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Postnatal Myocardial Performance Index (MPI) in Recipient Infants of Twin-Twin Transfusion Syndrome: A Pulsed-Doppler Study

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Introduction

Twin-twin transfusion syndrome (TTTS), which is a complication of monochorionic diamniotic (MD) twin gestations, is known to be one of the most hazardous events in the perinatal-neoatal period [1-4]. In the womb, TTTS sometimes result in hydrops fetalis, severe intrauterine growth restriction, and fetal death. In postnatal infants with TTTS, especially in their recipient infants, it may be possible that intractable cardiorespiratory disturbances emerge promptly after birth. Neuronal damage such as periventricular leukomalacia (PVL), which cause occurrence of cerebral palsy in the growth stage, may be followed by these early neonatal events. Several past studies revealed that the pathophysiological basis of TTTS lay upon fetal heart failure caused by major vascular anastomoses in the common placenta [1-4]. Although both early assessment of cardiac performance and appropriate care for heart failure are essential in these 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[5-8]. 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. Recently, Tei has proposed a new cardiac performance index based on Doppler echocardiography that allows assessment of both systolic and diastolic ventricular function [9-11]. An abnormal increase in this myocardial performance index (MPI) has been proved to be a reliable indicator of the early phase of chronic heart failure in adults [9-13]. Several authors have also suggested that MPI might be of value in children with congenital heart disease and cardiomyopathy [14-16], and more recently in fetuses, neonates and premature infants [17,18]. The purpose of the present study was to assess the usefulness of MPI for postnatal circulatory management of recipient infants of TTTS.

Materials and Methods

Between September 2004 and August 2007, 172 very low birth wight (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 a recipient group (n=5). All five couples of MD twin that included these five infants were diagnosed as stage 2 or 3 in Quintero staging classification for TTTS [15,16] in the womb. Three to five control infants matched for gestational age, birth weight and gender were selected for 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, 7. Each echocardiographic estimate was expressed as the mean value of 3-5 measurements. Doppler measurements of MPI were performed using the method proposed by Tei [9-11] (Figure 1). Pulsed-Doppler waveforms of mitral or tricuspid inflow were recorded from the apical or parasternal four-chamber view, while the ventricular outflow patterns obtained by pulsed-Doppler were visualized from the parasternal short axis view, and apical or suprasternal long axis view. MPI was expressed as the sum of the isovolumetric contraction time (ICT) and the isovolumetric relaxation time (IRT) divided by the ejection time (ET), and easily calculated as (a-b)/b (Figure 1). Maximum velocities of both the E-wave and A-wave on the ventricular inflow waveform were also measured,

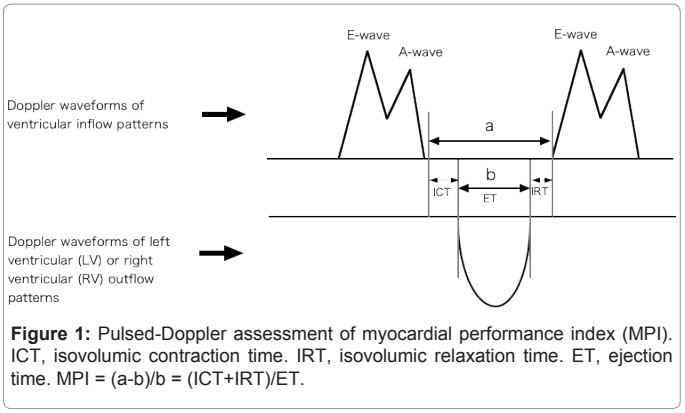

Figure 1: Pulsed-Doppler assessment of myocardial performance index (MPI). ICT, isovolumic contraction time. IRT, isovolumic relaxation time. ET, ejection time. MPI = (a-b)/b = (ICT+IRT)/ET.

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	Recipient group	Control group	p
	n=5	n=20	
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 minute 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
Dopamine	5(100)	19(95)	>0.99
Dopamine maximum dose(μg/kg/min)	6.3±2.4	2.5±1.3	0.002**
Dobutamine	4(80)	4(20)	0.024*
Dobutamine maximum dose(μg/kg/min)	7.6±4.3	0.9±1.9	0.002**
Albumin	5(100)	9(45)	0.046*
(Laboratory findings)			
Arterial pH	7.24±0.07	7.26±0.04	0.54
Arterial base deficit (mmol/l)	5.0±2.0	5.1±2.6	0.97
Arterial base deficit (mmol/l)	5.0±2.0	5.1±2.6	0.97
First hemoglobin (g/dl)	15.7±2.5	15.9±2.5	0.92
First IgM (mg/dl)	2.8±6.3	4.7±6.0	0.37
First IgM (mg/dl)	2.8±6.3	4.7±6.0	0.37
First CRP (mg/dl)	0.0±0.0	0.2±0.7	0.37
First WBC (x109/l)	12.7±4.0	11.3±6.7	0.25
First CPK (IU/l)	236±129	191±153	0.31

**p<0.01, ***p<0.001
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.

	Recipient group	Control group	p
	n=5	n=20	
Patent ductus arteriosus	1(20)	0(0)	0.20
Pulmonary hemorrhage	1(20)	0(0)	0.20
Pneumothorax	0(0)	0(0)	–
Intraventricular hemorrhage	1(20)	0(0)	0.20
Periventricular leukomalacia	3(60)	2(10)	0.038*
Septicemia	1(20)	3(15)	>0.99
Necrotizing enterocolitis	1(20)	1(5)	0.37
Chronic lung disease	2(40)	1(5)	0.091
Retinopathy of prematurity requiring photocoagulation	1(20)	1(5)	0.37
Transfusion (times)	3.8±4.5	0.6±1.3	0.039*
Alive at discharge	5(100)	20(100)	–

*p<0.05 Values are mean±SD or numbers (percentages)

Table 2: Comparison of adverse clinical events between the two groups.

and the ratio of both ventricular E velocities to A velocities (E/A) was calculated. Left ventricular ejection fraction (LVEF) was assessed by M-mode echocardiography from the parasternal long axis view according to the standardized method [19,20]. Doppler measurements of left ventricular output (LVO) and right ventricular output (RVO) [6] were assessed by the method of Alverson et al. [1]. All measurements were performed by one author (MM). Clinical information on each VLBW infant 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 by Bland-Altman plots.

Results

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. Use of dobutamine was also more frequent in the recipient group than that in the control group. In addition, both maximum dose of dopamine and dobutamine were significantly higher in the recipient group than those in the control group. Results of laboratory examinations on admission were similar in the two groups. Comparisons of neonatal complications in the two groups are shown in Table 2.

The occurrence of periventricular leukomalacia (PVL) in the recipient group was more frequent than that in the control group.

Figure 2 shows longitudinal comparisons of the diastolic thickness of both the interventricular septum (IVSTd) and the left ventricular posterior wall (LVPWd) in the early neonatal period. Both thickness of the LV wall in the recipient group appeared significantly greater than those in the control group throughout the neonatal period. We were unable to find any significant differences in the postnatal changes in left ventricular diastolic dimension (LVDd), LVEF, LVO, and RVO (Figure 3). Two-way ANOVA revealed a significant difference in the serial changes in right ventricular E/A (RV E/A) between the two groups ($p=0.036$), and the values of RV E/A in the recipient group were somewhat higher than those in the control group before 24 h after birth (Figure 4, median values at 24 h, RV E/A=0.58 in the recipient group vs. RV E/A=0.81 in the control group; $p=0.060$). Changes in both heart rate and arterial pressure during the neonatal period were similar in the two groups (Figure 5).

Comparisons of serial changes in LV MPI and RV MPI in the early neonatal period between the two groups are presented in Figure 6. Values for both ventricular MPIs immediately after birth rose significantly higher in the recipient group than in the control group, and then fell after 24 h, while in the early stage, values of RV MPI appeared to decrease more slowly than those of LV.

Figure 7 shows intraobserver variabilities both of LV and RV MPI using Bland-Altman plots. Mean differences (SD) are 0.003(0.034) and 0.006(0.045) in LV-MPI and RV-MPI, respectively ($r=0.97$ for LV-MPI, and $r=0.96$ for RV-MPI).Variabilities were higher in RV-MPI than those in LV-MPI.

Discussion

TTTS is known to occur in 10-20% of MD gestations, in which vascular anastomosis between two fetuses on a common placenta might be present in almost all pairs of twins [1,2,4]. If untreated, its natural history results in death of at least one of the twin fetuses in 90-100%

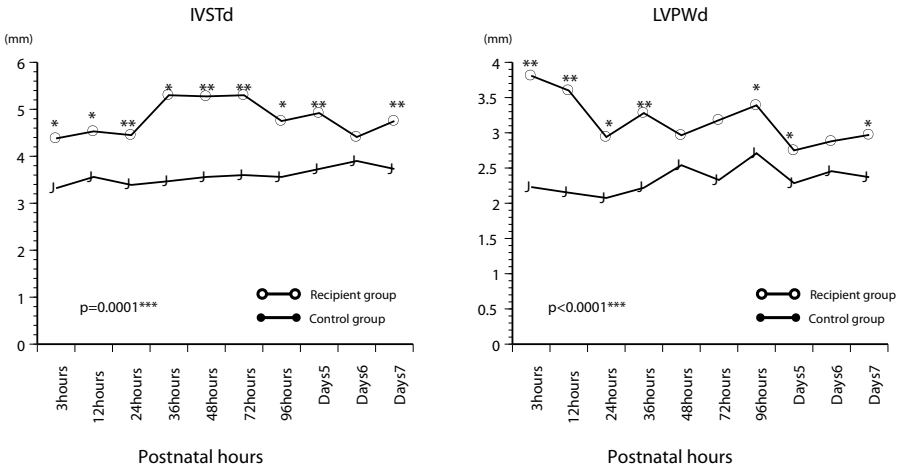

Figure 2: Comparisons of diastolic thickness of interventricular septum (IVSTd,left)and diastolic thickness of left ventricular posterior wall (LVPWd,right) in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median. * p<0.05, ** p<0.01.

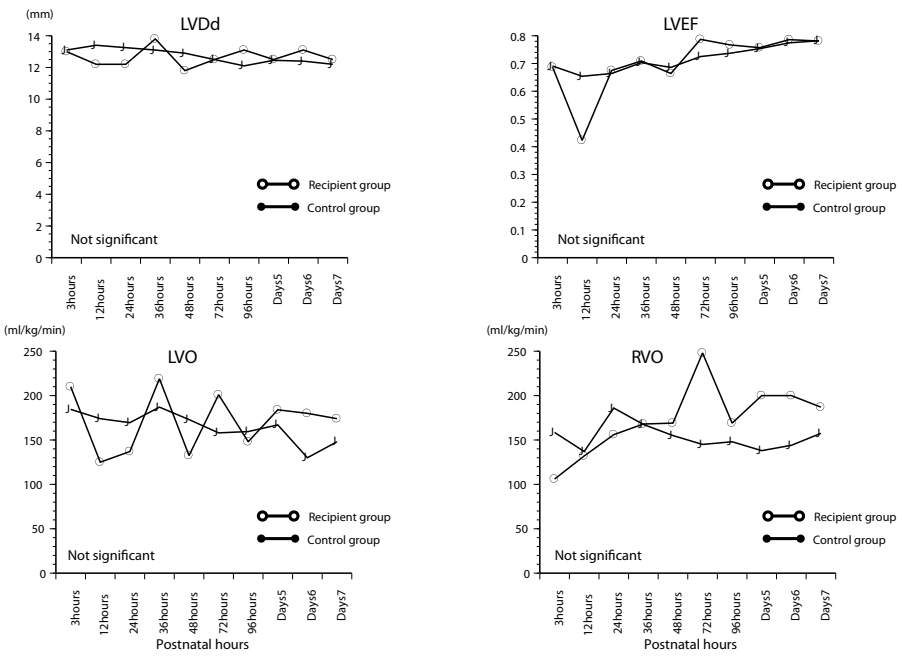

Figure 3: Longitudinal comparisons of left ventricular diastolic dimension(LVDd,upper,left), left ventricular ejection fraction(LVEF,upper,right), left ventricular output(LVO,lower,left), and right ventricular output(RVO,lower,right) in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median.

of cases [1,2,4]. Although strict obstetric management of pregnancy can allow to live births of both fetuses, the donor infant might exhibit severe anemia, hypoproteinemia, hypotension, and oliguria, while the recipient might suffer from polycythemia, hypertension, and polyuria. It is often seen that recipient infants of TTTS show signs of severe circulatory dysfunction such as myocardial hypertrophy, cardiac enlargement, atrioventricular valvular regurgitation, and myocardial dysfunction in the womb, and require close cardiorespiratory management promptly after birth [1,2,4]. Although these infants may exhibit clinical findings of circulatory failure suggesting severe myocardial dysfunction, various conventional indices obtained using two-dimensional or pulsed-Doppler echocardiography might be almost within the normal ranges, except for myocardial hypertrophy. Lack of an appropriate echographic index for assessment of cardiac function is probably a major reason for the lack of generally established guidelines for circulatory management of postnatal TTTS. In the present study, conventional echocardiographic indices for assessing cardiac function, such as LVDd, LVEF, LVO and RVO in the recipient group were not different from those in the control group, while both heart rate and arterial pressure in the two groups were also the same. Although the left ventricular wall in the recipient group was significantly thicker, none of the echocardiographic indices except RV E/A were slightly different between the two groups. Unlike these conventional indices, both RV and LV MPIs in the recipient group showed significantly higher values than those in the control group after birth.

A new cardiac index, the MPI, has been reported to have several important advantages over other well-known echocardiographic indices, and its clinical use in adult, pediatric, and neonatal cardiology has gradually spread [9-18,21]. MPI can be used to assess diastolic ventricular function and RV function [9-11], neither of which can be easily estimated using previous echo indices, and may not be significantly

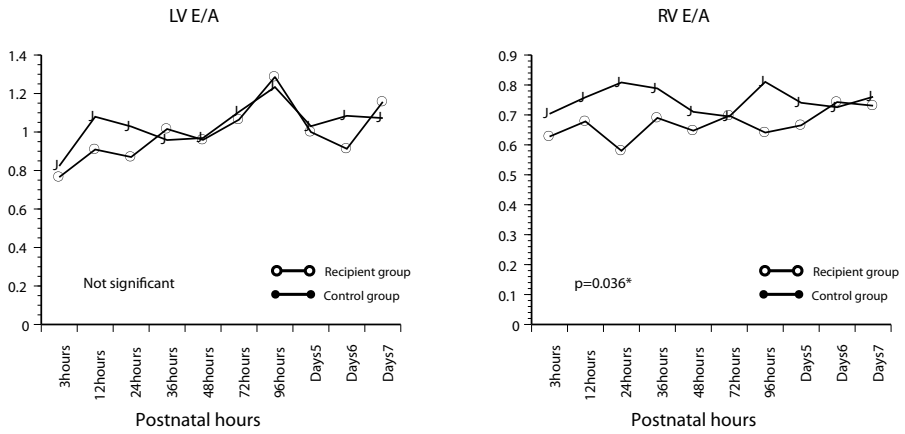

Figure 4: Longitudinal comparisons of E/A ratio of pulsed-Doppler inflow velocities through mitral(LV,left) and tricuspid(RV,right) valve between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median.

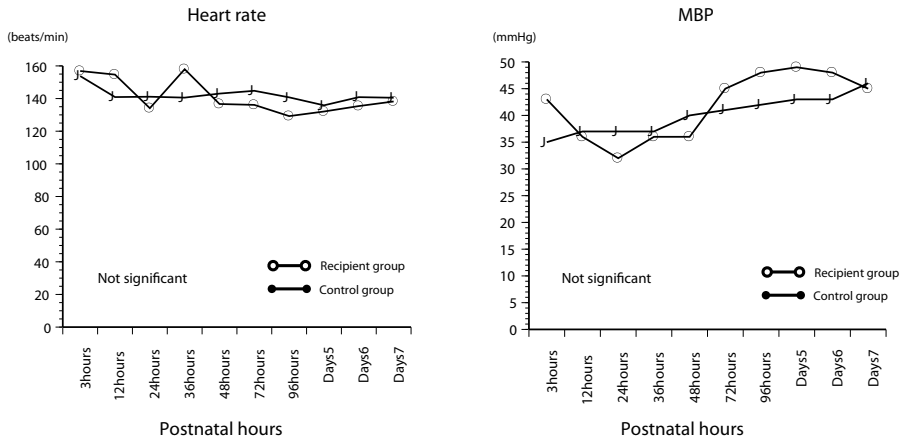

Figure 5: Longitudinal comparisons of heart rate (left) and mean blood pressure (MBP,right) in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median.

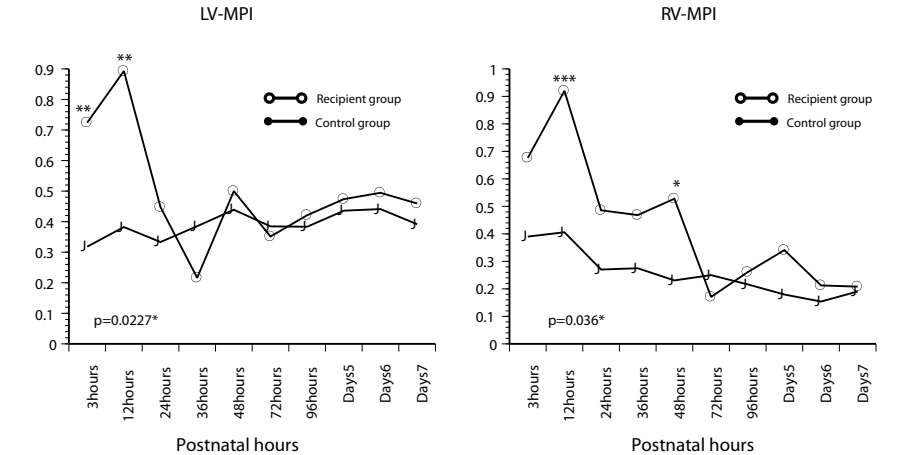

Figure 6: Longitudinal comparisons of left ventricular myocardial performance index (LV-MPI,left) and right ventricular performance index (RV-MPI,right) in the early neonatal period between infants in the recipient group (open circle) and infants in the control group (closed circle). Values are median. * p<0.05, ** p<0.01, *** p<0.001.

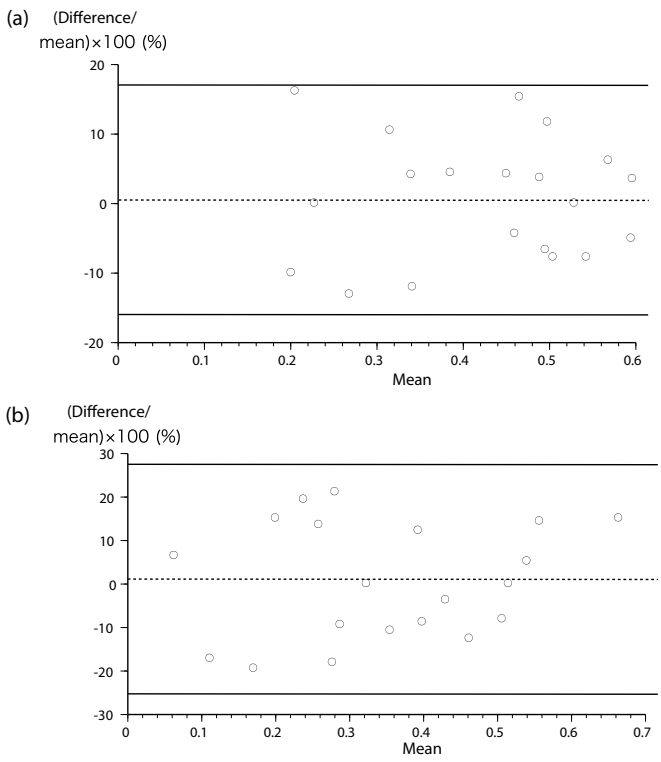

Figure 7: Bland-Altman plots of intraobserver variability of LV-MPI(a) and RV-MPI(b), with the differences between each pair of measurements expressed as a percentage of mean. Mean(broken lines) and 95% limits of agreement(solid lines) are shown.

influenced by ventricular deformity [20] and RV hypertrophy because it is calculated on the basis of measurement of time intervals only. Previously, we reported serial changes in both LV and RV MPIs in VLBW infants from birth to 28 days of life, and suggested some useful features of MPI for cardiorespiratory management of early VLBW infants [22]. Although few studies have assessed postnatal cardiac changes in infants with TTTS [23,24], rapid technological advances in fetal echocardiography[3,4,25-29] have revealed in detail the process of deterioration of circulatory dysfunction in recipient twin infants[4]. 1) 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. 2) 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. 3) 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. 4) Finally, severe ventricular dysfunction and atrioventricular insufficiency lead to low cardiac output, development of hydrops, and fetal death. Several studies have suggested that this process of deterioration in utero can be evaluated to a great extent by fetal assessment of MPIs [3,4,25-27,29].

To our knowledge, no previous report has documented in detail MPIs in infants with TTTS after birth. In our recipient group, significantly higher values of both LV and RV MPIs before 24 h of life, significantly thicker ventricular walls in the neonatal period, lower values of E/A for RV but not LV inflow, and absence of abnormal values for other conventional indices such as LVEF, LVFS, LVO, heart rate, and blood pressure suggested that these recipient infants might be at 2), the second stage of TTTS mentioned above, i.e. with mild ventricular wall thickening, mildly decreased ventricular compliance, emergence of diastolic dysfunction predominantly in the RV, and preserved systolic ventricular function [20]. It would be expected that latent ventricular dysfunction at this stage of TTTS would not be detected by conventional echo indices assessing mainly systolic function. Otherwise, most postnatal recipient infants at this stage of TTTS would exhibit features of circulatory dysfunction and require intensive cardiorespiratory support including mechanical ventilation and administration of inotropics, diuretics, and vasodilators. In our TTTS group, infants appeared to be treated with longer duration of mechanical ventilation, more frequent use of dobutamine, and higher doses of catecholamines and volume expander. Their general conditions might be strongly associated with worsening of cardiac function which were assessed by MPIs, not by conventional indices. Recently, we reported in two recipient cases of TTTS that early courses of MPIs were connected with those of lactate and base deficit in blood gas analysis [30]. It would be of great importance to evaluate myocardial dysfunction appropriately at this stage of latent ventricular dysfunction. Our present results suggest that MPI assessment in postnatal TTTS would promptly reveal latent ventricular and circulatory dysfunction, neither of which can be assessed easily using conventional indices. All these clinical findings summarized above show that early circulatory management of preterm TTTS by assessing MPIs may be of great use in present and future.

Several previous studies have shown that cardiac function in premature infants is dependent on gestational age at birth, and that standard values of echographic parameters vary with gestational age, and probably with birth weight [6-8]. Most of the previous studies of fetuses or infants with TTTS involved comparisons between donor and recipient, or between infants with TTTS and control infants with different gestational ages/birth weights [23,25-29]. These non-matched comparisons would have led to statistically unvalidated conclusions, because standard values of myocardial function may differ among infants with different gestational ages, or infants with different birth weights. Although in our previous study we suggested that both serial changes in LV and RV MPIs in VLBW infants might not be influenced by gestational age [22], we performed analysis involving controls matched for gestational age, birth weight and gender in the present study to obtain better validated findings. For this protocol, we were unable to analyze myocardial function in donor infants, but we were able to conclude that the present results for recipient infants are statistically more reliable.

There were several limitations to this study. First, 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. Strictly speaking,

most infants even in the control group were treated minimum dose of dopamine (1-3μg/kg/min) to maintain visceral and renal flows, and then these infants could not be regarded as true controls. Otherwise, especially in the TTTS group, higher doses of dopamine were used clinically, and then it may be possible that MPI course in TTTS group was strongly affected by high doses of dopamine. We may comment that use of this increase of dopamine was resulted from clinical findings and abnormally high values of MPI assessed in the early period, but statistically true course of MPI in infants with TTTS may be undecided. Then, it might not be possible that anyone get rigid findings more than clinical suggestions from our present analysis. Secondly, this was a single-center, retrospective analysis, in which the sample size was too small to produce statistical power. More patients and a multicenter protocol may be required to obtain accurate results. Finally, there may be problems with the actual measurement of MPIs in NICUs. For assessment of MPIs, as it is necessary to switch between two different echographic views [9-11], this approach may be associated with technical errors because the heart rate of some premature infants may vary within a short time [17,22]. In addition, a clear waveform of ventricular inflow on Doppler echography cannot always be obtained in early preterm infants whose heart rate might be rather high [14]. To solve this problem, some methodological innovations may be required, such as MPI assessment using tissue Doppler imaging, which has recently been reported by Harada et al. [31]. In the present analysis, however, both ventricular MPI could be applied for clinical use because intraobserver variabilities were relatively low.

In conclusion, assessment of both ventricular MPIs in postnatal recipient infants with TTTS makes it possible to detect myocardial dysfunction promptly and with certainty in comparison with conventional indices using two-dimensional or pulsed-Doppler echocardiography. We suggest that measurement of MPIs is essential for the cardiorespiratory management of postnatal infants with TTTS.

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