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

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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 /H11021 0.93), the development of an oligopolyhydramnios sequence (deepest pool /H11022 8 cm for the larger amniotic sac and /H11021 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,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 or arterial flow of the umbilical artery or reversal of flow during atrial contraction 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

**Figure 1.** Top, Measuring technique for MPI on Doppler flow velocity waveforms through semilunar and AV valves. a Indicates interval between time of closure and opening of AV valve; b, ventricular ejection time (ET); a−b, isovolumic period; ICT, isometric contraction time; and IRT, isometric relaxation time. Bottom, Doppler tracing within LV of donor (left) and his recipient twin (right) illustrating technique used to measure isometric contraction (ICT) and relaxation (IRT) times. Note longer IRT in recipient compared with donor twin.
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 allow the area under the curve to be statistically significant for each variable. The areas under the curves were statistically significant for PI of the MCA (0.842, \( P=0.004 \)), PIUA (0.89, \( P=0.015 \)), PI of the MCA (0.89, \( P=0.015 \)), PIUA (0.89, \( P=0.015 \)), and PI of the MCA (0.89, \( P=0.015 \)). The analysis of the other 3 variables (LVSF, LVMPI, and RVMPI) indicated a significant 2-way interaction between the twin and the condition factors. The type of interaction indicated that it was appropriate to analyze those variables through independent group \( t \) tests on intertwin differences for each of those 3 variables. Intertwin differences were all significantly associated with the condition and could therefore be used to distinguish the 2 groups. The intertwin differences (large minus small) for LVSF (\( \Delta \)LVSF) were positive for IUGR (1.964 ± 2.617) and negative for TTTS (−8.205 ± 9.833). The divergence between those 2 differences was statistically significant (\( P=0.003 \)). The intertwin differences for RVMPI (\( \Delta \)RVMPI) were significantly smaller (\( P=0.015 \)) for IUGR (0.011 ± 0.074) than for TTTS (0.176 ± 0.193). Finally, the differences between large and small babies for LVMPI (\( \Delta \)LVMPI) were significantly smaller (\( P<0.001 \)) for IUGR (0.023 ± 0.100) than for TTTS (0.262 ± 0.176). The elevated MPIs observed in the recipient twins were caused by a lengthening of the isovolumic periods (LV isovolumic period 0.105 ± 0.047, right ventricular [RV] isovolumic period 0.097 ± 0.026 seconds) compared with the donor twin (LV isovolumic period 0.0561 ± 0.046, RV isovolumic period 0.065 ± 0.03 seconds; \( P<0.001 \)). The ejection times were essentially the same in both groups of twins (for the recipient: LV ejection time 0.175 ± 0.017, RV ejection time 0.178 ± 0.015; for the donor: LV ejection time 0.177 ± 0.015, RV ejection time 0.172 ± 0.017; \( P=0.744 \) and 0.115, respectively). As illustrated in Figure 2, these changes in isovolumic period were mainly due to a significant prolongation of the isovolumic relaxation times.

Receiver operating characteristic curves were done for the intertwin differences between LVSF and MPIs. The areas under the curve were statistically significant for \( \Delta \)LVSF (area = 0.810, \( P=0.009 \)), \( \Delta \)RVMPI (area = 0.842, \( P=0.004 \)), and \( \Delta \)LVMPI (0.865, \( P=0.002 \)). Table 2 presents the sensi-
tivity 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 the $\Delta$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 only for pairs 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 raised afterload due to 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.

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**TABLE 2. Predictive Qualities of Various Levels of Differences as Statistically Significant Indicators of Twin–Twin Transfusion (Results of Receiver Operating Characteristic Curves)**

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<thead>
<tr>
<th>Differences</th>
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<th>1-Specificity, %</th>
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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: \(\Delta LVMPI 0.09\) and \(\Delta RVMP\) 0.05. The addition of the \(\Delta LVSF\) 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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