

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

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13 **Running head:** Myocardial performance index in donor and recipient twins

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ACCEPTED MANUSCRIPT

43 **ABSTRACT**

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

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

49 **Results:** Recipients showed prolonged ICT (46 ± 12 vs 31 ± 8 vs 30 ± 5 ms; $p < 0.001$), IRT (51 ± 9 vs
50 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 ; $p < 0.001$)
51 than donors and controls. Donors showed shorter ET than recipients and controls (157 ± 12 vs $169 \pm$
52 10 vs 168 ± 10 ms; $p < 0.001$) and higher MPI than controls (0.47 ± 0.09 vs 0.44 ± 0.05 ; $p = 0.006$).
53 Preoperative MPI changes were observed in all TTTS stages. Time intervals partially improved after
54 surgery.

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

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62 INTRODUCTION

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

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

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

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91 **METHODS**

92 **Study populations**

93 This was a prospective study including fetal pairs from normal monochorionic diamniotic twin
94 pregnancies and TTTS cases who underwent LPCV at Hospital Clínic in Barcelona (Spain) during a
95 30-month recruitment period. The study protocol was approved by the hospital ethics committee and
96 all patients provided written informed consent.

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

110 **Fetal ultrasound assessment**

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

120 spectral Doppler as previously described [11]. Briefly, in an apical or basal four-chamber view,
121 Doppler sample volume was placed to include both the lateral wall of the ascending aorta and the
122 mitral valve where the clicks corresponding to the opening and closing of the two valves were clearly
123 visualized. Following Doppler settings were used: sample volume 2-4 mm, high sweep velocity, high
124 WMF, and reduced gain [9]. ICT, ET, and IRT were calculated using the beginning of the mitral and
125 aortic valve clicks as landmarks and MPI was calculated as follows: $(ICT+IRT)/ET$. MPI measurements
126 were performed by experienced physicians in fetal echocardiography after reaching the learning curve
127 for MPI calculation¹⁹. Recorded time intervals and MPI represent an average of three measurements.

128 **Statistical analysis**

129 Normal distribution of the data was assessed with the Shapiro-Wilk test. One-way ANOVA or
130 Student's t-test were performed for continuous variables. Paired comparisons between preoperative
131 and postoperative measurements in the TTTS group were performed. All tests were two-tailed and p
132 values < 0.05 were considered statistically significant. Analyses were carried out using the Statistical
133 Package for the Social Sciences software (IBM SPSS Statistics 23, USA).

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135 RESULTS

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

142 Mean maternal age was similar in TTTS cases and controls (TTTS 31.6 ± 5.2 vs controls 32.4 ± 4.7
143 years, $p=0.336$). Mean gestational age at TTTS diagnosis and surgery was 20.1 ± 3 weeks. Staging at
144 presentation of TTTS patients were as follows: 12 (23.5%) were stage I, 15 (29.4%) stage II, 23
145 (45.1%) stage III, and 1 (2%) stage IV. No cases of right ventricular outflow tract abnormalities were
146 observed.

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

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

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163 **DISCUSSION**

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

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

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

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

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

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

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

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

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216 **REFERENCES**

- 217 1. Gratacós E, Ortiz JU, Martínez JM: A systematic approach to the differential diagnosis and
218 management of the complications of monochorionic twin pregnancies. *Fetal Diagn Ther*
219 2012;32:145-155.
- 220 2. Bermúdez C, Becerra CH, Bornick PW, Allen MH, Arroyo J, Quintero RA: Placental types and
221 twin-twin transfusion syndrome. *Am J Obstet Gynecol* 2002;187:489-494.
- 222 3. Van Mieghem T, Lewi L, Gucciardo L, Dekoninck P, Van Shoubroeck D, Devlieger R, Deprest
223 J: The fetal heart in twin-to-twin transfusion syndrome. *Int J Pediatr* DOI:
224 10.1155/2010/379792.
- 225 4. Senat MV, Deprest J, Boulvain M, Paupe A, Winer N, Ville Y: Endoscopic laser surgery versus
226 serial amnioreduction for severe twin-to-twin transfusion syndrome. *N Engl J*
227 *Med* 2004;35:136-144.
- 228 5. Mahajan A, Henry A, Meriki N, Hernandez-Andrade E, Crispi F, Wu L, Welsh AW: The
229 (pulsed-wave) Doppler fetal myocardial performance index: technical challenges, clinical
230 applications and future research. *Fetal Diagn Ther* 2015;38:1-13.
- 231 6. Figueroa H, Silva MC, Kottmann C, Viguera S, Valenzuela I, Hernandez-Andrade E, Gratacos
232 E, Arraztoa JA, Illanes S: Fetal evaluation of the modified-myocardial performance index in
233 pregnancies complicated by diabetes. *Prenat Diagn* 2012;32:943-948.
- 234 7. Cruz-Martinez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E: Changes in
235 myocardial performance index and aortic isthmus and ductus venosus Doppler in term, small-
236 for-gestational age fetuses with normal umbilical artery pulsatility index. *Ultrasound Obstet*
237 *Gynecol* 2011;38:400-405.
- 238 8. Hernandez-Andrade E, Crispi F, Benavides-Serralde JA, Plasencia W, Diesel HF, Eixarch E,
239 Acosta-Rojas R, Figueras F, Nicolaides K, Gratacós E: Contribution of the myocardial
240 performance index and aortic isthmus blood flow index to predicting mortality in preterm
241 growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2009;34:430-436.

- 242 9. Lobmaier SM, Cruz-Lemini M, Valenzuela-Alcaraz B, Ortiz JU, Martinez JM, Gratacos E,
243 Crispi F: Influence of equipment and settings on myocardial performance index repeability and
244 definition of settings to achieve optimal reproducibility. *Ultrasound Obstet Gynecol*
245 2014;43:632-639.
- 246 10. Hernandez-Andrade E, Benavides-Serralde JA, Cruz-Martinez R, Welsh A, Mancilla-Ramirez
247 J: Evaluation of conventional Doppler fetal cardiac function parameters: E/A ratios, outflow
248 tracts, and myocardial performance index. *Fetal Diagn Ther* 2012;32:22-29.
- 249 11. Hernandez-Andrade E, López-Tenorio J, Figueroa-Diesel H, Sanin-Blair J, Carreras E,
250 Cabero L, Gratacos E: A modified myocardial performance (Tei) index based on the use of
251 valve clicks improves reproducibility of fetal left cardiac function assessment. *Ultrasound*
252 *Obstet Gynecol* 2005;26:227-232.
- 253 12. Cruz-Martínez R, Figueras F, Bennasar M, García-Posadas R, Crispi F, Hernández-Andrade
254 E, Gratacós E: Normal reference ranges from 11 to 41 weeks' gestation of fetal left modified
255 myocardial performance index by conventional Doppler with the use of stringent criteria for
256 delimitation of the time periods. *Fetal Diagn Ther* 2012;32:79-86.
- 257 13. Stirnemann JJ, Mougeot M, Proulx F, Nasr B, Essaoui M, Fouron JC, Ville Y: Profiling fetal
258 cardiac function in twin-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2010;35:19-27.
- 259 14. Bensouda B, Fouron JC, Raboisson MJ, Lamoureux J, Lachance C, Leduc L: Relevance of
260 measuring diastolic time intervals in the ductus venosus during the early stages of twin-twin
261 transfusion syndrome. *Ultrasound Obstet Gynecol* 2007;30:983-987.
- 262 15. Rychik J, Tian Z, Bebbington M, Xu F, McCann M, Mann S, Wilson RD, Johnson MP: The
263 twin-twin transfusion syndrome: spectrum of cardiovascular abnormality and development of a
264 cardiovascular score to assess severity of disease. *Am J Obstet Gynecol* 2007;197:392.e1-8.
- 265 16. Van Mieghem T, Klaritsch P, Doné E, Gucciardo L, Lewi P, Verhaeghe J, Lewi L, Deprest J:
266 Assessment of fetal cardiac function before and after therapy for twin-to-twin transfusion
267 syndrome. *Am J Obstet Gynecol* 2009;200:400.e1-7.

- 268 17. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M: Staging of twin-twin
269 transfusion syndrome. *J Perinatol* 1999;19:550-555.
- 270 18. Cruz-Martinez R, Van Mieghem T, Lewi L, Eixarch E, Cobo T, Martinez JM, Deprest J,
271 Gratacos E: Incidence and clinical implications of early inadvertent septostomy after laser
272 therapy for twin-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2011;37:458-462.
- 273 19. Cruz-Martinez R, Figueras F, Jaramillo JJ, Meler E, Méndez A, Hernandez-Andrade E,
274 Gratacos E: Learning curve for Doppler measurement of fetal modified myocardial
275 performance index. *Ultrasound Obstet Gynecol* 2011;37:158-162.
- 276 20. Van Mieghem T, Giusca S, DeKoninck P, Gucciardo L, Doné E, Hindryckx A, D'Hooge J,
277 Deprest J: Prospective assessment of fetal cardiac function with speckle tracking in healthy
278 fetuses and recipient fetuses of twin-to-twin transfusion syndrome. *J Am Soc*
279 *Echocardiogr* 2010;23:301-308.
- 280 21. Habli M, Michelfelder E, Cnota J, Wall D, Polzin W, Lewis D, Lim FY, Crombleholme TM:
281 Prevalence and progression of recipient-twin cardiomyopathy in early-stage twin-twin
282 transfusion syndrome. *Ultrasound Obstet Gynecol* 2012;39:63-68.
- 283 22. Villa CR, Habli M, Votava-Smith JK, Cnota JF, Lim FY, Divanovic AA, Wang Y, Michelfelder
284 EC: Assessment of fetal cardiomyopathy in early-stage twin-twin transfusion syndrome:
285 comparison between commonly reported cardiovascular assessment scores. *Ultrasound*
286 *Obstet Gynecol* 2014;43:646-651.
- 287 23. Bijmens B, Cikes M, Butakoff C, Sitges M, Crispi F: Myocardial motion and deformation: what
288 does it tell us and how does it relate to function. *Fetal Diagn Ther* 2012;32:5-16.
- 289 24. Crispi F, Gratacós E: Fetal cardiac function: technical considerations and potential research
290 and clinical applications. *Fetal Diagn Ther* 2012;32:47-64.
- 291 25. Taylor-Clarke MC, Matsui H, Roughton M, Wimalasundera RC, Gardiner HM: Ventricular
292 strain changes in monozygotic twins with and without twin-to-twin transfusion syndrome. *Am*
293 *J Obstet Gynecol* 2013;208:462.e1-6.

- 294 26. Ortiz JU, Masoller Narcís, Gómez O, Bennasar M, Eixarch E, Lobmaier SM, Crispi F,
295 Gratacos E, Martinez JM: Rate and outcomes of pulmonary stenosis and functional pulmonary
296 atresia in recipient twins with twin-twin transfusion syndrome. *Fetal Diagn Ther* 2016 DOI:
297 10.1159/000448075
- 298 27. Szwasz A, Tian Z, McCann M, Donaghue D, Bebbington M, Johnson M, Wilson RD, Rychik J:
299 Impact of altered loading conditions on ventricular performance in fetuses with congenital
300 cystic adenomatoid malformation and twin-twin transfusion syndrome. *Ultrasound Obstet*
301 *Gynecol* 2007;30:40-46.
- 302 28. Rychik J, Zeng S, Bebbington M, Szwasz A, Quartermain M, Natarajan S, Johnson M, Tian Z:
303 Speckle tracking-derived myocardial tissue deformation imaging in twin-twin transfusion
304 syndrome: differences in strain and strain rate between donor and recipient twins. *Fetal Diagn*
305 *Ther* 2012;32:131-137.
- 306 29. Ortiz JU, Crispi F, Yamamoto R, Masoller N, Cruz-Lemini M, Gómez O, Bennasar M,
307 Lobmaier SM, Eixarch E, Martinez JM, Gratacós E: Longitudinal annular displacement by M-
308 mode (MAPSE and TAPSE) in twin-to-twin transfusion syndrome before and after laser
309 surgery. *Prenat Diagn* 2015;35:1197-1201.
- 310 30. Barrea C, Hornberger LK, Alkazaleh F, McCrindle BW, Roberts A, Berezovska O, Windrim R,
311 Seaward PG, Smallhorn JF, Ryan G: Impact of selective laser ablation of placental
312 anastomoses on the cardiovascular pathology of the recipient twin in severe twin-twin
313 transfusion syndrome. *Am J Obstet Gynecol* 2006;195:1388-1395.
- 314 31. Habli M, Michelfelder E, Livingston J, Harmon J, Lim FY, Polzin W, Crombleholme T: Acute
315 effects of selective fetoscopic laser photocoagulation on recipient cardiac function in twin-twin
316 transfusion syndrome. *Am J Obstet Gynecol* 2008;199:412.e1-6.
- 317 32. Moon-Grady AJ, Rand L, Gallardo S, Gosnell K, Lee H, Feldstein VA: Diastolic cardiac
318 pathology and clinical twin-twin transfusion syndrome in monochorionic/diamniotic twins. *Am J*
319 *Obstet Gynecol* 2011;205:279.e1-11.
- 320 33. Zanardini C, Prefumo F, Fichera A, Botteri E, Frusca T: Fetal cardiac parameters for
321 prediction of twin-to-twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2014;44:434-440.

322 **Table 1.** Comparison between pre and postoperative left time intervals and myocardial performance
 323 index (MPI) in twin-to-twin transfusion syndrome and non-complicated monochorionic twin (controls)
 324 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)*

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

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

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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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