Differential changes in myocardial performance index and its time intervals in donors and recipients of twin-to-twin transfusion syndrome before and after laser therapy

Javier U. Ortiz[1,2], Ximena Torres[1], Elisenda Eixarch[1], Mar Bennasar[1], Monica Cruz-Lemini[1,3], Olga Gómez[1], Silvia M. Lobmaier[1,2], Josep M. Martinez[1], Eduard Gratacós[1]*, Fatima Crispi[1]

[1] BCNatal – Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital Sant Joan de Deu), IDIBAPS, University of Barcelona, and Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain

[2] Frauenklinik und Poliklinik, Technische Universität München, Munich, Germany

[3] Fetal Medicine Mexico, Fetal Medicine and Surgery Research Unit, Unidad de Investigación en Neurodesarrollo, Instituto de Neurobiología, Universidad Nacional Autónoma de México (UNAM) Campus Juriquilla, Querétaro, Mexico

Running head: Myocardial performance index in donor and recipient twins

***Correspondence to:** Eduard Gratacós,

Barcelona Center for Maternal-Fetal and Neonatal Medicine, Hospital Clínic,

Sabino de Arana 1, 08028, Barcelona, Spain

e-mail: egratacos@clinic.cat

Telephone: 00 34 93 227 5400 Ext. 9906

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ABSTRACT

Objective: To evaluate left myocardial performance index (MPI) and time intervals in fetuses with twin-to-twin transfusion syndrome (TTTS) before and after laser surgery.

Methods: Fifty-one fetal pairs with TTTS and 47 uncomplicated monochorionic twin pairs were included. Left ventricular isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT) were measured using conventional Doppler.

Results: Recipients showed prolonged ICT (46 ± 12 vs 31 ± 8 vs 30 ± 5 ms; p <0.001), IRT (51 ± 9 vs 43 ± 8 vs 43 ± 5 ms; p <0.001), and higher MPI (0.57 ± 0.12 vs 0.47 ± 0.09 vs 0.44 ± 0.05; p <0.001) than donors and controls. Donors showed shorter ET than recipients and controls (157 ± 12 vs 169 ± 10 vs 168 ± 10 ms; p <0.001) and higher MPI than controls (0.47 ± 0.09 vs 0.44 ± 0.05; p= 0.006). Preoperative MPI changes were observed in all TTTS stages. Time intervals partially improved after surgery.

Conclusion: Donor and recipient twins had higher MPI due to different changes in the time intervals, possible reflecting the state of hypovolemia in the donor and hypervolemia and pressure overload in the recipient.

INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is the most common complication of monochorionic (MC) twin pregnancies occurring in 10-15% of cases [1]. It results from a chronic unbalanced blood transfusion from the donor twin to the recipient twin through placental vascular anastomoses, which leads to hypovolemia, oliguria, and oligohydramnios in the donor, together with hypervolemia, polyuria, and polyhydramnios in the recipient [1,2]. Therefore, TTTS represents a severe hemodynamic disorder for both fetuses. Furthermore, hypovolemia leads to activation of the renin-angiotensin-aldosterone system in the donor and, consequently, to release of vasoactive substances, which result in pressure overload of both fetuses [3]. Laser photocoagulation of communicating vessels (LPCV) is the treatment of choice for TTTS and radically improves survival rates [4].

Evaluation of the myocardial performance index (MPI) in normal and pathological fetal conditions has steadily gained acceptance in recent years [5-8]. MPI is a Doppler evaluation of both systolic and diastolic myocardial function [9]. It is calculated as the quotient of the sum of the duration of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by the ejection time (ET). Left MPI can be measured in a single waveform, as the aortic and mitral valves are located in close proximity to one another [10]. Our group has proposed strict methodological criteria based on the clicks of both mitral and aortic valves as landmarks for the measurement of the time periods improve its reproducibility [11,12]. MPI seems to be a sensitive and promising Doppler parameter that could bring further understanding of the cardiac adaptation in TTTS fetuses. However, most of the studies compare MPI values between recipients and donors [13-15]. The only study that compared MPI between TTTS and uncomplicated monochorionic twins showed a higher MPI in recipient twins and no changes in donors as compared to controls [16]. However, the sample size was relatively small, and the conclusions have not been validated by any other series. In addition, whereas MPI evaluates global myocardial function, time intervals can better differentiate between systolic and diastolic function.

The aim of this study was to evaluate left time intervals and MPI in fetuses with TTTS before and after laser surgery and to compare them with those of normal monochorionic twins. Secondary aims were to assess possible changes according to TTTS stages and within 72 hours after LPCV.

METHODS

Study populations

This was a prospective study including fetal pairs from normal monochorionic diamniotic twin pregnancies and TTTS cases who underwent LPCV at Hospital Clínic in Barcelona (Spain) during a 30-month recruitment period. The study protocol was approved by the hospital ethics committee and all patients provided written informed consent.

TTTS was diagnosed according to the criteria of the Eurofetus Group [4]., i.e. a deepest vertical pocket (DVP) of amniotic fluid <2 cm in the donor´s gestational sac and ≥8 cm or ≥10 cm before and after 20 weeks in the recipient´s sac, together with a distended bladder in the recipient and a collapsed bladder in the donor during most of the examination. Severity of TTTS was classified according to the staging system proposed by Quintero et al. [17]. Pregnancies with fetal structural/chromosomal anomalies, arrhythmias, TTTS stage V, selective intrauterine growth restriction, and monoamniotic, triplets or high-order pregnancies were excluded. All TTTS cases underwent LPCV performed as previously described with 8-10F diameter trocars housing 1-2 mm endoscopes and operative channels [4,18]. Selective coagulation along the intertwin vascular equator was performed using a diode laser. Amniotic fluid was drained at the end of the surgery until the DVP in the recipient´s sac was <8 cm. Fetal pairs from non-complicated monochorionic diamniotic twin pregnancies matched with cases by gestational age at ultrasound (±1 week) were included as controls. Gestational age was determined by measurement of the first-trimester crown-rump length.

Fetal ultrasound assessment

Ultrasound assessment was performed on a Voluson Expert 8 (General Electric Medical Systems, Milwaukee, USA) or a Siemens Sonoline Antares (Siemens Medical Systems, Erlangen, Germany) with 8- to 4-MHz or 6- to 4-MHz curved array probes, respectively. All fetuses underwent detailed ultrasound evaluation including fetal anatomy and Doppler measurements such as umbilical artery pulsatility index (PI), middle cerebral artery PI, ductus venosus PI, and left MPI. All Doppler evaluations were acquired at a normal fetal heart rate (FHR) in the absence of fetal body/respiratory movements, an angle of insonation as close to 0° as possible (but always <15°), and the mechanical and thermal indices were maintained below 1. Fetal ultrasound was performed within 24 hours before and within 72 hours after surgery in TTTS pregnancies. Left MPI was measured in real time using

spectral Doppler as previously described [11]. Briefly, in an apical or basal four-chamber view, Doppler sample volume was placed to include both the lateral wall of the ascending aorta and the mitral valve where the clicks corresponding to the opening and closing of the two valves were clearly visualized. Following Doppler settings were used: sample volume 2-4 mm, high sweep velocity, high WMF, and reduced gain [9]. ICT, ET, and IRT were calculated using the beginning of the mitral and aortic valve clicks as landmarks and MPI was calculated as follows: (ICT+IRT)/ET. MPI measurements were performed by experienced physicians in fetal echocardiography after reaching the learning curve for MPI calculation[19]. Recorded time intervals and MPI represent an average of three measurements.

Statistical analysis

Normal distribution of the data was assessed with the Shapiro-Wilk test. One-way ANOVA or Student´s t-test were performed for continuous variables. Paired comparisons between preoperative and postoperative measurements in the TTTS group were performed. All tests were two-tailed and p values < 0.05 were considered statistically significant. Analyses were carried out using the Statistical Package for the Social Sciences software (IBM SPSS Statistics 23, USA).

RESULTS

During the study period, 79 patients with TTTS underwent fetoscopy. Twenty-eight cases did not meet inclusion criteria (9 cord occlusion, 4 triplets, 3 monoamniotics, 5 donors and 3 recipients died after LPCV (single demises), 4 unsuccessful preoperative or postoperative measurements). Fifty-one TTTS pregnancies had complete measurements of donors and recipients both before and after LPCV. Forty-seven fetal pairs from non-complicated monochorionic diamniotic twin pregnancies were included as controls.

Mean maternal age was similar in TTTS cases and controls (TTTS 31.6 ± 5.2 vs controls 32.4 ± 4.7 years, p=0.336). Mean gestational age at TTTS diagnosis and surgery was 20.1 ± 3 weeks. Staging at presentation of TTTS patients were as follows: 12 (23.5%) were stage I, 15 (29.4%) stage II, 23 (45.1%) stage III, and 1 (2%) stage IV. No cases of right ventricular outflow tract abnormalities were observed.

Table 1 shows left MPI values in TTTS fetuses and controls. Mean gestational age at ultrasound was similar among groups. There was no difference between mean FHR of controls and mean preoperative FHR of donors (controls 147.1 ± 8.1 vs donors 147.6 ± 5.8 bpm; p= 0.70) and recipients (controls 147.1 ± 8.1 vs recipients 148.2 ± 7.2 bpm; p= 0.414). Preoperatively, recipients showed significantly more prolonged ICT, IRT and higher MPI than donors and controls. All three parameters showed a non-significant tendency to improve after surgery. On the other hand, donors showed significantly shorter preoperative ET than recipients and controls leading to higher MPI than controls. Both ET and MPI significantly improved after fetoscopy.

Additionally, TTTS fetuses were subdivided into stages I-II (n= 27) and stages III-IV (n=24) and compared with gestational age-matched controls (Table 2). Mean FHR was similar in all groups. Preoperative MPI values of both donors and recipients were significantly higher than controls at all severity groups. Postoperatively, donors showed a significantly improvement of ET at all severity stages and MPI at early stages, whereas in recipients only IRT at early stages showed significant improvement.

DISCUSSION

This study showed a decreased left myocardial performance in both donors and recipients regardless of the stage of TTTS. We could also demonstrate improvement of left cardiac function shortly after laser surgery. To our knowledge, this is the first investigation that compares time intervals and the largest study that compares left MPI between TTTS and uncomplicated monochorionic twin fetuses.

Our results showed prolonged ICT, IRT and higher MPI in recipients at all TTTS stages. This is in line with previous studies that have reported signs of systolic and diastolic dysfunction in recipient twins including TTTS stages I and II [13,14,20-22]. These echocardiographic findings can be in part due to an increased preload. A slow chronic increase in volume load can lead to increased ventricular dimensions explaining impaired relaxation and prolonged IRT [23,24]. On the other hand, ICT changes suggest an early cardiac systolic impairment in recipients. This could be explained, on the one hand, by volume overload (with the consequent change in ventricular shape and increase in local wall stress resulting in local fibrosis and cell death) and, in the other hand, by pressure overload due to release of vasoactive factors in the donor twin (which are also transferred to the recipient twin through vascular anastomoses). Both IRT and ICT lengthen with increasing cardiac dysfunction leading to higher MPI. Our findings also support previous series reporting that cardiac function is worse in recipients than donors [13-15,25]. It can be attributable to major changes in preload and afterload that could even lead to hypertrophic cardiomyopathy and right ventricular outflow tract abnormalities [26].

In contrast, donors showed an impaired left myocardial performance mainly due to a shorter ET at all severity stages. These findings differ from those reported by Van Mieghem et al. [16], who did not find MPI changes in donors as compared to uncomplicated monochorionic twins. This may be due to a smaller sample size and especially to the fact that groups were not matched for gestational age in the latter study. However, our results are in agreement with recent studies in donors showing signs of impaired systolic function such as ventricular ejection force, strain rate and mitral annular plane systolic excursion [27-29]. We hypothesize that chronic hypovolemia results in hypoxia and decreased stretching of myocardial fibers leading to an impaired systolic function and, consequently, to a shorter ET. Furthermore, chronic activation of the renin-angiotensin-aldosterone system could lead to pressure overload worsening systolic function.

Regarding postoperative data, cardiac function in donors and recipients (mainly at early stages) improved considerably within 72 hours after laser surgery. Previous studies have reported

improvement of MPI after surgery mainly 4 to 14 days after the procedure [16,30,31]. LPCV leads to sudden and drastic hemodynamic changes both in donor and recipient twins. This may have enabled us to show significant cardiac improvement very early after surgery.

From a clinical point of view, MPI seems a very sensitive marker of cardiac dysfunction and hemodynamic disturbances in monochorionic twins. Therefore, MPI could be useful in the initial evaluation of TTTS fetuses, helping refine their prognosis before surgery or even detecting monochorionic twins at risk for developing TTTS [32,33]. However, standardization of parameters that improve MPI reproducibility such as learning curve, the use of valve clicks, and adequate ultrasound settings must be considered [9,11,19].

This study has some strengths and limitations that merit comment. The prospective design, sample size, pre and postoperative paired observations, and inclusion of a gestational age-matched control group of uncomplicated monochorionic fetal pairs are the major strengths of this study. A weakness is that long-term impact of laser surgery on MPI was not evaluated. This is, however, inherent to the referral pattern of our population.

In conclusion, this study showed that both donor and recipient twins presented left myocardial impairment in all TTTS stages. Higher MPI values in both twins were due to different changes in the time intervals used for its calculation, possible reflecting the state of hypovolemia in the donor and hypervolemia and pressure overload in the recipient. These changes partially improved 72 hours after laser surgery. The findings of this study suggest that MPI is a highly sensitive parameter of early fetal cardiac dysfunction that probably represents initial stages of cardiac adaptation in TTTS fetuses.

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Table 1. Comparison between pre and postoperative left time intervals and myocardial performance index (MPI) in twin-to-twin transfusion syndrome and non-complicated monochorionic twin (controls) fetuses

	Controls	Donors		Recipients	
		preoperative	Postoperative	preoperative	postoperative
N	94	51	51	51	51
GA at scan (weeks)	19.9 (3)	20.1 (3)	20.1 (3)	20.1 (3)	20.1 (3)
ICT (ms)	30 (5)	31 (8)	31 (9)	46 (12)*‡	43 (11)*
IRT (ms)	43 (5)	43 (8)	42 (11)	51 (9)*‡	48 (9)*
ET (ms)	168 (10)	157 (12)*†	173 (14)*‡	169 (10)	171 (15)
MPI	0.44 (0.05)	0.47 (0.09)*	0.43 (0.11)‡	0.57 (0.12)*‡	0.54 (0.12)*

Data are mean (SD); *p <0.05 as compared to controls; †p <0.05 as compared to recipient´s preoperative value; ‡p < 0.05 as compared to donor´s preoperative value.

GA, gestational age; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time; MPI, myocardial performance index.

340 **Table 2**. Comparison between pre and postoperative left time intervals and myocardial performance
341 index (MPI) in twin-to-twin transfusion syndrome (TTTS) subdivided according to severity stages.

	Controls	Donors		Recipients	
		preoperative	postoperative	preoperative	postoperative
TTTS stages I-II					
N	94	27	27	27	27
GA at scan (weeks)	19.9 (3)	20.2 (2.5)	20.2 (2.5)	20.2 (2.5)	20.2 (2.5)
ICT (ms)	30 (5)	32 (8)	32 (8)	43 (11)*‡	42 (9)
IRT (ms)	43 (5)	42 (7)	41 (8)	52 (10)*‡	46 (6)¶
ET (ms)	168 (10)	156 (12)*†	173 (12)¶	170 (9)	171 (11)
MPI	0.44 (0.05)	0.48 (0.10)*	0.42 (0.09)¶	0.56 (0.11)*‡	0.52 (8)
TTTS stages III-IV					
N	94	24	24	24	24
GA at scan (weeks)	19.9 (3)	19.9 (3.5)	19.9 (3.5)	19.9 (3.5)	19.9 (3.5)
ICT (ms)	30 (5)	29 (7)	31 (10)	48 (14)*‡	44 (13)
IRT (ms)	43 (5)	43 (9)	43 (13)	51 (9)*‡	50 (12)
ET (ms)	168 (10)	157 (13)*†	172 (16)¶	168 (11)	172 (18)
MPI	0.44 (0.05)	0.47 (0.09)*	0.43 (0.14)	0.59 (0.12)*‡	0.56 (0.15)

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343 Data are mean (SD); *p <0.05 as compared to controls; †p <0.05 as compared to recipient´s
344 preoperative value; ‡p < 0.05 as compared to donor´s preoperative value; ¶p <0.05 as compared to
345 preoperative values.
346 GA, gestational age; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET,
347 ejection time; MPI, myocardial performance index

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