Prenatal Features of Ductus Arteriosus Constriction and Restrictive Foramen Ovale in d-Transposition of the Great Arteries

Yasuki V. Maeno, MD; Steven A. Kamenir, MD; Brian Sinclair, MD; Mary E. van der Velde, MD; Jeffrey F. Smallhorn, MD; Lisa K. Hornberger, MD

Background—Although most neonates with d-transposition of the great arteries (TGA) have an uncomplicated preoperative course, some with a restrictive foramen ovale (FO), ductus arteriosus (DA) constriction, or pulmonary hypertension may be severely hypoxemic and even die shortly after birth. Our goal was to determine whether prenatal echocardiography can identify these high-risk fetuses with TGA.

Methods and Results—We reviewed the prenatal and postnatal echocardiograms and outcomes of 16 fetuses with TGA/intact ventricular septum or small ventricular septal defect. Of the 16 fetuses, 6 prenatally had an abnormal FO (fixed position, flat, and/or redundant septum primum). Five of the 6 had restrictive FO at birth. Five fetuses had DA narrowing at the pulmonary artery end in utero, and 6 had a small DA (diameter \( \text{z score} \leq 2.0 \)). Of 4 fetuses with the most diminutive DA, 2 also had an abnormal appearance of the FO, and both died immediately after birth. One other fetus had persistent pulmonary hypertension. Eight fetuses had abnormal Doppler flow pattern in the DA (continuous high-velocity flow, \( n = 5 \); retrograde diastolic flow, \( n = 7 \)).

Conclusions—Abnormal features of the FO, DA, or both are present in fetuses with TGA at high risk for postnatal hypoxemia. These features may result from the abnormal intrauterine hemodynamics in TGA. A combination of restrictive FO and DA constriction in TGA may be associated with early neonatal death. (Circulation. 1999;99:1209-1214.)

Key Words: heart defects, congenital \( \square \) transposition of great vessels \( \square \) echocardiography

The prenatal diagnosis of transposition of the great arteries (TGA) has been well established.\(^1\)\(^-\)\(^5\) However, even with an antenatal diagnosis, some fetuses with TGA will have profound hypoxemia and may even die in the neonatal period as a result of a restrictive foramen ovale, ductus arteriosus constriction, or pulmonary hypertension.\(^6\)\(^-\)\(^11\) The goal of our study was to determine whether prenatal echocardiography can identify these high-risk fetuses with TGA. In this collaborative study, which combines the experience of 3 prenatal echocardiographic referral centers, we assess the foramen ovale and the ductus arteriosus in 16 fetuses with TGA. We demonstrate the prenatal features of restriction of the foramen ovale and constriction of the ductus arteriosus in affected fetuses with profound hypoxemia at birth and even early neonatal death in 2.

Methods

Patients

Sixteen patients with a prenatal diagnosis of TGA and intact ventricular septum or small ventricular septal defect were identified in 3 prenatal echocardiographic referral centers. All prenatal and initial postnatal echocardiograms were reviewed. Eight fetuses had serial antenatal studies.

Echocardiographic Examinations and Measurements

The fetal echocardiographic examinations were performed with a 3.5-, 5-, or 7.5-MHz transducer on an Acuson 128 or Hewlett-Packard system, or a 7- to 4-MHz curved-array probe on an Advanced Technology Laboratories high-density imaging system. All images were recorded on videotape for offline analysis.

Based on the findings of Wilson et al,\(^12\) the prenatal atrial septal appearance was described as redundant if the aneurysmal septum primum bulged \( \geq 50\% \) of the way across the left atrial free wall; flat, if the angle between the septum primum and the rest of the atrial septum was \( < 30\degree \); or fixed, if the septum primum did not have the typical swinging motion during the cardiac cycle.

The diameter of the ductus arteriosus was measured as described by Tan et al,\(^13\) and the measurements were converted to \( z \) scores by use of data from normal fetuses. When there was an anatomic narrowing within the vessel, typically at the pulmonary end, the diameter was measured at the narrowest portion. Spectral Doppler and color flow mapping were used to record flow in the ductus...
arteriosus, which was considered antegrade if directed from pulmonary artery to aorta and retrograde if the opposite. By Doppler, laminar antegrade flow throughout systole and part or all of diastole was considered to be normal ductus arteriosus flow.

Postnatal Course
Postnatal history, arterial blood gas data, postnatal echocardiographic reports, and autopsy reports were collected from each center, and the postnatal course was assessed. A restrictive foramen ovale after birth was confirmed by postnatal echocardiography or at autopsy, both in conjunction with a consistent clinical history defined as severe hypoxemia (PaO2 < 25) and acidosis (pH < 7.30) after birth, necessitating urgent balloon atrial septostomy. The foramen ovale was considered restrictive by echocardiography if there was a diminutive interatrial communication (< 5 mm), with flow acceleration by color Doppler suggesting a gradient.

Calculations and Statistical Analysis
The mean z scores for ductus arteriosus diameter in all 16 fetuses were tested against the normal mean of 0 with the use of a single-group t test.

Results
Among the 16 fetuses with TGA and intact ventricular septum or with a small ventricular septal defect, 5 had a restrictive foramen ovale postnatally, and 2 of these 5 also had a constricted ductus arteriosus and died shortly after birth. An additional patient had a complicated postnatal course associated with persistent pulmonary hypertension. The other 9 patients were in stable condition after birth. The observations made in the last prenatal echocardiograms performed before delivery at a mean age of 30.5 weeks (range, 24 to 40 weeks) are summarized in the Table.

<table>
<thead>
<tr>
<th>Patient</th>
<th>GA, wk</th>
<th>Septum Primum Appearance</th>
<th>Anatomic Narrowing</th>
<th>z score</th>
<th>Doppler Findings</th>
<th>Postnatal Course</th>
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<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>Fixed; bulging from RA to LA</td>
<td>Diffuse, most at PA end</td>
<td>-6.3</td>
<td>Continuous high-velocity turbulent</td>
<td>Early demise</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Fixed, flat; small</td>
<td>Mild at PA end</td>
<td>-2.9</td>
<td>Bidirectional; retrograde in diastole</td>
<td>Early demise</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Redundant, fixed, bulging from RA to LA</td>
<td>No</td>
<td>-1.3</td>
<td>Intermittently bidirectional</td>
<td>Restrictive FO</td>
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<tr>
<td>4</td>
<td>32</td>
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<td>No</td>
<td>-0.1</td>
<td>Normal</td>
<td>Restrictive FO</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>Flat, thick</td>
<td>No</td>
<td>-1.0</td>
<td>Normal</td>
<td>Restrictive FO</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
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<td>Diffuse; most at PA end</td>
<td>-4.0</td>
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<td>PPHN</td>
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<td>7</td>
<td>40</td>
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<td>No</td>
<td>-2.5</td>
<td>Bidirectional; retrograde in diastole</td>
<td>RV dysfunction</td>
</tr>
<tr>
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<td>-1.2</td>
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<td>Uneventful</td>
</tr>
<tr>
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<td>Mild at PA end</td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>No</td>
<td>-1.2</td>
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<td>Uneventful</td>
</tr>
<tr>
<td>13</td>
<td>28</td>
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<td>Uneventful</td>
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<tr>
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</tr>
<tr>
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<td>No</td>
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<tr>
<td>16</td>
<td>36</td>
<td>Normal</td>
<td>No</td>
<td>-1.3</td>
<td>Normal</td>
<td>Uneventful</td>
</tr>
</tbody>
</table>

GA indicates gestational age; DA, ductus arteriosus; RA, right atrium; LA, left atrium; PA, pulmonary artery; FO, foramen ovale; PPHN, persistent pulmonary hypertension in newborn; and RV, right ventricle.

Foramen Ovale
Prenatal echocardiography demonstrated an abnormal appearance of the foramen ovale in 6 of the 16 fetuses with TGA (38%) (Figures 1 and 2). Five of the 6 had postnatal evidence of restrictive foramen ovale. In 2 with serial antenatal studies, the septum primum was more mobile in the earlier studies performed at 27 weeks (patient 2) and 19 weeks (patient 3) than in the studies performed later in gestation, at 32 weeks and 28 weeks, respectively. None of the fetuses with a normal appearance of the foramen ovale in utero had evidence of a restrictive foramen ovale after birth.

Two of the 6 patients (patients 1 and 2) with autopsy confirmation of a restrictive foramen ovale and a constricted...
ductus arteriosus died shortly after birth. At 35 weeks of gestation, patient 1 had an atrial septum that bulged tensely from the right atrium toward the left atrium in a fixed position without the normal phasic movement and had only a small gap (Figure 3). In patient 2, at 32 weeks of gestation, the atrial septum was thick and flat without normal movement, and there was only a small flow orifice through the septum primum. Both fetuses had normal function of the left ventricle and no pulmonary or mitral insufficiency. Their conditions immediately after delivery were good, with good muscle tone and a strong cry. Within minutes, however, both developed profound hypoxemia and poor cardiac output unresponsive to aggressive resuscitation, which included immediate institution of prostaglandin therapy in both and an unsuccessful attempt at balloon atrial septostomy from both the umbilical and femoral veins in patient 2. Autopsy in both neonates revealed a nearly closed ductus arteriosus and closed foramen ovale. Patient 2 also had an interrupted inferior vena cava with azygous continuation, which was the cause of the failed balloon septostomy from both the umbilical and femoral veins in patient 2. The lung pathology in patient 1 revealed intimal proliferation (Heath-Edwards grade 2 changes) in the pulmonary artery.

Ductus Arteriosus

For all 16 fetuses with TGA, the mean z score of the ductus arteriosus diameter was significantly below the published normal data (P<0.0001), ranging from −0.1 to −6.3. This was significantly below published normal data (P<0.0001). Fifth and 95th percentile CIs for ductus arteriosus diameters measured in normal fetuses are shown as dotted lines. ○, Ductus arteriosus with anatomic narrowing at pulmonary artery end; ●, ductus arteriosus without focal narrowing. *Patients with early death; †patients with persistent pulmonary hypertension after birth.

Ductus Arteriosus

For all 16 fetuses with TGA, the mean z score of the ductus arteriosus diameter was significantly below the published normal data (P<0.0001), ranging from −0.1 to −6.3, with a mean of −1.8 (Figure 4). None had maternal indomethacin administration.

In 5 of the 16 fetuses (31%), the ductus arteriosus appeared anatomically constricted or narrowed at the pulmonary artery end (Figure 5). In patient 2, the ductus arteriosus appeared narrowed in an earlier study performed at 27 weeks. However, in patients 8 and 9, the ductus arteriosus had a normal appearance at 20 and 22 weeks, respectively, but appeared constricted later in gestation. Ductal constriction was associated with a restrictive foramen ovale in 2 fetuses with early neonatal death (patients 1 and 2) (see above). Persistent pulmonary hypertension developed postnataally in 1 patient with a severely narrowed ductus arteriosus in utero, which remained patent at birth (patient 6). The last 2 cases (patients 8 and 9) had an uneventful postnatal course.

Eight of the 16 fetuses (50%) had an abnormal Doppler flow pattern in the ductus arteriosus. Continuous, high-velocity antegrade flow (Figure 3) was observed in 1 fetus (patient 1). The other 7 had bidirectional flow in the ductus arteriosus (Figure 6). In 2, this pattern was observed throughout the examination, and in 4 it was intermittent, with a normal pattern observed at other times (Table). Bidirectional flow was identified as early as 27 weeks in patient 2, 24 weeks in patient 7 (Figure 6), and 19 weeks in patient 13. However, in 2 others with serial antenatal studies (patients 3 and 11), there was antegrade flow in the ductus arteriosus throughout the cardiac cycle in the earlier examinations (at 28 and 23 weeks, respectively). Three fetuses with bidirectional ductal flow had prenatal narrowing of the ductus arteriosus and/or restrictive foramen ovale (patients 2, 3, and 6).
Discussion

A primary goal of the prenatal diagnosis of congenital heart disease is to improve the perinatal outcome of neonates affected with critical congenital heart disease. To achieve this goal, affected fetuses at high risk of neonatal morbidity and mortality need to be identified to permit planning for appropriate perinatal management. Our study has shown that fetuses with TGA and a restrictive foramen ovale with or without constriction of the ductus arteriosus can be identified prenatally and are most obvious later in gestation. These antenatal features are predictive of significant neonatal morbidity and mortality.

Prediction of Early Neonatal Death in TGA

We found the combination of foramen ovale restriction and ductus arteriosus constriction to be fatal in 2 patients after discontinuation of the placental circulation in TGA. With neither site available for mixing, the systemic and pulmonary circulations were entirely in parallel, resulting in severe hypoxemia. Retrospectively, the prenatal echocardiograms had demonstrated abnormal features of both structures.

The incidence of this lethal combination remains unclear. Our study was probably biased because the experience with the 2 cases motivated our retrospective review of fetal TGA. Both a multi-institutional prospective study and an institutional retrospective study at The Hospital for Sick Children, Toronto, suggested that as many as 4% of neonates with TGA die before repair.6,11 One problem with ascertaining the number of infants with TGA and the lethal combination of restrictive foramen ovale and ductal constriction is that the neonate may die before a diagnosis of TGA is made and referral to a tertiary care center can be arranged. In fact, a further review of autopsy records at The Hospital for Sick Children in the past 10 years identified 2 more cases of very early death after delivery at outside hospitals with TGA, and autopsy confirmed the presence of ductus arteriosus and foramen ovale restriction. Because the surgical mortality for the arterial switch operation is as low as 2% in many institutions and <5% in most,16 the preoperative mortality is an important issue in the management and outcome of infants with TGA.

Nevertheless, the management of infants with this lethal condition is still problematic. Balloon atrial septostomy before interruption of the placental circulation may improve the outcome of these infants.

Prenatal Nature of the Foramen Ovale in TGA

Our study demonstrated that in the fetus or prenatally, TGA is frequently associated with an abnormal foramen ovale with either an abnormal septum primum angle, abnormal motility of the septum primum, or an aneurysmal septum primum. The fixed position and the angle of <30° may represent restrictive foramen ovale, with a continuous pressure difference between the left and right atria.17 Two explanations have been proposed for a restrictive foramen ovale in utero: primary restriction and secondary restriction, with the latter being the result of hemodynamic alterations (eg, elevated left atrial pressure).17 For the fetuses with TGA, we suspect that the latter mechanism may explain the prenatal restriction. Three of the 4 fetuses with echocardiographic features of foramen ovale restriction had abnormal flow in the ductus arteriosus, and the other had large pulmonary veins with a prominent color flow signal. These findings are consistent with increased pulmonary blood flow, which might increase left atrial pressure and lead to foramen restriction as normally occurs after birth. In support of this, Rizzo et al18 found an abnormal pulmonary venous flow pattern in a fetus with TGA consistent with increased left atrial pressure.
cava to the superior vena cava, more highly oxygenated blood from the umbilical vein, typically connected to the hepatic vein, should cross the foramen ovale as usual. We speculate that the increased oxygen content in the pulmonary artery may lead to ductal constriction and decreased pulmonary vascular resistance. In the fetal lamb, Konduri et al. found that a 13% increase in oxygen saturation increased pulmonary blood flow 3-fold and increased the left atrial pressure from 4 to 8 mm Hg. This lower pulmonary vascular resistance may explain the retrograde diastolic flow in the ductus arteriosus in many of the fetuses with TGA even as early as 19 weeks of gestation.

The smaller diameter of the ductus arteriosus that we observed in fetuses with TGA may also be explained by the abnormal intravascular hemodynamics. In the normal fetal circulation, 30% to 40% of the total cardiac output passes through the ductus arteriosus. In fetuses with TGA, however, the amount of blood crossing the ductus arteriosus may be the same as the amount that passes through the foramen ovale (Figure 7) in the absence of significant retrograde diastolic ductal flow. This amount would represent ≈20% of the total cardiac output, according to observations in normal fetuses. Both an elevated left atrial pressure and prenatal restriction of the foramen ovale probably contribute to a further reduction in ductus arteriosus flow later in gestation. If the ductal diameter is a function of flow volume, as is thought to be the case for other vascular structures, one would expect the diameter to be smaller than in the normal fetus, even in the absence of active constriction.

Observations in human and animal fetuses with normal cardiovascular anatomy have shown that prenatal constriction of the ductus arteriosus produces anatomic changes in small pulmonary arteries, similar to neonates with idiopathic persistent pulmonary hypertension. This may be related to an increase in pulmonary blood flow and pressure. One could speculate that the common occurrence of persistent pulmonary hypertension and early progression of pulmonary vascular disease in the infants with TGA and intact ventricular septum may be related to the prenatal increase in pulmonary blood flow and prenatal alteration of the pulmonary vascular bed.7–9,25–27 In our study, in fact, patient 1, with prenatal constriction of the ductus arteriosus, had such pulmonary vascular changes as previously described in TGA. Furthermore, on review of the autopsy records at the Hospital for Sick Children, in the past 10 years, we found that 3 of 7 newborns with TGA/intact ventricular septum and preoperative death had established pulmonary vascular changes. All 3 had refractory hypoxemia and acidosis after birth despite balloon atrial septostomy in 2, with death occurring within 5 days of life. An early arterial switch operation even before complete stabilization, with postoperative use of extracorporeal membrane oxygenation, if necessary, may improve the mortality of neonates with TGA and significant pulmonary hypertension.

**Limitations**

Because of the retrospective nature of our study, several of the antenatal cases were examined only once early in gestation, hence it is difficult to extrapolate the status of the ductus arteriosus and to lungs and subsequently returns to left heart. However, less oxygenated blood from pulmonary veins reduces oxygen saturation in left ventricle. B, In fetuses with TGA, this more highly oxygenated blood in left ventricle is pumped to ductus arteriosus and to lungs and subsequently returns to left heart. Of note, amount of blood through ductus arteriosus must be same as amount that passes through foramen ovale. Abbreviations as in previous figures.

![Diagram of hemodynamics](Image)

One other mechanism of foramen restriction, as suggested by 1 of our 5 cases, was the presence of a redundant septum primum that nearly occluded a large foramen ovale orifice after birth. Although a redundant septum primum may be found in as many as 6% of normal fetuses and was found in our series in 1 fetus with TGA but no postnatal restriction, its presence should alert the fetal echocardiographer to the possibility of foramen restriction at birth. Therefore, our study provides evidence for at least 2 potential mechanisms of foramen ovale restriction in TGA: (1) elevated left atrial pressure with reduced foramen flow orifice in utero and altered atrial septal configuration and (2) a redundant septum primum occluding the foramen orifice after birth.

**Prenatal Nature of the Ductus Arteriosus and Pulmonary Vascular Bed in TGA**

The common occurrence of both an abnormal foramen ovale and abnormal structure and flow through the ductus arteriosus in fetal TGA may be explained by the pathophysiology of TGA (Figure 7). In the normal fetal circulation, more highly oxygenated blood from the placenta crosses foramen ovale to left atrium and left ventricle. However, if the ductal diameter is a function of flow volume, one would expect the diameter to be smaller than in the normal fetus, even in the absence of active constriction.
arteriosus and the foramen ovale later in gestation. From these cases with serial studies, however, it would appear that the abnormalities of the foramen ovale and ductus arteriosus become more obvious later in gestation.

Conclusions
Fetuses with TGA and functionally intact ventricular septum often have abnormal features of the foramen ovale and the ductus arteriosus, which may be related to the pathophysiology of TGA in utero. A fixed septum primum with little mobility or a redundant septum primum prenatally may suggest the potential for restriction of the foramen ovale at birth. A restrictive foramen ovale in combination with ductal constriction, which can also be identified prenatally, may be associated with very early neonatal death despite aggressive resuscitation. We recommend that follow-up fetal echocardiography be performed near term in fetuses with TGA to reassess the ductus arteriosus and the foramen ovale before delivery. Prenatal detection of restriction of the foramen ovale with or without constriction of the ductus arteriosus with better-planned perinatal management should improve the neonatal outcome of infants prenatally diagnosed with TGA.

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References
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