Early Intertwin Differences in Myocardial Performance During the Twin-to-Twin Transfusion Syndrome

M.J. Raboisson, MD; J.C. Fouron, MD; J. Lamoureux, MSc; L. Leduc, MD; A. Grignon, MD; F. Proulx, RT; S. Gamache, RT

**Background**—In the twin-to-twin transfusion syndrome (TTTS), pressure rather than volume overload is increasingly considered as a key factor in the pathogenesis of the cardiomyopathy of the recipient twin. If this is the case, cardiac dysfunction should be among the first signs observed with TTTS. The objective of this study was to determine whether intertwin differences in myocardial function are modified early in the course of TTTS and whether they can help to differentiate this condition from intrauterine growth restriction (IUGR).

**Methods and Results**—Eight variables were analyzed on the first fetal echocardiography on 21 pairs of twins with TTTS and 11 with IUGR. No difference was found between the 2 groups for the cardiothoracic ratio, pulsatility indices in the umbilical and middle cerebral arteries, and peak velocity of the middle cerebral artery. Significant difference was found for ventricular septal thickness, but with no association with the conditions under study. With TTTS, left ventricular shortening fraction was consistently greater in the donor twins, and myocardial performance indices (MPIs) were elevated in the recipient twins. This increase in MPI was caused by a lengthening of the isovolumic periods compared with those of the donor twin: left ventricular and right ventricular isovolumic periods 0.105±0.047 and 0.097±0.026 seconds, respectively, for the recipient twins versus 0.056±0.46 and 0.065±0.03 seconds, respectively, for the donor twins (P<0.001). These changes in the isovolumic periods were mainly due to significant prolongation of isovolumic relaxation times. A change in left ventricular MPI ≥0.09 combined with a change in right ventricular MPI ≥0.05 would identify a TTTS with a sensitivity of 75% and a false-positive rate of 9%.

**Conclusions**—The observed diastolic function impairment goes along with the pressure-overload pathogenic concept proposed in TTTS. Assessment of intertwin difference in MPI is a valuable tool for early differential diagnosis between TTTS and isolated IUGR. (Circulation. 2004;110:3043-3048.)

**Key Words:** fetofetal transfusion ■ myocardium ■ cardiomyopathy ■ diastole

Twin-to-twin transfusion syndrome (TTTS) is a severe complication that occurs in 10% to 15% of monochorionic multiple pregnancies. Both fetuses are at risk of death and of short- and long-term cardiocirculatory complications, which have been reported to decrease when early treatment is provided. Unfortunately, early in the process, TTTS is difficult to differentiate from intrauterine growth restriction (IUGR) due to placental circulatory insufficiency; at this stage, discordances in fetal growth and amniotic fluid volumes are first signs shared by both conditions. During the course of TTTS, hypertrophic cardiomyopathy is observed in the recipient twin; its pathogenesis remains unclear. Pressure rather than volume overload is increasingly considered as a key factor given the reports of elevated concentration of endothelin in the recipient twin and upregulation of the renin-angiotensin system in the donor twin. If this were the case, subclinical evidence of cardiac dysfunction could be among the first signs observed with TTTS, whereas in IUGR, no difference in myocardial performance should be expected, at least early in the process when impairment in fetal oxygenation is still well compensated. A previous report has also demonstrated an absence of intertwin difference in cardiac structure or function of uncomplicated monochorionic diamniotic twin pregnancies. The objectives of this study were 2-fold: first, to test the pressure-overload hypothesis and look for early intertwin differences in ultrasonographic variables assessing myocardial function in fetuses with TTTS; second, if such differences were present, to evaluate the clinical significance of these differences as markers of TTTS as opposed to IUGR.

**Methods**

All available Doppler echographic examinations of monochorionic/diamniotic twin pregnancies recorded in our unit from September 1998 to September 2002 were systematically reviewed. The present report concerns only data collected during the first examination. The patients were divided into 2 groups depending on whether the final
diagnosis was TTTS (group I) or IUGR (group II), based on the evolution of the pregnancy and perinatal data.

Monochorionicity was identified by the presence of twins of the same sex with a single placenta and echographic evidence of a thin (<2 mm) amniotic membrane. This was confirmed after birth by pathological examination of the placenta. The diagnosis of TTTS was first suspected because of difference in fetal growth (ratio between the 2 abdominal circumferences ≥0.93), the development of an oligopolyhydramnios sequence (deepest pool ≥8 cm for the larger amniotic sac and <1 cm for the smaller one), and progressive appearance of cardiomyopathy in the recipient twin. Placental insufficiency was considered when the dimensions of the smaller fetus were below the 10th percentile, with a pulsatility index of the umbilical artery (PIUA) rising above the 95th percentile during the course of the pregnancy. In this case, the ultrasonographic appearance of cardiomyopathy in the recipient twin. Placental insufficiency was considered when the dimensions of the smaller fetus were below the 10th percentile,13 with a pulsatility index of the umbilical artery (PIUA) rising above the 95th percentile14 during the course of the pregnancy. In this case, the ultrasonographic appearance of the bigger fetus was normal. Fetal weight and gestational age were determined by the earliest second-trimester ultrasound measurements of head and abdominal circumferences and femur length.15,16 The severity of the TTTS at the time of the first echocardiography was assessed according to criteria proposed by Quintero et al17: stage I, isolated oligopolyhydramnios sequence; stage II, absent visible bladder in the donor; stage III, absent/reversed end-diastolic arterial flow of the umbilical artery or reversal of flow during atrial contraction in the umbilical artery or reversal of flow during atrial contraction in ductus venosus; and stage IV, hydrops in either fetus.

Ultrasound Studies
Cardiocirculatory investigations were performed with a 128 XP/10c or Sequoia sonographic equipment from Acuson with either a 5 or a 6 C2 MHz transducer. Studies were recorded on videotape for further analysis. The following parameters were routinely measured in all fetuses according to techniques described previously: cardiothoracic ratio,18 PIUA,14 the pulsatility index (PI) and peak systolic velocity of the middle cerebral artery (MCA),19 left ventricular shortening fraction (LVSF), and end-diastolic interventricular septal thickness (IVST).20 Ventricular myocardial performance index (MPI), defined as the isovolumetric period (sum of isovolumetric contraction and relaxation times) divided by the ventricular ejection time,21 was also measured. Pulsed Doppler waveforms recorded above the pulmonary and aortic valves and at the tip of the tricuspid and mitral valves were used for right ventricular (RVMPI) and left ventricular (LVMPI) MPI measurements, respectively. The isovolumetric period was obtained by subtracting the ventricular ejection time from the period between cessation and onset of the AV valve inflow signal (top of Figure 1). In addition, isovolumetric contraction and relaxation times were measured on transmitral and ventricular ejection Doppler waveforms recorded on the same tracing by placing the Doppler sample volume in the left ventricular (LV) outlet chamber, as described previously.22 Doppler echographic signals of closure and opening of the mitral valve and the brief marker of aortic closure could be recorded on the same tracing, as shown at the bottom of Figure 1. The duration of the cardiac cycle that preceded each waveform was also noted for heart rate calculation. The data represent the average of 3 consecutive measurements.

Statistical Analysis
The data were analyzed in 2 steps. First, ANOVAs were done to identify significant predictors of TTTS. Differences between the 2 conditions (TTTS and IUGR) were evaluated by an ANOVA with 1 between-subjects factor (condition) and 2 within-subject factors (variables measured and twins). Owing to sample size discrepancies between the 2 groups, the Pillai’s trace multivariate test was used because it is more robust in this case.23 It was believed that there would be significant interactions between the factors; therefore, the full factorial model was planned to identify the presence of statistically significant interactions. In case of significant interaction...
Results

During the study period, 34 monochorionic/diamniotic twin pregnancies with fetal growth discrepancy were seen in our unit and ultimately diagnosed as TTTS in 23 cases (group I) or IUGR of 1 twin in 11 pregnancies (group II). Two recipient fetuses of group I were already hydropic at the first visit. Because TTTS was clinically obvious in these cases, they were not kept in the study, which ultimately included 64 pregnancies. Seven subanalyses (for each variable) were therefore undertaken. The variations between factors, appropriate subanalyses were planned. Probability values of less than 0.05 were considered significant, except for the Levene test of equality of variances, which was considered significant if \( P < 0.001 \). All analyses were done with the SPSS system version 11.5. In the second part of the analyses, diagnostic characteristics were computed for the relevant variables. Receiver operating characteristic curves and probability tables were constructed that expressed the sensitivity, specificity, and false-positive rate of various levels of intertwin differences, with the objective of finding the difference values at which the diagnosis of TTTS could be established with confidence.

#### Table 1: Descriptive Statistics for Cardiocirculatory Data From the First Echo-Doppler Assessment

<table>
<thead>
<tr>
<th>Group I (TTTS; ( n=21 ))</th>
<th>Group II (IUGR; ( n=11 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donor</strong></td>
<td><strong>Recipient</strong></td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>LVMI, units</td>
<td>0.307 (0.117)</td>
</tr>
<tr>
<td>RVMI, units</td>
<td>0.384 (0.175)</td>
</tr>
<tr>
<td>LVSF, %</td>
<td>39.12 (5.77)</td>
</tr>
<tr>
<td>IVST, mm</td>
<td>2.24 (0.47)</td>
</tr>
<tr>
<td>PI of MCA</td>
<td>1.58 (0.45)</td>
</tr>
<tr>
<td>PIUA</td>
<td>1.77 (0.46)</td>
</tr>
<tr>
<td>Vmax of MCA, m/s</td>
<td>0.291 (0.100)</td>
</tr>
<tr>
<td>CTR, %</td>
<td>52.0 (6.2)</td>
</tr>
<tr>
<td>Small Fetus</td>
<td>0.446 (0.088)</td>
</tr>
<tr>
<td>Large Fetus</td>
<td>0.443 (0.055)</td>
</tr>
<tr>
<td>Difference</td>
<td>0.348 (2.95)</td>
</tr>
<tr>
<td>Small Fetus</td>
<td>2.41 (0.62)</td>
</tr>
<tr>
<td>Large Fetus</td>
<td>1.55 (1.04)</td>
</tr>
<tr>
<td>Difference</td>
<td>1.64 (0.26)</td>
</tr>
<tr>
<td>Small Fetus</td>
<td>0.345 (0.133)</td>
</tr>
<tr>
<td>Large Fetus</td>
<td>52.1 (3.2)</td>
</tr>
</tbody>
</table>

*Pl of MCA indicates pulsatility index of MCA; Vmax of MCA, peak systolic velocity of MCA; and CTR, cardiothoracic ratio.*

Values are mean (SD). Mean intertwin difference is calculated as the large (recipient) fetus value minus the small (donor) fetus value.
activity and specificity of various differences in those 3 variables for the early diagnosis of TTTS as opposed to IUGR. The results reveal that a cutoff value of 0.09 for $\Delta LVMPI$ could identify twins with TTTS with a sensitivity of 79% and a false-positive rate of 33%. A cutoff value of 0.05 for $\Delta RVMPI$ has a sensitivity of 82% and a false-positive rate of 32%. Finally, a cutoff value of 0 for $\Delta LVSF$ has a sensitivity of 79% and a false-positive rate of 33%. Moreover, if we were to diagnose TTTS for any pair of twins that showed at least 1 of those characteristics, the sensitivity of this diagnosis would be 100%, and the false-positive rate would be 64%. This means that 64% of twins without TTTS show at least 1 of those characteristics. If we were to predict TTTS for any pair of twins that showed any combination of 2 of those intertwin differences, the sensitivity of this diagnostic would be 90%, and the false-positive rate would be 18%. An examination of all specific combinations revealed that if we were to diagnose TTTS for any pair of twins whose 2 criteria were specifically $\Delta LVMPI$ of 0.09 and $\Delta RVMPI$ of 0.05, the sensitivity of the diagnosis would be 75%, and the false-positive rate would be 9%. Any other combination of 2 specific criteria would have lower predictive power (lower sensitivity and higher false-positive rate). Finally, if we were to predict TTTS for only pairs of twins that showed all of those characteristics concomitantly, the sensitivity of this diagnostic would be 50%, and the false-positive rate would be 9%.

**Discussion**

The MPI is a ratio of time interval and is not dependent on size and geometric assumptions. This index has been studied in normal fetuses and in pathological conditions such as intrauterine ductus arteriosus constriction and fetal hydrops. The present study shows that early in the evolution of TTTS, the MPI of the recipient twin is systematically higher than that of the donor, which remains within normal range. The abnormal MPIs were essentially due to an increase in the isovolumic relaxation times, which suggests myocardial diastolic dysfunction. The concomitant findings in the same fetus of a normal ejection time along with normal shortening fractions further suggest that at this early stage, this diastolic functional impairment was isolated.

This observation goes along with the concept that the pathogenesis of the cardiomyopathy described in TTTS is not related to a simple transfer of blood volume or hemoglobin from 1 twin to the other. Reports that the severity of the syndrome does not always correlate with intertwin differences in hemoglobin or erythropoietin support this proposition. The alternate hypothesis is that cardiac dysfunction in the recipient twin results from increased systemic resistance and pressure. The renin-angiotensin system has been shown to be upregulated in donor twins and downregulated in recipient twins. This potentially beneficial adaptive mechanism against hypovolemia in the donor could become deleterious to the co-twin, however, owing to transfer of effectors such as angiotensin II through placental shunts, inducing a cardiomyopathy both by direct effect on the myocytes and by peripheral vasoconstriction.
that leads to elevated afterload.\textsuperscript{31,32} Concentrations of endothelin, a potent vasoconstrictor, have also been found to be 2.5 times higher in recipient twins than in their co-twins.\textsuperscript{10} Experimental\textsuperscript{33} and clinical\textsuperscript{34} investigations suggest that endothelin and angiotensin could induce pressure-overload cardiac hypertrophy through a common pathway. The present data show that this cardiac hypertrophy, demonstrated by increased IVST, is an early finding during the development of TTTS. In contrast with postnatal life, increase in fetal systemic afterload results in biventricular myocardial hypertrophy because of the parallel disposition of the 2 ventricles. In rare cases, this hypertrophy could lead to severe acquired RV outflow tract obstruction.\textsuperscript{35}

The results of the probability studies show that various levels of differences between the recipient and donor twins for LVMPIs and LVSF could identify twins with TTTS with a sensitivity between 80\% and 90\% but a relatively poor specificity. TTTS could be diagnosed, however, with a sensitivity of 75\% and a false-positive rate of 9\% when a combination of the following 2 cutoff values is applied: ΔLVMPI 0.09 and ΔRVMPI 0.05. The addition of the ΔLVSF to this combination decreases the sensitivity to 50\%.

In a previous investigation, the LVSF of donor and recipient twins was also found to be significantly different during the evolution of TTTS.\textsuperscript{36} The present study confirms that this difference occurs early and is due to a higher shortening fraction in the donor, with the recipient being normal. Compared with MPI, the measurement of fetal shortening fraction is challenging, requiring a perpendicular approach to the ventricular free walls, and consequently, it shows poorer repeatability than the Doppler technique.\textsuperscript{37} This could explain the loss of sensitivity observed when LVSF was added to the combination of the 2 ventricular MPIs.

Because a significant difference was found between IVST of twins in both groups, this variable is of little help in the differential diagnosis process. Similarly, as reported previously, Doppler investigation of the umbilical artery was not contributive\textsuperscript{38}; as could be expected, a greater value was observed for the PIUA of the smaller fetus with placental circulatory insufficiency, but the difference was not yet significant at this early stage of the disease. Higher peak velocity has been reported in the MCA of the smaller twin in TTTS,\textsuperscript{39} which reflects circulatory adjustment to anemia. No differences were found in any of our 2 groups of twins for either the PI or the peak velocity of the MCA. This could be related to a lesser severity of anemia at this early stage of the TTTS.

In conclusion, increased myocardial systolic performance of the donor twin and impairment of diastolic function of the recipient are observed early in TTTS. This diastolic impairment strengthens the pressure-overload concept in the pathogenesis of the hypertrophic cardiomyopathy observed in the recipient twin. Assessment of intertwin differences of ventricular MPIs appears to be a valuable tool for early differential diagnosis between TTTS and isolated IUGR.

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References


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