Cardiovascular compromise in monochorionic twins

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CHAPTER 3

CARDIAC TIME INTERVALS AND MYOCARDIAL PERFORMANCE INDEX FOR PREDICTION OF TWIN-TWIN TRANSFUSION SYNDROME

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ABSTRACT

Objectives: To explore whether intertwin discordance in myocardial performance index (MPI) or cardiac time intervals enables the prediction of twin-twin transfusion syndrome (TTTS) in monochorionic diamniotic (MCDA) pregnancies with amniotic fluid discordance.

Methods: Prospective cohort study of MCDA pregnancies with amniotic fluid discordance ≥ 4cm. Serial ultrasound examinations consisted of evaluation of amniotic fluid, fetal Dopplers and fetal cardiac function.

Results: We included 21 'pre-TTTS' (group I), 18 selective fetal growth restriction (sFGR, group II) and 20 uncomplicated MCDA twin pairs (group III). Group I had a higher intertwin difference in left ventricle (LV) MPI and right ventricle (RV) MPI compared to group II and III. The intertwin difference in global heart relaxation time was significantly higher in group I compared to group III. Future recipient twins had significantly higher relaxation times of the global heart and RV and lower contraction times of the global heart and RV compared to the 'expected recipients' in group II and III.

Conclusions: Intertwin discordance in LV-MPI and RV-MPI differentiate between TTTS and MCDA pregnancies with transient discordant amniotic fluid volume. Cardiac time intervals identify future recipient twins. The clinical utility of cardiac time intervals and MPI should be investigated in large prospective studies.

INTRODUCTION

Improved prediction of twin-twin transfusion syndrome (TTTS) is needed to identify pregnancies that will benefit most from expert follow-up.[1] Early detection of TTTS allows for referral of patients to a fetal therapy center where laser surgery can be performed. Complications may be prevented with early detection and appropriate treatment. The preceding events of TTTS are however underexplored, and the pathophysiological triggers involved in the transition from balanced to unbalanced intertwin transfusion resulting in TTTS remain largely unknown.[2, 3]

Previous attempts to find improved methods to stratify the risk for TTTS include different measures of fetal cardiac dysfunction. In a study by Zanardini *et al.*[4] in 100 uncomplicated monochorionic twin pregnancies at 18 weeks' gestation the myocardial performance index (MPI) assessed by Tissue Doppler Imaging in the left ventricle of the future recipient showed a cut-off > 0.52 to detect more than 90% of subsequent TTTS cases, for a false-positive rate of 10%.[4] In this study however, the analysis was done based on the MPI of the future recipient twin, whereas, at baseline, both twins are supposed to have still normal amniotic fluid levels and it would therefore be impossible to foretell which of the twins will become the recipient. It would be more useful to predict which pregnancy will develop TTTS, from a cohort of pregnancies with some amniotic fluid difference ('pre-TTTS'). Wohlmuth *et al.*[5] attempted to discriminate between 'pre-TTTS' and monochorionic diamniotic (MCDA) controls using ventricular strain. No differences in right or left ventricular strain discordance between 'pre-TTTS' and MCDA controls were found.[5] As we believe that cardiac function is already compromised in 'pre-TTTS', modalities with better test characteristics than ventricular strain, such as the MPI and measurement of cardiac time intervals[6] by color-coded Tissue Doppler Imaging (cTDI), may be able to discriminate between normal and abnormal cardiac function.[4, 7, 8]

The aim of this prospective study was therefore to explore whether intertwin discordance in MPI or cardiac time intervals by cTDI in MCDA pregnancies with amniotic fluid difference not yet fulfilling TTTS criteria could distinguish future TTTS pregnancies from those only affected by discordant growth or discordant amniotic fluid volume without TTTS.

METHODS

This study was a single center prospective cohort study performed at the Leiden University Medical Center (LUMC) between January 2015 and March 2017. The LUMC is the national referral center for fetal therapy. In this study, all consecutive patients attending our monochorionic twin pregnancy clinic and patients that were referred to our center for the suspicion of TTTS were included. In case of amniotic fluid discrepancy, the frequency of ultrasound examination was at least twice per week. We excluded monoamniotic pregnancies, triplets and cases with congenital anomalies (including acquired right ventricular outflow tract obstruction [RVOTO]) or twin anemia polycythemia sequence (TAPS)[9]. The study was approved by the medical ethical committee of the LUMC (NL 45251.058.13).

Each ultrasound examination consisted of amniotic fluid evaluation (deepest vertical pocket), fetal Dopplers and evaluation of fetal cardiac function. Fetal biometry was measured every two weeks. Selective fetal growth restriction (sFGR) was defined as: estimated fetal weight (EFW) of one twin < 3rd percentile or at least two of four contributory parameters (EFW of one twin < 10th percentile, abdominal circumference of one twin < 10th centile, EFW discordance ≥ 25%, and umbilical artery pulsatility index of the smaller twin > 95th percentile).[10] TTTS was diagnosed using standard European diagnostic ultrasound criteria,[11] and pregnancies were staged prospectively according to the Quintero staging system.[12] If TTTS criteria were not (yet) fulfilled, 'pre-TTTS' was defined as an intertwin amniotic fluid discordance ≥ 4 cm. 'Future TTTS' pregnancies were those which progressed to TTTS stage 1 or higher (group I). 'sFGR' pregnancies were those diagnosed with sFGR and who never progressed to TTTS (group II). 'Uncomplicated' MCDA pregnancies never fulfilled the criteria of the beforementioned groups (group III). In group III the amniotic fluid discordance remained stable or decreased. The 'expected recipient' was the fetus with the largest deepest vertical pocket, the 'expected donor' was the fetus with the smallest deepest vertical pocket (in sFGR also the smallest fetus).

Fetal echocardiography was performed by two experienced sonographers (M.G. and S.E) using a Canon Aplio 500 (Canon Medical Systems Corporation, Tochigi, Japan) with a PVT-674BT 6 MHz transducer in early second trimester and a PVT-375BT 3.5 MHz transducer in late second trimester. The left ventricle (LV)-MPI and right ventricle (RV)-MPI were obtained with pulsed-wave Doppler, in the absence of fetal movements. LV-MPI was measured according to the Mod-MPI technique of Hernandez-Andrade *et al*.[13] Briefly, the isovolumetric contraction (ICT) and isovolumetric relaxation (IRT) times were obtained by measuring the time interval between the closure of the atrioventricular valve and its subsequent opening in the next cardiac cycle (atrioventricular valve

time). In the left ventricle, the ejection time (ET) was measured from the opening to the closure of the mitral valve. Mod-MPI was calculated as (ICT+IRT)/ET. In the right ventricle measurements were obtained separately for the tricuspid and pulmonary valves due to the right-sided valves' anatomical configuration. RV-MPI was calculated as (isovolumetric time - ET)/ET. Discrepant fetal heart rate was not an exclusion criterion, since large fluctuations in fetal heart rate could potentially be part of underlying pathological processes.[14, 15] Additionally, cTDI clips containing five or more cardiac cycles in the absence of fetal movements, were stored in an apical or basal four-chamber view. Three regions of interest (ROIs) were examined in each clip, according to our previously described technique.[6] A large ROI was used covering the whole heart to evaluate global heart function. Two small ROI's were used to evaluate the RV wall and the LV wall just above the atrioventricular valves. In images derived from cTDI, the change in direction of myocardial movement results in nadirs in the curve (Figure 1). Shortening time (St) was defined as the duration of myocardial motion during ventricular contraction. Lengthening time (Lt) was defined as the duration of myocardial motion during ventricular relaxation or expansion. Both St and Lt were expressed as a percentage of the total duration of one cardiac cycle. Measurements were performed without blinding to twin pairing or pregnancy outcome.

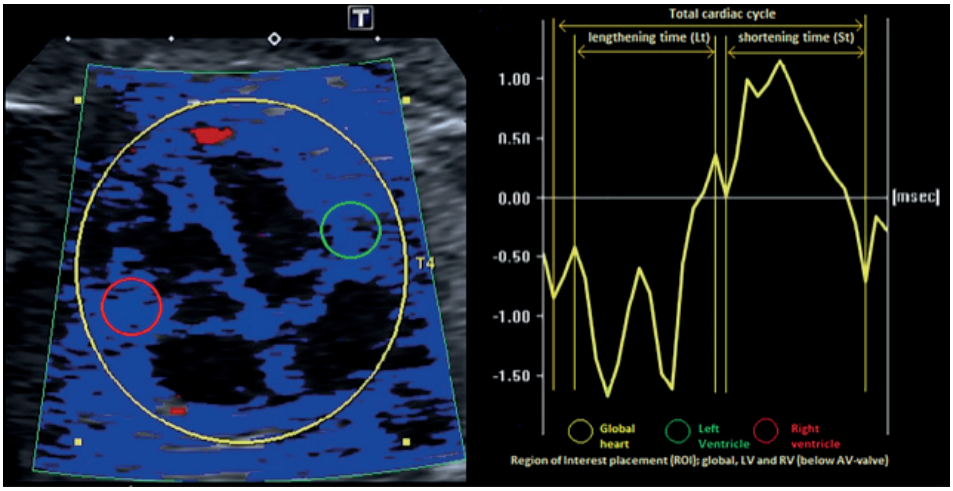

Figure 1. Schematic illustration of the cardiac cycle using cTDI, placement of regions of interest (ROI's) and demarcations of lengthening time (Lt) and shortening time (St) in the derived image. Adapted from 'Measurement of cardiac function by cardiac time intervals, applicability in normal pregnancy and twin-to-twin transfusion syndrome' by S J. Eschbach *et al.*, 2018, Journal of Echocardiography. Copyright 2018, The Authors.

Statistical analysis

Intertwin discordances of MPI measurements and cardiac time intervals were calculated as 'expected recipient' minus 'expected donor'. Individual measurements and intertwin discordances were compared between 'future TTTS' and 'sFGR' and between 'future TTTS' and 'uncomplicated' twins using the one-way ANOVA. Consecutive ultrasound examinations of one twin pair were included in the analysis, if available. Best cut-off points were identified by analysis of the receiver-operating characteristics (ROC) curve. To maximize both sensitivity and specificity, the Youden's J-statistic was applied (sensitivity + specificity - 1).[16] Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$.

RESULTS

A total of 59 MCDA pregnancies with 'pre-TTTS' were included. 21 pregnancies were allocated to group I: pre-TTTS that evolved to TTTS, all treated by laser. Growth discordance pre-laser was present in 14 of 21 twin pairs. The disease severity according to Quintero stages was distributed as follows: Stage I n = 5; Stage II n = 9; Stage III n = 7. The median gestational age at laser was 17+6 weeks (interquartile range 15+4 to 20+1). 18 pregnancies were allocated to group II: pregnancies only complicated by sFGR, of which 9 were Gratacos stage I, 3 were Gratacos stage II and 6 were Gratacos stage III. The remaining 20 pregnancies were allocated to group III: no sFGR, no TTTS, no TAPS, amniotic fluid discordance remained stable or decreased. A total of 111 ultrasound scans were available. The median gestational age at first ultrasound was 30 ± 4 years in group I, 30 ± 5 years in group II and 31 ± 5 years in group III. The mean body mass index (BMI) of mothers was 25 (21 - 28) kg/m2 in group I, 25 (22 - 28) kg/m2 in group II and 26 (23 - 28) kg/m2 in group III. 67% of patients in group I was nulliparous, compared to 59% in group II and 74% in group III.

Myocardial performance index by pulsed-wave Doppler

Group I (future TTTS) had a higher intertwin difference in LV-MPI and RV-MPI compared to group II (sFGR) and group III (uncomplicated), but a statistically difference was only found between group I and III. Compared to group III, the intertwin discordance in LV-MPI and RV-MPI in group I was twice as large (0.15 vs. 0.08, p = 0.03 and 0 25 vs. 0.12, p = 0.02). Comparing group I with both group II + III showed similar results (Table 1). Individual MPI measurements were not statistically significant different across future TTTS stages in group I (data not shown). Pregnancies that evolved into a higher TTTS stage showed a larger intertwin difference in RV-MPI (Stage 1: 0.06, Stage 2: 0.26 and Stage 3: 0.36, p = 0.001).

Cardiac time intervals by color-coded Tissue Doppler Imaging

Overall contraction times were higher and relaxation times were lower in future recipients (group I), compared to the 'expected recipient' in group II or III. The intertwin difference in global heart relaxation time (dGlobal RT) was significantly higher in group I compared to group III. Future recipient twins had significantly higher relaxation times of the global heart, right ventricle and left ventricle compared to the 'expected recipients' in group II + III. Future recipient twins had significantly lower contraction times of the global heart and right ventricle compared to the 'expected recipients' in group II + III (Table 2).

Table 1. Myocardial performance index

Parameter	Group I (TTTS)	Group II (sFGR)	Group III (Uncomplicated)	Group II + III (no TTTS)
LV-MPI donor	0.50	0.51	0.57*	0.53
LV-MPI recipient	0.58	0.58	0.61	0.60
dLV-MPI	0.15	0.10	0.08*	0.09*
RV-MPI donor	0.53	0.51	0.55	0.53
RV-MPI recipient	0.64	0.64	0.62	0.63
dRV-MPI	0 25	0.18	0.12*	0.15*

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; LV, left ventricle; MPI, myocardial performance index; d, delta; RV, right ventricle.
* $p < 0.05$, compared to Group I.

Table 2. Cardiac time intervals using cTDI

Parameter	Group I (TTTS)	Group II (sFGR)	Group III (Uncomplicated)	Group II + III (no TTTS)
Global Ct donor	44%	44%	45%	44%
Global Ct recipient	49%	46%*	45%*	45%*
dGlobal Ct	7.1%	4 4%	6.8%	5.5%
Global Rt donor	46%	44%	44%	44%
Global Rt recipient	37%	41%*	43%*	42%*
dGlobal Rt	11.6%	6.3%*	7.7%	6.9%*
RV Ct recipient	51%	45%*	45%*	45%*
RV Rt recipient	37%	45%*	44%*	45%*

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; Ct, contraction time; d, delta; Rt, relaxation time; RV, right ventricle; LV, left ventricle.
* $p < 0.05$, compared to Group I.

Cut-off values

The best cut-off point for each parameter was identified from its ROC curve to assess its predictive value in MCDA pregnancies an amniotic fluid difference ≥ 4 cm. Tables 3 to 5 give the predictive performance of cardiac parameters, for the subsequent development of TTTS. The chance of TTTS was higher in case of lower values of relaxation times (Rt).

Table 3. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group II + III (no-TTTS)

Parameter	Cut-off	Sensitivity	Specificity
dLV-MPI	0.13	63 4%	76.9%
dRV-MPI	0.21	66.7%	78.6%
Global Ct recipient	48.2%	70.8%	72.3%
Global Rt recipient	40.0%	58 2%	75.0%
dGlobal Rt	9.9%	64.3%	79 4%
RV Ct recipient	49.9%	65 2%	81.5%
RV Rt recipient	38.7%	87.0%	73.9%

TTTS, twin-twin transfusion syndrome; d, delta; LV, left ventricle; MPI, myocardial performance index; RV, right ventricle; Ct, contraction time; Rt, relaxation time.

Table 4. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group II (sFGR)

Parameter	Cut-off	Sensitivity	Specificity
Global Ct recipient	48.2%	71.8%	73.1%
Global Rt recipient	35 2%	92.3%	50.0%
dGlobal Rt	9.9%	64.3%	88.9%
RV Ct recipient	49.9%	65 2%	88.0%
RV Rt recipient	38.7%	96.0%	73.9%

TTTS, twin-twin transfusion syndrome; sFGR, selective fetal growth restriction; Ct, contraction time; Rt, relaxation time; d, delta; RV, right ventricle.

Table 5. Analysis of cut-off points, sensitivity and specificity; group I (TTTS) vs group III (uncomplicated)

Parameter	Cut-off	Sensitivity	Specificity
dLV-MPI	0.09	72.7%	73.3%
dRV-MPI	0.21	66.7%	83.3%
Global Ct recipient	47.8%	70.8%	72 4%
Global Rt recipient	40.0%	65.5%	75.0%
RV Ct recipient	49.8%	65 2%	75.9%
RV Rt recipient	40.8%	76.9%	82.6%

TTTS, twin-twin transfusion syndrome; d, delta; LV, left ventricle; RV, right ventricle; Ct, contraction time; Rt, relaxation time.

DISCUSSION

We assessed the MPI and cardiac time intervals in MCDA twins with discordant amniotic fluid. In this exploratory analysis we have found that intertwin discordance in LV-MPI and RV-MPI may help to differentiate between future TTTS and MCDA pregnancies with discordant amniotic fluid volume without TTTS. Using cardiac time intervals measured by cTDI clinicians at tertiary care centers can furthermore identify future recipient twins and differentiate between future TTTS and sFGR and uncomplicated MCDA pregnancies. Identifying recipient twins may especially help in cases where the cardiac function of the 'stuck' donor or extremely small fetus cannot be assessed, and intertwin discordance cannot be estimated.

The increased intertwin discordance in cardiac parameters in future TTTS twins found in this study is in line with a previous study where impaired ventricular strain was found in pre-recipient twins.[5] The development of unbalanced intertwin transfusion seems to be associated with early signs of cardiac function changes.

Worldwide, the MPI technique is gaining popularity and the number of articles on cardiac function as measured by MPI is increasing, but even study groups that have invested extensive research efforts into MPI acknowledge the limitations in reproducibility.[7, 17] Furthermore, most studies in the literature are focused mainly on fetal cardiac function in monochorionic pregnancies already complicated by TTTS. Due to the limited number of articles investigating 'pre-TTTS', and the fact that results regarding the utility of the MPI and other cardiac parameters to predict TTTS are conflicting, cardiac parameters are currently not used in the risk stratification of TTTS. In this study, the intertwin difference in LV-MPI and RV-MPI were found to be predictors for TTTS, with a specificity of approximately 80%. Higher MPI values found in the larger twin in sFGR may be explained by an increase in cardiac output and potentially a hyperdynamic circulation, as a result of perfusion of the placenta of the smaller one via arterio-arterial (AA) anastomoses. This resembles a milder form of the situation observed in monochorionic twins with an acardiac fetus.[18]

The results of our study furthermore show that Tissue Doppler is even more sensitive to detect subtle cardiac dysfunction compared to conventional Doppler. In line with findings of our previous study where recipient twins could be discriminated from uncomplicated monochorionic twins,[6] we have found decreased contraction times and increased relaxation times in the future recipient twins. The right ventricular relaxation time in the 'expected recipient' showed a high sensitivity (87%) to detect the future TTTS recipient. Right ventricular contraction time in the 'expected recipient' shows a good

specificity of 82%. The clinical problem of dealing with a large fluid discrepancy in a selective growth-restricted twin pair may furthermore be overcome using cardiac time intervals, since the future TTTS can be differentiated from sFGR by identification of the future recipient twin as shown by data in Tables 2 and 4.

Using both indices (MPI and cardiac time intervals using cTDI), follow-up could be planned with a larger interval. This could allow a significant reduction in the number of ultrasounds and prevent unnecessary travels to a fetal therapy center far from home. However, the safety of this approach needs to be validated in larger prospective studies.

There are limitations to this study. Our study cohort consists partly of monochorionic twins referred to our center for the suspicion of TTTS, which could have introduced a selection bias. We have used the modified MPI technique to improve reproducibility, however, reproducibility of (manual) measurement of MPI is known to be still limited. This study includes a limited number of patients. The clinical applicability of our measurements therefore have be confirmed by large prospective (multicenter) studies. Multiple comparisons performed in this study may have increased the likelihood of statistically significant differences resulting from random rather than systematic variation. Correction for multiple testing is however a subject of debate, and is not always advised if study aims have an exploratory nature.[19, 20]

CONCLUSIONS

Fetal cardiac function evaluation improves early detection of TTTS. If referring hospitals are able to stratify between future TTTS and MCDA pregnancies with transient amniotic fluid differences, unnecessary hospital visits or referrals (important in countries with large travelling distances) may be avoided, and pregnant women who are likely to develop TTTS will benefit from timely expert follow-up. The potential utility of cardiac time intervals and MPI in the triage of amniotic fluid discordance should be confirmed in large prospective (multicenter) studies, validating our estimated cut-off points. Furthermore, automatized measurements are needed since measurements of MPI or cardiac time intervals require expert hands and are time consuming.

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