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# Tissue Doppler Analysis of Postnatal Circulatory Dysfunction in Recipient Infants of Twin-Twin Transfusion Syndrome

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## Abstract

**Background:** A recipient infant of twin-twin transfusion syndrome (TTTS) may often suffer from severe circulatory dysfunction postnatally, but an adequate method that can assess early cardiac failure has not been established.

**Objectives:** To examine the clinical utility of tissue Doppler imaging (TDI) echocardiography for management of circulatory dysfunction in preterm TTTS.

**Methods:** Out of 172 very low birth weight (VLBW) infants admitted from 2004 to 2007, five recipient infants of monochorionic diamniotic twins were defined as recipient group (n=5). Three to five control infants matched for gestational age, birth weight, gender were selected from the remaining VLBW infants in the same study period (control group, n=20). Serial echocardiographic examinations including TDI were performed from birth to days 7, then peak systolic velocities (S), early diastolic velocities (Ea), late diastolic velocities (Aa), and myocardial performance index (MPI) were measured at the lateral annulus of mitral and tricuspid valves.

**Results:** There were no significant differences in longitudinal changes of mitral S, Ea, Aa. Values of left ventricular MPIs assessed by TDI in the recipient group before 24 hours after birth appeared to be significantly higher than those in the control group. Early values of tricuspid S and Ea values in the recipients significantly decreased compared to those in the controls. Right ventricular MPIs of recipient infants before 24 hours were also significantly higher than those in the control infants.

**Conclusions:** These preliminary comparisons suggested that early circulatory disturbances of the recipient infants with preterm TTTS might be accurately assessed by TDI.

**Keywords:** Tissue doppler imaging; Echocardiography; Premature infant; Twin-twin transfusion syndrome

## Introduction

Twin-twin transfusion syndrome (TTTS), a complication of monochorionic diamniotic (MD) twin gestations, is one of the most hazardous events that can occur in the perinatal-neonatal period [1,2]. In the womb, TTTS sometimes results in hydrops fetalis, severe intrauterine growth restriction, and fetal death. In postnatal infants with TTTS, especially in the recipient infant, intractable cardiorespiratory disturbances may emerge soon after birth. Although both early assessment of cardiac performance and appropriate care for heart failure are essential in such infants for stabilization of their general status in the early neonatal period, accurate, detailed examination of cardiac function using methods such as invasive cardiac catheterization may be difficult or impossible [3,4]. Despite improvements in neonatal echocardiography as a non-invasive tool for assessing early cardiac function, there is still no consensus about which indices are most useful for this purpose in very premature infants.

Tissue Doppler imaging (TDI) is a new echocardiographic technique that directly measures myocardial velocities in the myocardium and at the valve annulus [5,6]. This makes it possible to analyze both the systolic and diastolic function of the ventricles, and the data can be correlated with the findings of invasive catheterization, being also valuable in adult cardiology for long-term management of cardiac failure [5,6]. Recently, it has also been suggested that TDI might be applicable to the management of children with [7,8] and without [9,10] heart disease, healthy infants [11,12], critically ill infants [13-16], and fetuses [17,18]. In preterm infants, however, few authors have reported the clinical use of TDI for early management of circulatory dysfunction [19]. In this comparison, we examined the clinical utility of TDI assessment for management of early circulatory dysfunction in the recipient infant in preterm TTTS.

## Materials and Methods

Between September 2004 and August 2007, 172 very low birth weight (VLBW) infants weighing less than 1500 g were admitted to the neonatal intensive care unit at Kakogawa Municipal Hospital. Among these babies, small for gestational age (SGA) infants, infants with congenital abnormalities including chromosomal anomalies, and infants who died within 48 h of birth were excluded from the study; the remaining 103 VLBW infants were included in the analysis. These infants included 28 that were the products of multiple births, comprising 11 who were one of MD twins, 13 who were one of dichorionic diamniotic (DD) twins, and 4 who were one of triplets. Among the 11 MD infants, 10 were 5 pairs of VLBW twins. We designated 5 infants whose birth weight was larger than that of the other infant in each pair as the recipients (n=5). All five pairs of MD twins that included these five infants were diagnosed as stage 2 or 3 by the Quintero staging classification for TTTS in the womb [1]. Three to five control infants matched for gestational age, birth weight and gender were selected for

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each infant in the recipient group, and 20 such infants were included in the analysis (control group, n=20). Gestational age was calculated from the mother's last menstrual day and confirmed by echography during pregnancy by obstetricians. The study was approved by the ethics committee of Kakogawa Municipal Hospital, and written informed parental consent was obtained in all cases upon study entry.

A Hewlett-Packard SONOS 2000 with a 5.5/7.5-MHz transducer was used. The 7.5-MHz transducer was used for two-dimensional studies, while the 5.5-MHz transducer was employed for color-Doppler flow recordings. Serial echocardiographic examinations of VLBW infants were started 3 h after birth, with subsequent measurements at 12, 24, 36, 48, 72 and 96 h, and on days 5, 6, and 7. Each echocardiographic estimate was expressed as the mean value of 3-5 measurements. Pulsed-wave TDI measurements were performed at the lateral annulus of both the mitral and tricuspid valves using an apical four-chamber view as shown in Figure 1. The sample volume was set at 1 mm, and filters were set to exclude high-frequency signals. Angle corrections were not used, and gains were minimized to allow for a clear tissue signal with minimal background noise. From the consecutive recordings, peak systolic velocities (S), early diastolic velocities (Ea), and late diastolic velocities (Aa) were measured. The TDI-derived myocardial performance index (MPI) was also calculated using the method described by Tei et al. [20] and modified by Harada et al. [21] as follows; MPI=(a-b)/b in Figure 1. Pulsed Doppler waveforms of ventricular inflow in both the right and left ventricles were also recorded, maximum velocities of early diastole (E) and late diastole (A) waves were measured, and then the ventricular E/Ea (E/E') was calculated [9,10]. All measurements were performed by one of the authors (MM). Clinical information was obtained from our nursery records.

Statistical analysis was performed using a statistical software package, JMP 7.0.2 (SAS Institute Inc., Japan). The Mann-Whitney U test was used to compare continuous variables, and Fisher's exact test for categorical variables. Longitudinal changes in the values for the two groups were assessed by two-way repeated-measures analysis of variance (ANOVA). Differences at $p < 0.05$ were considered significant. Intraobserver variability was assessed using Bland-Altman plots.

## Results

The gestational age of the 5 infants in the recipient group ranged from 27 to 32 weeks, and their birth weight ranged from 1108 to 1408 g. The difference in birth weight between donor and recipient in the 5 pairs of MD twins ranged from 252 to 712 g, and the discordance rate ranged from 21% to 48%. The clinical features of the two groups are presented in Table 1. The duration of mechanical ventilation in the recipient group was longer than that in the control group, and bolus infusions of albumin were used more frequently in the recipient group.

Figure 2 shows longitudinal comparisons of tissue Doppler velocities in the lateral annulus of the mitral valve (MV) between the two groups. There were no significant differences in the postnatal changes in MV S-velocity, MV Ea-velocity, ratio of Ea to Aa (MV Ea/Aa), and LV E/Ea. Both early velocities of tricuspid (TV) S and Ea in the recipient group were significantly lower than those in the control group (Figure 3). RV E/Ea values for recipient infants appeared higher than those for controls. Both values of LV MPI and RV MPI assessed by TDI in the recipient group before 24 hours of life were significant higher than those in the control group (Figure 4). As previously reported, there were not any significant differences in the longitudinal changes of conventional echo indices such as left ventricular ejection fraction (LVEF), left ventricular diastolic dimension (LVDd), left and right ventricular output (LVO and RVO), left and right ventricular E/A. We found no statistical difference in detection of echocardiographically significant tricuspid and mitral regurgitation (TR and MR) while the pressure gradient of RV-RA estimated by TR jet velocities was significantly higher in the recipient group at 3 hours than that in the control group (mean ± SD; 57 ± 15 mmHg vs. 33 ± 10 mmHg, p=.002).

Figure 5 shows the intraobserver variability of MV-S velocity, TV-S velocity, MV-Ea velocity, and TV-Ea velocity using Bland-Altman plots. Mean differences (SD) were -0.09(0.43), -0.03(0.48), 0.016(0.53), and 0.08(0.58) for MV-S, MV-Ea, TV-S, and TV-Ea, respectively ($r=0.95$ for MV-S, $r=0.97$ for MV-Ea, $r=0.94$ for TV-S, and $r=0.97$ for TV-Ea, $p<0.0001$). Variability appeared to be somewhat higher in TV than in MV.

## Discussion

Our present study revealed that both TDI-derived ventricular MPIs

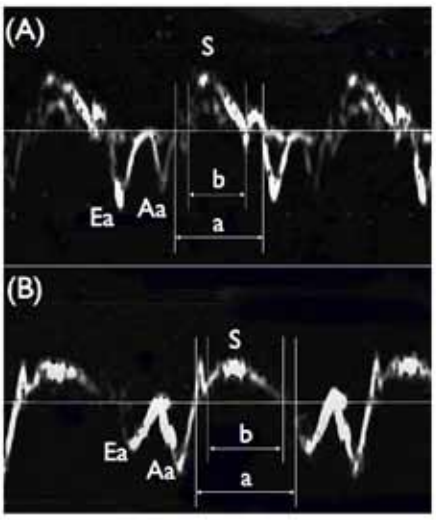


**Figure 1:** Assessment of tissue Doppler imaging (TDI) at the lateral annulus both of (A) mitral valve (MV) and (B) tricuspid valve (TV).S, peak systolic velocity, Ea, early diastolic velocity, Aa, late diastolic velocity. TDI derived MPI = (a-b)/b.

| | Recipient group (n=5) | Control group (n=20) | p |
|---|---|---|---|
| Gender, male/female | 2/3 | 9/11 | >0.99 |
| Gestational age, weeks | 29.5(1.9) | 30.1(2.0) | 0.52 |
| Birth weight, g | 1274(164) | 1272(161) | 0.89 |
| 1 minute Apgar | 6.2(1.3) | 6.8(1.5) | 0.46 |
| 5 minutes Apgar | 8.2(0.8) | 8.5(0.9) | 0.59 |
| Outborn patients | 0(0) | 2(10) | >0.99 |
| Cesarean section | 5(100) | 16(80) | 0.55 |
| Mechanical ventilation | 5(100) | 17(85) | 0.27 |
| Times of ventilation#, hours | 16.6(17.1) | 2.7(3.2) | 0.002** |
| Days of oxygen treatment$, days | 48.6(31.7) | 30.4(22.6) | 0.25 |
| Surfactant | 5(100) | 17(85) | 0.27 |
| Catecholamines | 5(100) | 19(95) | >0.99 |
| Albumin | 5(100) | 9(45) | 0.046* |

Values are mean (SD) or numbers (percentages)
#...mean length of time only in infants who were successfully extubated
$...mean length of day only in infants who were discharged without oxygen

**Table 1:** Comparisons of clinical characteristics between the two groups.

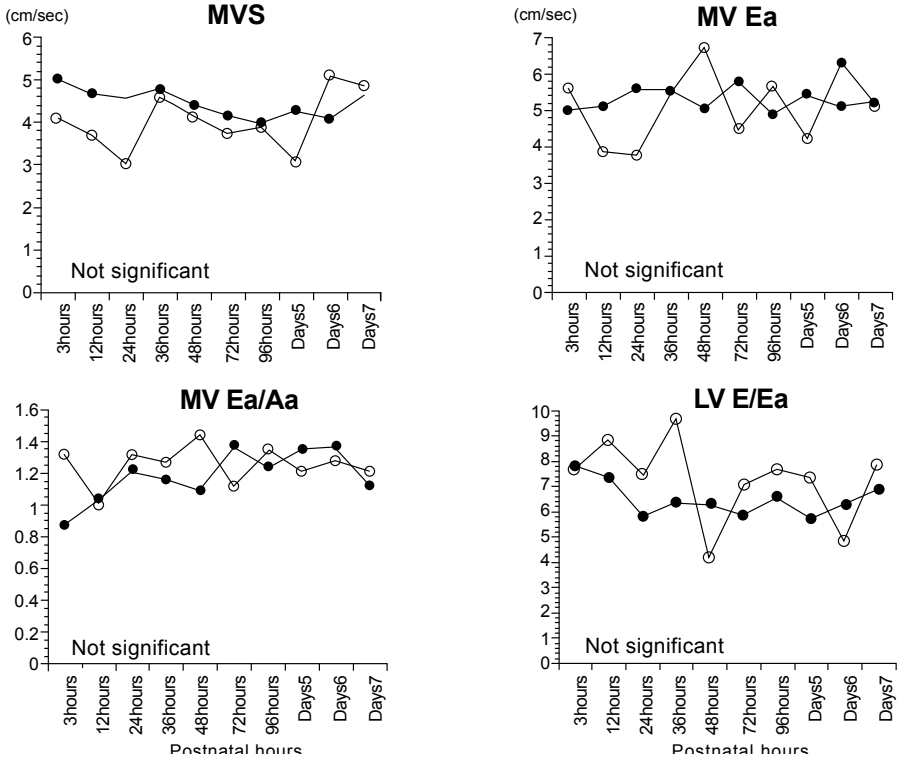


**Figure 2:** Longitudinal comparisons of tissue Doppler velocities in the lateral portion of mitral valve (MV) anulus in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median.

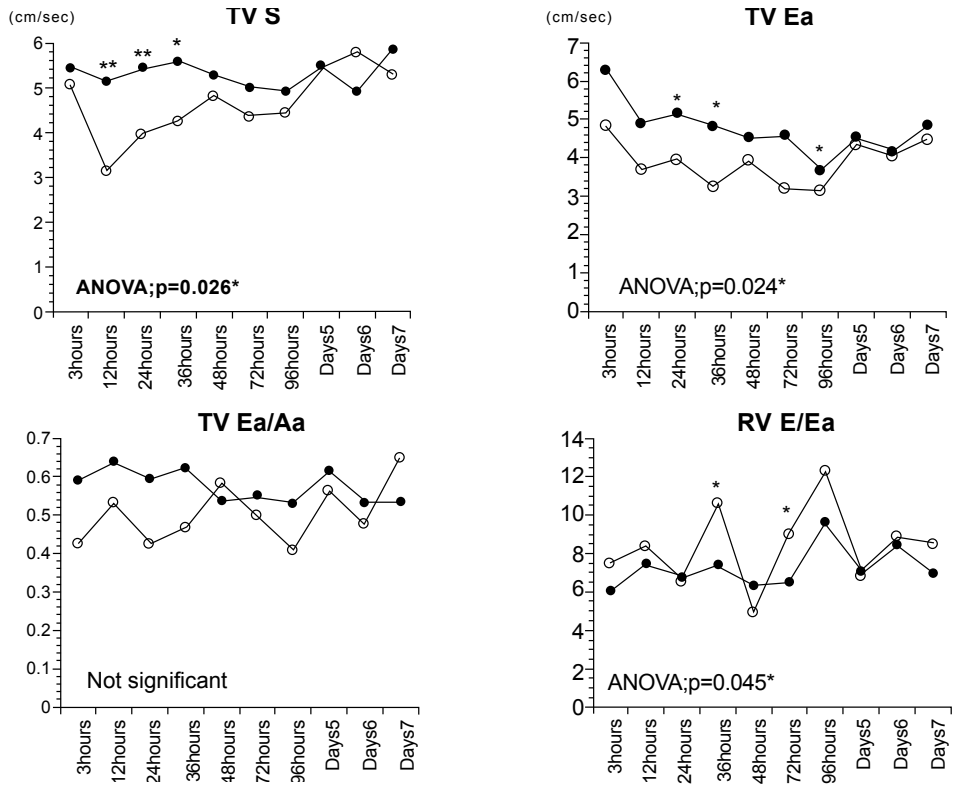


**Figure 3:** Longitudinal comparisons of tissue Doppler velocities in the lateral portion of tricuspid valve (TV) anulus in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median. * p<0.05, ** p<0.01.

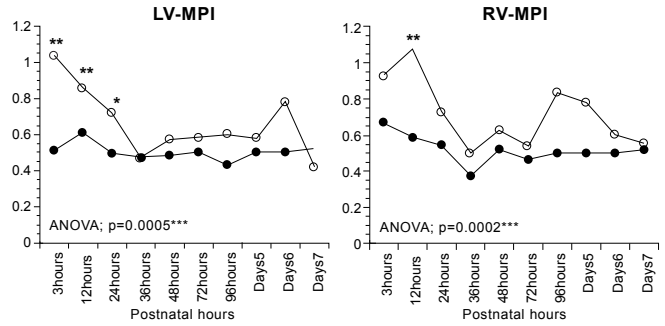


**Figure 4:** Longitudinal comparisons of TDI derived Left(LV) and Right(RV) Ventricular MPIs in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median. * p<0.05, ** p<0.01.

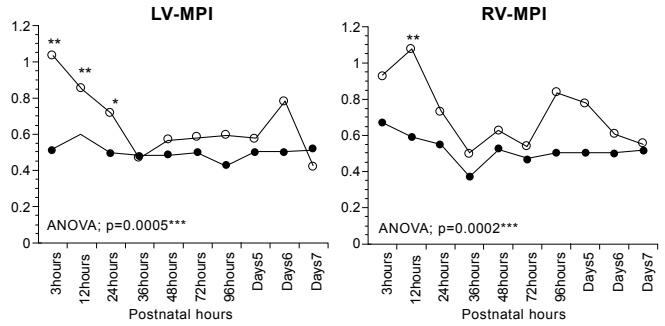


**Figure 5:** Bland-Altman plots of intraobserver variability of MV-S(a), TV-S(b), MV-Ea(c), and TV-Ea(d) with the differences between each pair of measurements expressed as a percentage of mean. Mean (broken lines) and 95% limits of agreement (solid lines) are shown.

in recipient infants were significantly higher than in controls. These results are the same as the study analyzing pulsed-Doppler derived MPIs with the same patient groups, which we reported previously [22]. It was also found in the present analysis that both tricuspid S-velocities and tricuspid Ea-velocities in recipient infants were significantly lower in the very early neonatal period than in controls, while tissue velocities at the MV annulus did not differ significantly between the groups. Although few studies have assessed postnatal cardiac changes in infants with TTTS [22-24], rapid technological advances in fetal echocardiography have revealed in detail the process of deterioration of circulatory function in recipient twin infants [1,2]. In the early stage, ventricular cavity dilatation, mild ventricular hypertrophy, and mild atrioventricular valve regurgitation are evident, but both systolic and diastolic ventricular performance is preserved. In the second stage, ventricular wall thickening takes place, with a consequent negative effect on ventricular compliance and diastolic function. These changes are typically observed in the RV rather than in the LV. In the progressive stage, diastolic dysfunction is exacerbated, and systolic ventricular dysfunction may be observed as a decrease in the ventricular shortening fraction and worsening of atrioventricular valve regurgitation, initially on the right and then progressing to the left side of the heart. Finally, severe ventricular dysfunction and atrioventricular insufficiency lead to low cardiac output, development of hydrops, and fetal death [1,2]. It was unable for us to perform detailed assessment of fetal cardiac status including MPI and TDI in the twin fetus because of methodological difficulties for obstetricians in our hospital. But presently documented circulatory status in our recipient group, where both ventricular MPIs are abnormally elevated, and the tissue velocities of S and Ea are reduced predominantly in the RV, accurately correspond to the second stage of circulatory dysfunction in TTTS. These results probably suggest that echocardiographic assessment of ventricular function in infants with TTTS using TDI can reveal both systolic and diastolic heart failure more promptly and more accurately than conventional echo, including pulsed Doppler [15,16,21].

To our knowledge, few reported studies have examined echocardiographic assessment using TDI in the early neonatal period [11-16], and hardly ever in critically ill premature infants such as those with VLBW [19]. Mori et al. [11] reported tissue velocities at the MV annulus, TV annulus, and interventricular septum in 130 neonates within 24 hours after birth, and in 135 neonates 1-7 days after birth [11]. Ekici et al. [12] also reported myocardial velocities at three different portions in both the lateral and interventricular sides of the left ventricle in 50 term neonates within 5 days after birth. TDI assessment of the fetal myocardium was reported by Harada et al. (1999) [17] and Larsen et al. [18], who suggested reduction of S-velocities in growth-restricted fetuses. For sick neonates, Wei et al. [15] observed significant reduction of left ventricular S-velocities in newborns with asphyxia. Matter also reported reduction of both ventricular S and higher values of both ventricular MPIs in asphyxiated full-term infants [16]. Patel et al. [14] assessed right ventricular function using TDI in term infants with pulmonary hypertension within 1 month after birth, and suggested lower values of both S and Ea. More recently, a study by Yates et al. [19] who analyzed myocardial tissue velocities in very preterm infants (25-28 weeks) with bronchopulmonary dysplasia (BPD), appears to be the only attempt to assess TDI in preterm infants. They suggested higher values of both left ventricular MPI and right ventricular E/E' in BPD infants [19], although their patients were already over term age at the time of examination. Our present report appears to be one of only a few studies to have included TDI assessment of premature infants in the early postnatal period. As we found that several echo parameters obtained by TDI allowed assessment of myocardial dysfunction in postnatal recipient infants with TTTS more precisely than pulsed Doppler [22], we conclude that TDI assessment of early ill preterm infants in the acute phase has considerable potential value.

This study had several important limitations. First, it was a single-center, retrospective analysis in which the sample size was too small to produce statistical power. Observation of only five infants in the recipient group did not allow us to make any definitive conclusions, and therefore the present report can only be regarded as a preliminary comparison. More patients and a multicenter protocol will be required to obtain accurate results. Secondly, some of the infants in the recipient group were critically ill and suffering from severe respiratory failure, receiving various types of support such as mechanical ventilation and administration of inotropics, albumin, etc. As these support measures themselves would probably have affected myocardial function, our findings obtained from echographic measurements in the recipient group might not have reflected natural sequential changes. However, it would be theoretically impossible to obtain clinical data from critically ill infants with TTTS who have never received any life-saving cardiorespiratory support. In evaluating the present findings, it is necessary to bear in mind that infants in one of the two groups received more care than infants in the other group. Finally, assessment of cardiac function using TDI in preterm infants has never been established as a generally standardized method. Although none of the tissue velocities presented here showed large differences in scale in comparison with

several previous studies [11-16], intraobserver variability was rather high, and technical errors due to certain conditions, such as tachycardia, lack of rest, a narrow echo window, and a limited examination time for ill infants, could not be ignored. We didn't use a high-resolution, S12 probe for TDI measurement because we wanted to shorten entire time of examination in ill infants, so there might be a possible limitation for accuracy and reproducibility. For the clinical use of TDI in premature babies, it will be necessary to minimize these methodological problems and devise actual guidelines including some provisional standards.

On the basis of this preliminary comparison, we can conclude that echocardiographic assessment using TDI would be appropriate and useful for evaluating postnatal ventricular dysfunction of recipient infants in cases of TTTS. Further larger and multi-faceted studies of the clinical use of TDI for preterm infants in the acute phase are warranted.

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