In addition to the cross-sectional ultrasonic findings as a tool for detection of transposition, colour flow and pulsed Doppler may be useful in confirming the abnormality. In the normal situation, colour Doppler shows the crossing of the outflow tracts of the ventricles, this adjunct being useful when the quality of imaging is very poor (Fig. 3). Pulsed Doppler may also show a typical pattern. It is known that the pulmonary and aortic valves have a different pattern of ejection. During the second and third trimesters, the acceleration time of the flow of blood through the pulmonary valve is much shorter than that across the aortic valve, reflecting the elevated impedance to ejection that is present for the ventricle that is ejecting to the pulmonary arteries and the arterial duct. This is due to the marked reflection of pressure from the arterial duct, which alters the velocity of the ejection of the blood from the onset of opening of the pulmonary valve, resulting in shortening of the acceleration time. In fetuses with discordant ventriculo-arterial connections, the pulmonary valve is still facing the pulmonary arteries and the arterial duct, and it retains the characteristically short pattern of acceleration (Fig. 4). The waveforms of the inflow through the mitral valve, and outflow through the pulmonary valve, are easily obtained in the setting of discordant ventriculo-arterial connections because the two valves are in fibrous continuity in the roof of the morphologically left ventricle. An inflow/outflow waveform from the left ventricular outflow tract, coupled with an ejection pattern typical of the pulmonary valve, therefore, is diagnostic for the fetus with transposition.

Haemodynamics

The arterial duct. There is now evidence that the flow of blood to the lungs in the human fetus with transposition can be altered by constriction of the arterial duct. This redirects an increasing amount of flow to the lungs, and away from the placenta, with the later result that the left side of the heart can become enlarged, with elevation of the pulmonary vascular resistance. Little data is available regarding the size or Doppler findings in the fetus with transposition, but

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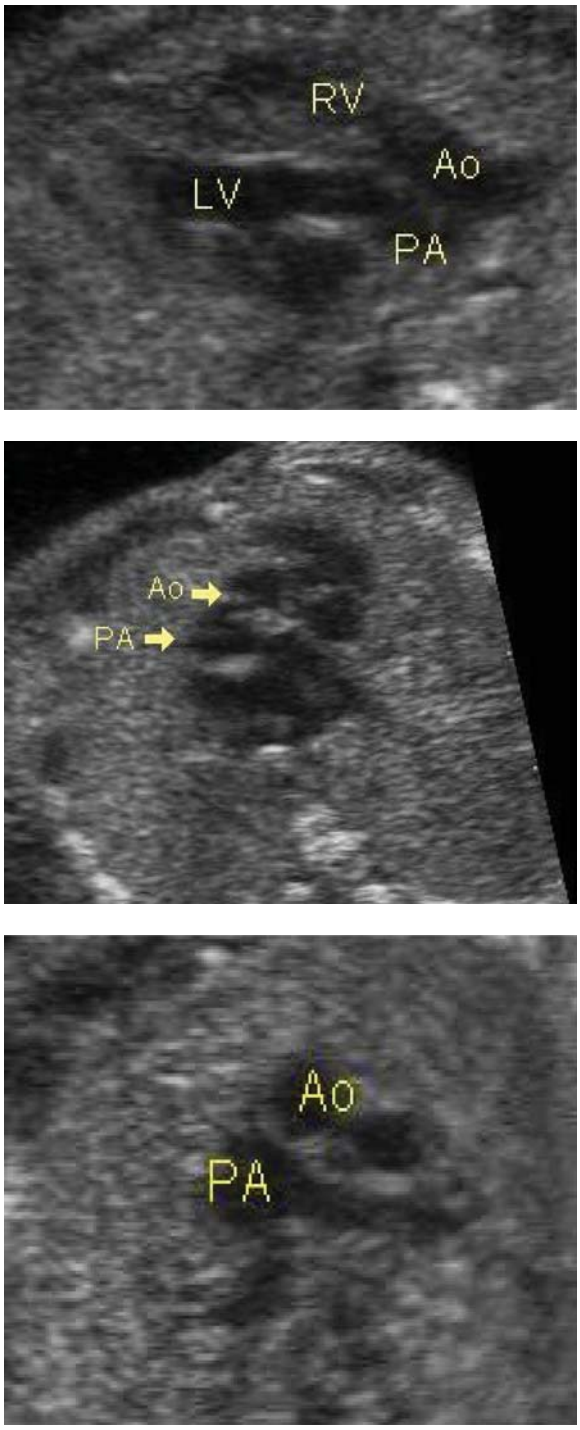

Figure 2.
Echocardiography at 21 weeks in a fetus with transposition. Note the parallel course of the aorta (Ao) arising from the right ventricle (RV), and the pulmonary trunk (PA) arising from the left ventricle (LV) (upper panel). In cross sectional view, the aorta is seen anterior to the pulmonary trunk (middle and lower panels).

in our review of cases, the flow is from the pulmonary trunk to the descending aorta, and the pulsatility index is within the normal range of those fetuses with concordant ventriculo-arterial connections. The known normal values of the pulsatility index, from 1.9 to 3.0, provide a guide when screening the arterial duct in the setting of transposition.[3] Constriction of the duct in fetal life increases the risk for pulmonary hypertension after birth. If identified during fetal life, appropriate precautions should be considered, such as attendance at the delivery, along with the availability of nitric oxide or extracorporeal circulation. In a recent fetus evaluated by our group, we discovered a closed arterial duct, with marked enlargement of the pulmonary arteries. There was bidirectional shunting across the oval foramen. After birth, the neonate had an initial saturation of 40 percent, and continued to demonstrate severe cyanosis. Because of an associated cerebral malformation, further treatment was not indicated.

The oval foramen. In the normal fetal circulation, the oval foramen serves to conduct flow from the hepatic veins and the venous duct to the left atrium. This is also the case in fetuses with transposition, with the size of the foramen being proportional to the amount of flow. From other studies in the fetus, we know that there is an inverse relationship between flow across the foramen and flow of blood to the lungs. Thus, one cause of a small or restrictive oval foramen in the fetus with transposition could be an increase in the flow of blood to the lungs. This detail of the size of the oval foramen size is important in all fetuses with transposition, because it may give information about the likelihood that an emergency balloon atrial septotomy will be needed immediately after birth. The extremely rare finding of an intact oval foramen in such fetuses (Fig. 5) could have severe consequences, and has only rarely been documented in the literature.[4]

Pulmonary vascular resistance. Prior to birth, the pulmonary vascular resistance is determined by the normal pressures of perfusion, and the absence of any downstream obstruction.[5] Anything that will raise the pulmonary arterial pressure in the fetus has the potential to cause extension of smooth muscle into the periphery of the vascular bed, and will result in a propensity for persistent pulmonary hypertension after birth. This could be caused by constriction of the arterial duct, as noted above. This, in turn, could interfere with the normal process of multiplication of vessels, the end result being a decreased number of pulmonary vessels. Assessment of the pulmonary resistance can be attempted using the pulsed Doppler findings in the proximal and distal branches of the pulmonary arteries. After 30 weeks gestation, these baseline values can be tested functionally by administering oxygen to the mother, as described by Rasanen et al.[6] The normal response is a prompt decrease in the pulsatility index, and an increase in the diastolic velocity. An abnormal response, such as no change in

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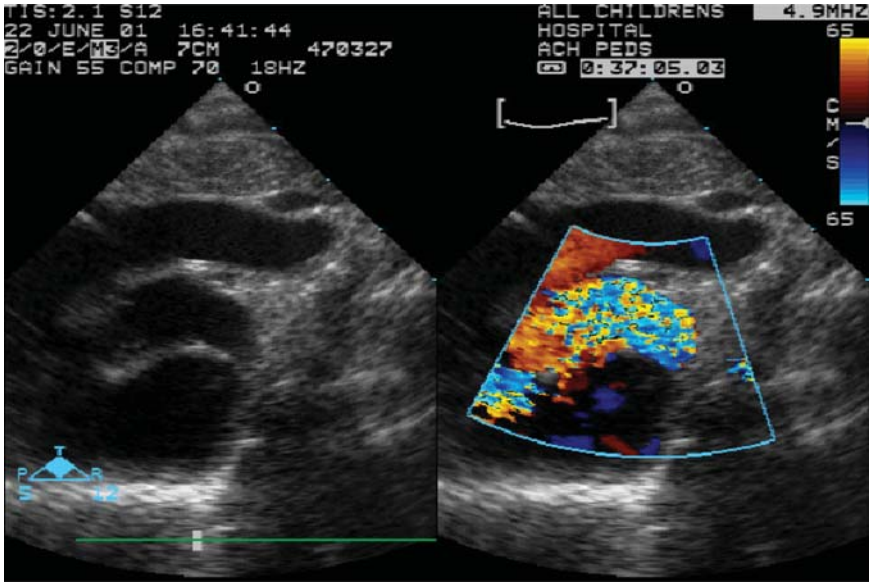

Figure 3.
Postnatal echocardiography showing the parallel course of the great arteries as seen by cross-sectional imaging (left panel) and colour Doppler (right panel).

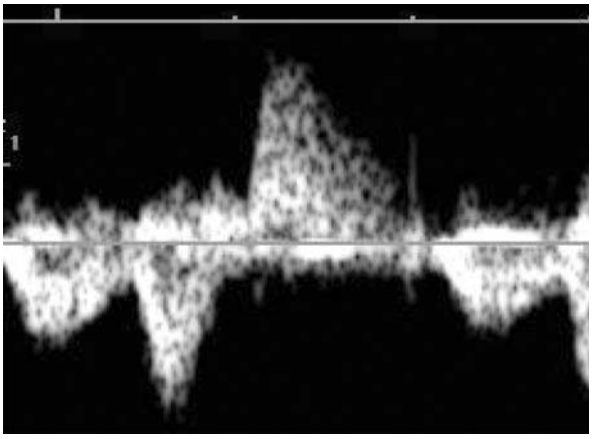

Figure 4.
Pulsed Doppler velocity waveforms at the junction of the inflow and outflow of the left ventricle. Note the short acceleration time of the velocity of ejection, above the zero line, identifying this artery as the pulmonary trunk.

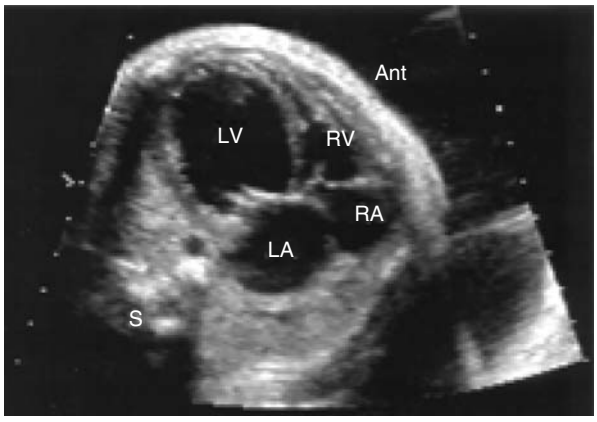

Figure 5.
Premature closure of the oval foramen and arterial duct in a fetus with transposition of the great arteries. Reproduced with permission from Donofrio, Circulation 2002; 105: e65.

the velocities of blood subsequent to challenge with oxygen in the last 3 months of gestation would suggest elevated pulmonary arterial resistance. The flows through the heart are modulated by the pulmonary vascular resistance. If the resistance falls, there is increased left atrial filling from the lungs, and inversely decreasing flow across the oval foramen.

Cerebral perfusion. The saturations of oxygen in the fetal brain, to the best of my knowledge, have never been measured in the human. The levels of oxygen in the blood perfusing the fetal brain, however, can be assessed roughly by measuring the pulsatility index of the waveform of the velocity of the blood. When this is done in fetuses with transposition, the lower pulsatility indexes found are consistent with a lower level of oxygen in the blood.[7] This makes some intuitive sense, because the oxygenated blood from the inferior caval vein is directed preferentially across the oval foramen to the left ventricle, and then to the pulmonary trunk and through the arterial duct to the placenta. The brain, however, is perfused with the blood having lower saturations of oxygen, derived from the superior caval vein via the right ventricle and the aorta. I have already discussed the fact that, in the fetus, the flow of higher oxygenated blood across the oval foramen is inversely proportional to the flow of blood to the lungs. It is possible to speculate, therefore, that administration of oxygen to the fetus with transposition could increase the tension of cerebral oxygen, and have a potentially therapeutic benefit in

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the presence of fetal hypoxaemia, such as is found with severe intrauterine restriction of growth.

Outcomes

The outcomes for fetuses with transposition are difficult to ascertain so far due to limited postnatal follow-up. The best information we have currently is derived from the early mortality of the neonate after the arterial switch procedure. The impact of fetal diagnosis is nowhere more dramatic than in this lesion, which presents shortly after birth with cyanosis. If the affected individual is transferred during fetal life to a cardiac surgical center, the delivery can be orchestrated to achieve the optimal result from preoperative management, intraoperative conduct, and postoperative care. Bonnet et al.[8] have reported significant improvements following such fetal diagnosis in their experience with a large series of patients from France.

Surgical repair. Surgical management of neonatal transposition has now progressed to the point that this is one of the most satisfying surgical results seen by the paediatric cardiologist.[9] There is now a low incidence of residual lesions, such as pulmonary stenosis, and the patients often require no medications. Reviewing the Cardioaccess database for the region of Tampa Bay, we carried out 89 neonatal repairs from 1996 until 2003 using the arterial switch for infants with an intact ventricular septum or a ventricular septal defect. Only one of these patients died within 30 days of the operative procedure. The excellence of such early outcomes makes one realize the increasing importance of the prenatal factors associated with mortality, which historically have led to around one-twentieth of afflicted neonates dying prior to cardiac surgery. Also, these fine early surgical results highlight the growing importance of long-term outcomes, and the need to identify the optimal regime to protect the brain intraoperatively to achieve the best neurodevelopmental result later in life. Late evaluation for coronary arterial stenoses, growth of the aortic root, and function of the neoaortic valve, however, are still lacking.

The aetiology of transposition remains unknown, but there is hope that the genetic cause and, perhaps, a preventative treatment could be achieved. Discordant ventriculo-arterial connections are readily created in a mouse model using retinoic acid.[10] Since that agent is commonly in use by teenagers in the management of acne, it is mandatory to warn female patients of the risks of becoming pregnant while taking this medication. It is also known that there is an association between the genetic deletion of *NKX2.5* and transposition.[11] The association of diabetes and transposition may be linked to this gene.

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