Sensitivity and Specificity of Prenatal Features of Physiological Shunts to Predict Neonatal Clinical Status in Transposition of the Great Arteries

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Background—Although prenatal diagnosis of transposition of the great arteries (TGA) reduces neonatal mortality, the preoperative course can be complicated in infants with a restrictive foramen ovale (FO) or a ductus arteriosus (DA) constriction. We sought to determine the specificity and sensitivity of prenatal features of physiological shunts in predicting postnatal clinical status in prenatally diagnosed TGA in babies delivered in a tertiary care center providing all facilities for neonatal urgent care.

Methods and Results—The outcomes of 130 fetuses with TGA were reviewed over a period of 5.5 years. Restriction of the FO and/or constriction of the DA could be analyzed in 119/130 fetuses at 36.2 weeks of gestation. Twenty-four out of 119 had at least 1 abnormal shunt (23 FO, 5 DA, and 4 both). Thirteen of 130 neonates had profound hypoxemia (PaO₂ < 25 mm Hg) and metabolic acidosis (pH < 7.15) in the first 30 minutes and required immediate balloon atrioseptostomy. Two who had abnormal FO and DA died despite aggressive resuscitation. The specificity and sensitivity of the fetal echo in predicting neonatal emergency were 84% and 54%, respectively. The specificity and sensitivity of a combination of restrictive FO and DA constriction were 100% and 31%, respectively.

Conclusions—Restriction of the FO and/or of the DA has a high specificity to predict the need for emergency neonatal care in fetuses with TGA, but the sensitivity is too low to detect all high-risk fetuses. Exceptional procedures should be considered for fetuses that have a combination of restrictive FO and DA constriction. (Circulation. 2004;110:1743-1746.)

Key Words: heart defects, congenital • transposition of great vessels • echocardiography

Prenatal detection of transposition of the great arteries (TGA) has been well established.1–4 Of those neonates admitted with TGA, mortality is estimated around 4% and is mostly due to inadequate interatrial mixing despite prostaglandin E1 infusion.5 We have previously reported that prenatal diagnosis of TGA reduced neonatal mortality and morbidity.1 However, early demise of neonates with TGA has been reported even after a prenatal diagnosis, suggesting that there was no site available for mixing immediately after birth.3,5–8 Indeed, antenatal restriction of the foramen ovale and/or the ductus arteriosus were found predictive of significant neonatal morbidity and mortality.9 Because the surgical mortality for the arterial switch operation is as low as 2% in many institutions,10–11 the preoperative mortality is a major issue in the management and outcome of infants with TGA. Here, we reviewed the prenatal features of the foramen ovale and of the ductus arteriosus in all our cases of prenatally diagnosed TGA to address the relation between prenatal echo features and need for urgent intervention.

Methods

Population

One hundred thirty consecutive patients with a prenatal diagnosis of TGA were identified over a period of 5.5 years (November 1, 1997 to February 28, 2003). TGA was suspected during routine prenatal ultrasonographic examination and confirmed in all cases by 2 investigators (L.F. and J.L.B.). One hundred eight had TGA with intact ventricular septum or small ventricular septal defect, 17 had TGA with ventricular septal defect, and 5 TGA with ventricular septal defect and potential coarctation of the aorta. Fetuses who were not potential arterial switch candidates were excluded, ie, those with TGA with ventricular septal defect and pulmonary stenosis, TGA with multiple ventricular septal defects, and malpositions of the great arteries with ventricular septal defects. Fetuses with extra-cardiac anomalies were also excluded (n = 1; spina bifida leading to termination of pregnancy). Fetal karyotype was normal in all cases but one (1 case of balanced translocation [46,XY,t(9q;20q)] inherited from the father).

Echocardiographic Examinations and Measurements

The fetal echocardiographic examinations were performed with various probes on an Acuson 128XP (1997 to 1999) or Acuson...
Sequoia (1999 to 2003) (Acuson). All images were recorded on videotape for off-line analysis. Prenatal features of the foramen ovale and of the ductus arteriosus were reviewed retrospectively for the period November 1997 and November 1999 and described prospectively during the second period of the study. According to Maeno et al.\(^7\) and Wilson et al.,\(^{14}\) the foramen ovale was considered at risk of postnatal early restriction if the annulval septum primum bulged >50% of the way across to the left atrial free wall; if the angle between the septum primum and the rest of the atrial septum was <30°; or if the septum did not have the typical swinging motion during the cardiac cycle. For the ductus arteriosus, the diameter was measured at the narrowest portion, typically at the pulmonary end. The Doppler flow pattern was considered abnormal if it was either antegrade and continuous or bidirectional.

**Immediate Neonatal Management**

All fetuses were delivered in our institution. For each patient, a senior pediatric cardiologist and a senior pediatric intensivist were in charge of immediate evaluation and management. Echocardiography and catheterization equipment were available in the maternity ward, as was prostaglandin E1. The catheterization laboratory was left free before delivery to allow early balloon atrioseptostomy (BAS).

Clinical status at birth was evaluated by Apgar score, transcutaneous oxygen saturation at 10 minutes, need for mechanical ventilation, and acidosis (pH <7.15). The physicians in charge of the patient made the decision to perform BAS, regardless of the prenatal findings. It was based on the infant clinical condition and neonatal restriction of the foramen ovale.

Neonates were considered to be in “critical condition” at birth if they had a PaO\(_2\) level <25 mm Hg and a pH <7.15. All patients in this group underwent BAS within the first 30 minutes after delivery. Patients were considered to be in “stable condition” if they did not fulfill the above criteria. In this group, BAS was performed any time after delivery according to the decision of the pediatric cardiologist.

Prostaglandin E1 infusion was started when mixing was considered insufficient in patients with isolated TGA or TGA with ventricular septal defect, and in all patients with TGA and coarctation of the aorta. The arterial switch was performed in our institution in the majority of the patients (n=119) by one single surgeon (P.R.V.); the remaining 11 patients were operated on in 2 other surgical units.

**Statistical Analysis**

Summary statistics are presented as mean±SD and range. Percentages are presented as %±95% confidence interval (CI). Comparisons of data were made by unpaired Student’s t test or the Mann-Whitney test as appropriate for interval variables. \(\chi^2\) analysis or Fisher’s exact test was used for categorical variables. Statistical significance was assessed by use of a cutoff value of \(P<0.05\).

**Results**

All fetuses were alive at delivery. The mean gestational age at birth was 39±0.2 weeks (range: 34 to 41 weeks). The mean birth-weight was 3159±67 g (range: 2075 to 4270 g). Two patients with TGA and intact ventricular septum died shortly after birth despite aggressive resuscitation, BAS, and prostaglandin E1 infusion (1.5%; 95% CI, 0% to 3%). The remaining 128 underwent arterial switch operation and repair of additional anomalies. Two patients died postoperatively of myocardial ischemia (1.6%; 95% CI, 0% to 3%). The overall mortality of infants with prenatal diagnosis of TGA was 3% (95% CI, 0% to 6%).

**Prenatal Findings at Late Echocardiographic Control**

One hundred nineteen late fetal echos performed at 36±2.7 weeks of gestation were available for review (Table 1). The

| Table 1: Abnormal Prenatal Shunts and Neonatal Condition |
|---------------------------------|-----------------|-----------------|-----------------|
| Abnormal (N=24)                | Normal (N=95)   |
| FO and DA                       | FO or DA*       | Normal          |
| Critical condition (n=7)         | 4               | 20 (19 FO; 1 DA) |
| Stable condition (n=17)          | 0               | 3 (2 FO; 1 DA)  |
| F0 indicates foramen ovale; DA, ductus arteriosus. |

\*This subgroup included 1 fetus in whom the FO was restrictive but the DA could not be analyzed.

11 cases that could not be adequately reviewed included 6 cases of isolated TGA and 5 cases of TGA with ventricular septal defect.

An abnormal prenatal feature of the foramen ovale and/or the ductus arteriosus at 34 to 38 weeks was noted in 24/119 cases (20.2%, 95% CI, 12.8 to 27.5%). Twenty-three of 119 fetuses (19.3%; mean gestational age 36±3 weeks gestation) had an abnormal appearance of the foramen ovale. The ductus arteriosus appearance could be assessed in 22/23 of them. In 5/104 fetuses (4.8%), the ductus arteriosus appeared constricted at the pulmonary artery end (diameter <3 mm; mean gestational age, 35±3 weeks gestation). Four of these 5 had a continuous accelerated pulmonary artery-to-aorta flow through the ductus arteriosus with associated restrictive foramen ovale. The remaining fetus had a constricted ductus arteriosus with a bidirectional turbulent flow without abnormal appearance of the foramen ovale. Finally, 95/119 fetuses had normal prenatal features of the foramen ovale and of the ductus arteriosus.

**Relation Between Prenatal Findings of Risk of Early Demise and Neonatal Management and Outcome**

In the group of 24 patients with either potential restriction foramen ovale and/or the ductus arteriosus, 7/24 were in critical condition. In the 95 neonates in whom prenatal shunts were considered normal at last fetal echo, only 6/95 were in critical condition \((P<0.01)\). None of the 11 neonates whose late fetal echo was not available were in critical condition. The specificity of these features to indicate neonatal critical condition was 84%, but the sensitivity was low (54%). The positive predictive value was 29% and the negative predictive value was 94%.

The 5 patients who had a restrictive ductus arteriosus were in critical condition at birth. The 2 neonatal deaths that occurred before surgery were observed in patients with both abnormal physiological shunts at 36 weeks’ gestation. For the first patient, Apgar scores were 3 and 1 at 1 and 5 minutes, respectively. Immediately after birth, the child exhibited general profound cyanosis associated with bradycardia (50 bpm). Blood gas analysis at 18 minutes of life showed major acidosis (pH=6.8, base excess = −16 mmol/L). Despite resuscitation, BAS, and prostaglandin E1 infusion, she died after 3 days with severe cerebral damages. In the second case, the hemodynamic condition rapidly deteriorated after birth. The first attempt of BAS failed to achieve a sufficient atrial septotomy, and the hemodynamic conditions worsened de-
spite intravenous infusion of prostaglandin E1 and mechanical ventilation. A second attempt for BAS performed at 4 hours of life successfully achieved significant interatrial mixing. This child died at 3 days of life after neurological deterioration with iterative convulsions. The specificity of 2 abnormal shunts in predicting neonatal emergency was 100%, but the sensitivity remained at 31%. The positive predictive value of 2 abnormal prenatal shunts for critical condition was 100%, and the negative predictive value was 92%.

In the 128 neonates who survived, we did not observe any severe acidosis, multiorgan failure, or neurological complications during the preoperative period.

Discussion

Early and late results of the arterial switch operation have dramatically improved in the past 20 years. A recently reported series shows a surgical mortality as low as 2% to 5%.10–13 The overall mortality rate of neonates with TGA is the combination of pre- and postoperative deaths. To reduce the overall mortality of TGA, strategies to save patients at risk of death before surgery have to be developed. Indeed, there is now a significant number of reported cases of patients with TGA who presented either at autopsy without prior diagnosis or of children who were moribund on admission and who died within a few hours of birth.5–9,15,16 We showed that prenatal diagnosis reduced the mortality rate of patients with TGA.3 However, Soongswang et al5 and Maeno et al9 reported 3 cases of prenatally diagnosed TGA in patients who died immediately after birth. In addition, fetal surveillance with assessment of the foramen ovale and the ductus arteriosus before delivery could help to detect patients at risk of early death. Consequently, it has been suggested that prenatal transfer in a tertiary care center and better-planned perinatal management should improve the neonatal outcome of infants prenatally diagnosed with TGA. After our initial report, we modified our perinatal management of infants with prenatally diagnosed TGA as described in the Methods section.

In this series, only 10% of the patients required urgent management. This percentage is higher than the reported preoperative mortality of 4%. As the facilities of our institution allowed us to perform a BAS in an emergency, it is possible that some of these patients could have been stabilized over a few hours with prostaglandin E1 infusion, mechanical ventilation, and volume expansion. However, 2 patients of the present series died immediately after birth despite aggressive resuscitation, confirming that there is a subset of patients with TGA and intact ventricular septum with tenuous intercirculatory mixing in utero. These 2 patients had a restrictive foramen ovale and a constricted ductus arteriosus. In addition, the 2 other patients who exhibited the same prenatal echo features required immediate aggressive management. This suggests that this subgroup of patients may be helped only by immediate BAS before discontinuation of the placental circulation or immediate cannulation for mechanical cardiopulmonary support.17 Indeed, the positive predictive value of at least 1 abnormal prenatal shunt was 30%, but it became 100% if we considered only the fetuses who had restrictive foramen ovale and constricted ductus arteriosus. We are aware that most institutions cannot easily create a delivery suite for all prenatally diagnosed infants, but our results show that in this particular situation, exceptional delivery procedure and neonatal management should be considered.

Fetal appearance of the physiological shunts is helpful in predicting which infants will indeed require emergent intervention, but its sensitivity is not sufficient to detect all fetuses at risk. This low sensitivity might be explained by the limitations of our study. Fortunately, none of the 11 neonates who could not be fully reviewed prenatally were in critical condition. The last fetal echocardiography was performed at 36 ± 2.7 weeks of gestation and the appearance of the shunts could have changed during the last weeks of gestation. To improve the sensitivity of these abnormal features, we will attempt to examine the foramen ovale and the ductus arteriosus the day before delivery, as we have a policy of planned delivery. Finally, the fetal echocardiographic criteria that we used for neonatal restriction of the foramen ovale or the ductus arteriosus might not be sufficiently stringent. Sequential measures of the size of the foramen ovale during the third trimester are currently performed in our new cases of fetal TGA to attempt to increase sensitivity.

Conclusions

Prenatal diagnosis of TGA reduces neonatal mortality but does not eliminate the risk of death. Assessment of the restriction of the foramen ovale and of the ductus arteriosus shortly before delivery detects a subgroup of fetuses that will need early BAS. A combination of restrictive foramen ovale and ductus arteriosus constriction is highly predictive of early neonatal distress. However, the current sensitivity of these echocardiographic parameters is not satisfactory, and efforts have to be made to find additional echocardiographic parameters that will refine criteria that determine the group at risk of neonatal death.

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