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N-terminal Pro-brain Natriuretic Peptide Levels in Dichorionic Diamniotic Twins with Selective Intrauterine Growth Restriction

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Monochorionic diamniotic (MD) twins with selective intrauterine growth restriction (sIUGR) have known associations with cardiac complications. However, the cardiac load of dichorionic diamniotic (DD) twins with sIUGR (DD-sIUGR) remains unclear. N-terminal pro-brain natriuretic peptide (NT-pro BNP) is a convenient marker of cardiac dysfunction in neonates, and is elevated in MD twins with sIUGR (MD-sIUGR). However, there are no reports assessing serum NT-pro BNP levels in DD-sIUGR. Here, we aimed to clarify serum NT-pro BNP levels at birth in DD-sIUGR, and to compare them with those of MD-sIUGR. Forty-one DD twin pairs admitted to our center between October 2007 and January 2013 were enrolled in this study and separated into two groups: nine twins with sIUGR (DD-sIUGR group) and 32 twins without sIUGR (DD without sIUGR group). Sixteen MD twins with sIUGR (MD-sIUGR group) served as positive controls. Serum NT-pro BNP levels at birth in DD-sIUGR [median 2,115 pg/ml (range, 443–6,590 pg/ml)] were significantly higher than in DD without sIUGR [1,080 pg/ml (range, 313–3,470 pg/ml); p=0.001], and significantly lower than in MD twins with sIUGR [4,520 pg/ml (range, 529–62,400 pg/ml); p=0.04]. Serum NT-pro BNP levels between larger and smaller DD co-twins were significantly correlated (r = 0.582; p<0.0001). In conclusion, serum NT-pro BNP levels at birth in DD twins with sIUGR were higher than those without, and lower than in MD twins with sIUGR.

INTRODUCTION

Twin pairs are associated with a variety of adverse outcomes, including neonatal death and handicaps (2), and the incidence of intrauterine growth restriction (IUGR) is higher in twin pregnancies than in singletons (15–47% vs. 3–10%; 8, 19). IUGR is a serious obstetric complication that threatens fetal health, and its phenotype in twins can be separated into two categories: selective IUGR (sIUGR) in which just one of the twins meets the criteria for IUGR, and non-selective IUGR in which both fetuses are IUGRs. The sIUGR incidence is much greater than that of non-selective IUGR, and is associated with a higher prevalence of brain injury (11).

Monochorionic diamniotic (MD) twin pregnancies, which have vascular anastomoses between the co-twins, are less common than dichorionic diamniotic (DD) twin pregnancies, and are associated with higher morbidity and mortality (1), especially in cases complicated by discordant fetal growth (18), twin-to-twin transfusion syndrome (TTTS) (22), or sIUGR (12). We previously clarified a disorganized cardiovascular adaptation in MD twins with birth weight discordance (9), in those with TTTS (10), and in those with sIUGR (8), suggesting the existence of possible associations between poor neonatal outcomes and postnatal cardiovascular instability.

Two previous case reports of DD twin pregnancies without vascular anastomoses between the co-twins revealed poor outcomes (14, 16). Moreover, a US nationwide survey of multiple pregnancies found that twins with birth weight discordance have an increased risk of neonatal mortality, with no discrimination between MD and DD twins (5). Minakami et al. reported that DD as well as MD twins with birth weight discordance greater than or equal to 25% were associated with adverse infant outcomes (18), while DD twins with sIUGR have been shown to suffer brain injury, although morbidity is less common (11). However, the pathophysiology of DD twins with sIUGR remains unclear.

N-terminal pro-brain natriuretic peptide (NT-pro BNP), which is a precursor of and a more stable alternative to BNP (7), is a convenient and objective diagnostic marker of cardiac dysfunction in neonates, adults, and children (25, 26). NT-pro BNP derives from the fetus itself and does not reflect the transplacental exchange of maternal NT-pro BNP (15). High BNP levels in umbilical cord blood were reported to be predictive for cardiac dysfunction and hypotension soon after birth (19). Recently, we reported that serum NT-pro BNP levels at birth

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are significantly elevated in MD twins with sIUGR and are associated with cardiac complications (8). However, no reports have assessed the cardiac workload in DD twins with sIUGR by measuring the serum NT-pro BNP levels at birth, so the present study aimed to (i) compare serum NT-pro BNP levels at birth in DD twins with sIUGR with those without sIUGR, and (ii) compare them in DD twins with sIUGR and MD twins with sIUGR.

METHODS

Study design and patient groups

This observational study was conducted under the approval of the ethical committee of Hyogo Prefectural Kobe Children's Hospital with informed consent waivered, because of the retrospective nature of the data collection.

Of the 152 DD twins who were born at Kobe Children's Hospital between October 2007 and January 2013, NT-pro BNP levels were measured at birth in 46 DD twin pairs. Patients with congenital or chromosomal anomalies and twins whose serum NT-pro BNP levels were not measured because of sample insufficiencies were excluded from the study. Patients who were referred to our center after 26 weeks of gestation were also excluded because of the indistinct diagnosis of sIUGR (n=10).

sIUGR was defined in twins when the estimated fetal weight was below the 10^{th} percentile in the smaller twin at 18 to 26 weeks and when the twin pair did not meet the criteria of TTTS (12). MD twins with sIUGR whose NT-pro BNP levels were obtained and who were admitted during the same periods served as positive controls.

The condition of the fetus was monitored conventionally by ultrasonography in combination with fetal heart rate monitoring or fetal biophysical profiling. Indications for deliveries were at the discretion of the attending physicians, and mainly depended on fetal deterioration. Abnormal Doppler waveforms, including reversed flow in the ductus venosus and umbilical artery, were taken into consideration as indications for delivery in some cases as previously reported (8, 10). Serum NT-pro BNP was measured at birth to determine intrauterine cardiac load in MD or DD twins.

Forty-one DD twin pairs were divided into two groups: nine twin pairs (18 newborn infants) with sIUGR (DD-sIUGR group) and 32 twin pairs (64 newborn infants) without sIUGR (DD without sIUGR group). Sixteen MD twin pairs (32 newborn infants) with sIUGR (MD-sIUGR group) were extracted and served for comparative analysis. Clinical data and serum NT-pro BNP levels at birth of both smaller and larger twins were compared between (i) DD-sIUGR and DD without sIUGR groups, and (ii) DD-sIUGR and MD-sIUGR groups.

Clinical data of the patients

Clinical data were collected from patient records, and included gestational age, birth weight, Apgar scores (at 1 and 5 min), gender, maternal age, the presence or absence of assisted reproductive technology, cesarean section, pregnancy-induced hypertension (maternal systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg during pregnancy), premature rupture of the membranes (more than 24 h before delivery), abnormal cardiotocogram findings, small for gestational age (SGA; birth weight (BW) less than 10th percentile of median BW at the same gestational age in Japanese newborns (21)), discordant rate [(BW of the larger twin - BW of the smaller twin) / BW of the larger twin × 100 (%)].

Sample collection and measurements of serum NT-pro BNP levels

Blood samples were collected at birth, promptly ice-cooled, and centrifuged. Serum samples were stored at –20°C until assay. Serum NT-pro BNP was measured by electro-chemiluminescence immunoassay on the EClusys 2010 analyzer (Roche Diagnostics K.K., Tokyo, Japan), as previously described (8, 10).

Statistical analysis

Data are expressed as the median (range) or percentage. Statistical analyses were performed with the Mann-Whitney nonparametric rank test, Chi-square test, or Fisher's exact test as appropriate. Multivariate stepwise regression analysis was performed to clarify the independent factors associated with NT-pro BNP levels. Correlation analysis was performed by using all DD twins whose NT-pro BNP were measured to compare serum NT-pro BNP levels at birth between larger and smaller DD co-twins. The correlation coefficient (r) was also calculated. Differences and correlations were deemed statistically significant when $p<0.05$. Analyses were performed using GraphPad Prism 5.0 (Graphpad Software, Inc., San Diego, CA) and JMP version 8.0.2 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Clinical backgrounds in the DD-sIUGR and DD without sIUGR groups

Clinical characteristics in the DD-sIUGR and DD without sIUGR groups are shown in Table I. The gender and maternal age were similar in both groups. There were no significant differences in the incidence of assisted reproductive technology, cesarean section, pregnancy-induced hypertension, premature rupture of the membrane, or abnormal cardiotocogram findings. Gestational age, birth weight, and Apgar scores were significantly lower, while SGA and discordant rate were significantly higher in the DD-sIUGR group compared with the DD without sIUGR group.

Table I. Clinical backgrounds in the DD-sIUGR and DD without sIUGR groups

		DD-sIUGR n=18	DD without sIUGR n=64	*P* value
Neonatal Backgrounds				
Gestational age (weeks)		**32 (26–37)**	**36 (24–37)**	**<0.0001**
Birth weight (g)		**1223 (452.0–2458)**	**2207 (596.0–2830)**	**<0.0001**
Apgar score	**1 min**	**7 (2–9)**	**8 (4–9)**	**0.007**
	5 min	**8 (5–9)**	**9 (7–10)**	**<0.0001**
Male (%)		9/18 (50%)	35/64 (54.7%)	0.72
SGA (%)		**11/18 (61.1%)**	**17/64 (26.6%)**	**0.006**
Discordant rate (%)		**31.6 (4.8–74.8)**	**7.0 (0.4–33.2)**	**0.003**
Maternal Backgrounds				
Maternal age (years)		32（26–37）	31（23–44）	0.65
Assisted reproductive technology (%)		5/9 (55.6%)	16/32 (50%)	0.77
Cesarean section (%)		9/9 (100%)	29/32 (90.6%)	0.34
Pregnancy-induced hypertension (%)		0/9 (0%)	0/32 (0%)	-
Premature rupture of the membranes (%)		2/9 (22.2%)	3/32 (9.4%)	0.30
Abnormal cardiotocogram findings (%)		2/18 (11.1%)	1/64 (1.6%)	0.06

Abbreviation: DD; dichorionic diamniotic, sIUGR; selective intrauterine growth restriction, and SGA; small for gestational age.
Significant differences in characteristics between the groups are shown in bold.

Comparison of serum NT-pro BNP levels between the DD-sIUGR and DD without sIUGR groups

Serum NT-pro BNP levels at birth were significantly higher in the DD-sIUGR group than in the DD without sIUGR group [2,115 pg/ml (range, 443–6,590 pg/ml) vs. 1,080 pg/ml (range, 313–3,470 pg/ml), p=0.001] (Figure 1).

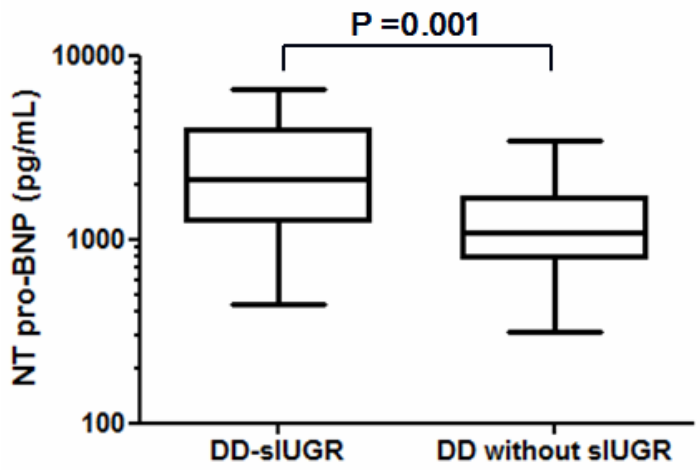


Figure 1. Comparison of serum NT-pro BNP levels between the DD-sIUGR and DD without sIUGR groups.

Multivariate stepwise regression analysis of factors associated with NT-pro BNP levels

To clarify the independent factors associated with NT-pro BNP levels, multivariate analysis was performed using a stepwise regression model, including gestational age, birth weight, Apgar score at 5 min, SGA, discordant rate, and DD-sIUGR. The stepwise regression analysis showed that only birth weight (r^2=0.45, p<0.0001) was independently associated with NT-pro BNP levels at birth. DD-sIUGR was not associated with NT-pro BNP levels at birth.

Clinical backgrounds in the DD-sIUGR and MD-sIUGR groups

Clinical characteristics in the DD-sIUGR and MD-sIUGR group are shown in Table II. There were no significant differences in clinical backgrounds between the two groups.

Table II. Clinical backgrounds in the DD-sIUGR and MD-sIUGR groups.

		DD-sIUGR n=18	MD-sIUGR n=32	*P* value
Neonatal Backgrounds				
Gestational age (weeks)		32 (26–37)	33 (27–37)	0.28
Birth weight (g)		1223 (452–2458)	1573 (494–2428)	0.19
Apgar score	1 min	7 (2–9)	7 (2–9)	0.75
	5 min	8 (5–9)	8 (6–9)	0.38
Male (%)		9/18 (50%)	14/32 (43.8%)	0.67
SGA (%)		11/18 (61.1%)	18/32 (56.3%)	0.74
Discordant rate (%)		31.6 (4.8–74.8)	19.5 (2.3–45.7)	0.20
Maternal Backgrounds				
Maternal age (years)		32（26–37）	31（27–39）	0.63
Assisted reproductive technology (%)		5/9 (55.6%)	4/16 (25%)	0.13
Cesarean section (%)		9/9 (100%)	16/16 (100%)	-
Pregnancy-induced hypertension (%)		0/9 (0%)	1/16 (6.3%)	0.44
Premature rupture of the membranes (%)		2/9 (22.2%)	2/16 (12.5%)	0.52
Abnormal cardiotocogram findings (%)		2/18 (11.1%)	3/32 (9.4%)	0.84

Abbreviation: DD; dichorionic diamniotic, MD; monochorionic diamniotic, sIUGR; selective intrauterine growth restriction, and SGA; small for gestational age

Comparison of serum NT-pro BNP levels between the DD-sIUGR and MD-sIUGR groups

Serum NT-pro BNP levels at birth were significantly lower in the DD-sIUGR group than in the MD-sIUGR group [2,115 pg/ml (range, 443–6,590 pg/ml) vs. 4,520 pg/ml (range, 529–62,400 pg/ml), *p*=0.04] (Figure 2).

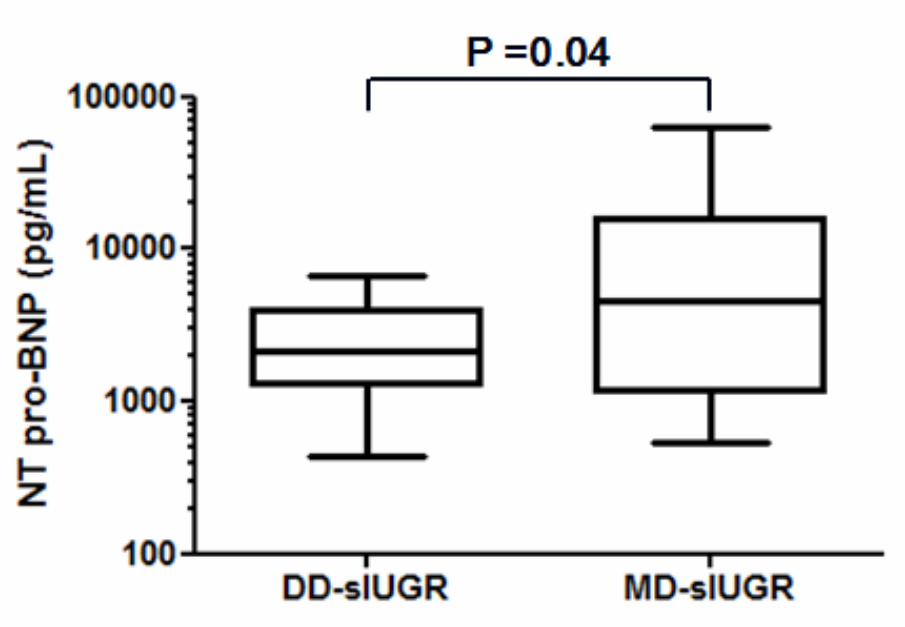


Figure 2. Comparison of serum NT-pro BNP levels between the DD-sIUGR and the MD-sIUGR group

Correlation of serum NT-pro BNP levels between larger and smaller DD co-twins

As shown in Figure 3, serum NT-pro BNP levels between larger and smaller DD co-twins were significantly correlated (n=46, r = 0.582; p<0.0001).

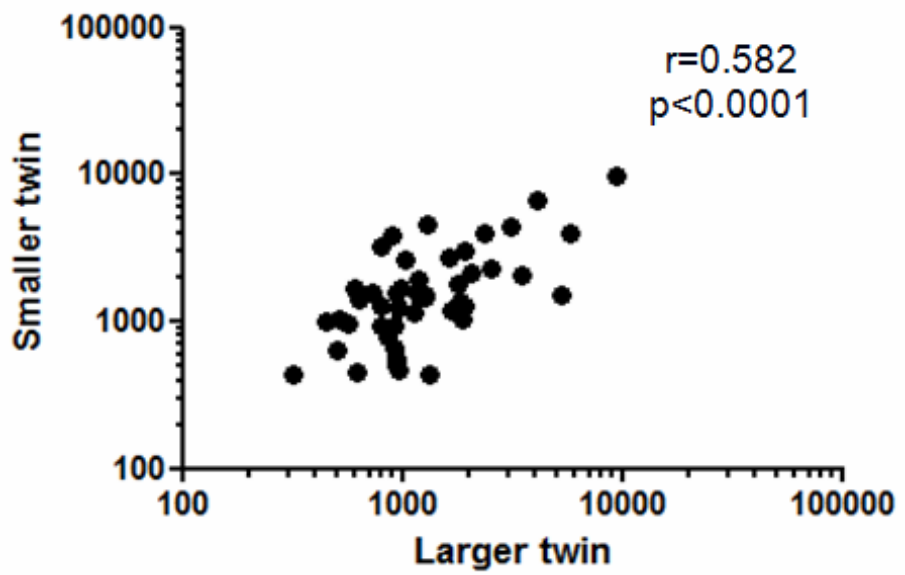


Figure 3. Correlation of serum NT-pro BNP levels between larger and smaller DD co-twins.

DISCUSSION

The present study has demonstrated for the first time that serum NT-pro BNP levels at birth in DD twins with sIUGR are significantly higher than in DD twins without sIUGR, and significantly lower than in MD twins with sIUGR. We also found moderate correlations in serum NT-pro BNP levels between smaller and larger DD-twins.

Although there have been many investigations into intrauterine cardiac functions in MD twin pregnancies (4, 20), very few have assessed cardiac load at birth in DD twins, with the exception of our preliminary study assessing cord blood levels of renin, aldosterone, BNP, and human atrial natriuretic peptide in discordant MD and

DD twins (9). We did not find any significant differences in natriuretic peptides between the two groups in this previous study. More recently, we reported the cardiac load at birth in MD twins with sIUGR by measuring NT-pro BNP (8), however, we were unable to clarify the mechanisms of fetal cardiac load from this study.

During TTTS, intertwin transfusional imbalances with net volume shifts from one fetus to the other via placental vascular anastomoses were proposed to lead to an increase in cardiac load (24). In addition, the increased cardiac output and hyperdynamic circulation via vascular anastomoses in the placenta previously resulted in a significantly increased prevalence of hypertrophic cardiomyopathy-like changes in the MD twin with sIUGR who showed normal growth (20). However, most studies regarding cardiac functions in MD twins used uncomplicated MD twins as controls instead of DD twins without placental anastomoses. We previously raised this as an unsatisfactory interpretation of such a study (9).

On the other hand, it was reported that cardiac hypertrophy and increased BNP occurred in single SGA infants compared with appropriate for gestational age (AGA) infants, suggesting prolonged exposure to an increased myocardial workload in IUGR fetuses (17). Bahlmann et al. also reported a significant increase in cord blood levels of NT-pro BNP in IUGR fetuses with abnormal Doppler findings of the umbilical artery flow compared to AGA infants (3). Based on these findings, it would be desirable to assess the cardiac load in DD twins with sIUGR, and compare it with that of MD twins with sIUGR to elucidate the mechanisms of cardiac load on this disease entity.

In the present study, therefore, we showed that serum NT-pro BNP levels in DD twins with sIUGR were significantly higher than those without sIUGR, suggesting the existence of higher intrauterine cardiac load in this group. However, as the clinical characteristics of these two groups were significantly different, we performed stepwise regression analysis to clarify the factors associated with NT-pro BNP levels at birth. After multivariate analysis, only birth weight was associated with NT-pro BNP levels, indicating that DD-sIUGR was not directly associated with increased cardiac load at birth.

We also showed that serum NT-pro BNP levels in DD twins with sIUGR were significantly lower than those in MD twins with sIUGR, suggesting a lower intrauterine cardiac workload in the former group. In these two groups, the clinical backgrounds were equivalent in all respects tested, except for the possible presence of vascular anastomoses in the placenta of MD twins. The vast majority of MD twins have intertwin anastomoses in their placentas regardless of whether the pregnancy is regarded as complicated or uncomplicated (6). We propose that the inter-twin blood volume imbalance via placental anastomoses contributes to the differences in fetal cardiac load between DD and MD twins with sIUGR, as the absence or presence of inter-twin vascular anastomoses is a unique difference between the two groups.

We also found that there was a significant correlation in the NT-pro BNP levels between larger and smaller DD twins with sIUGR, albeit a weaker correlation than in MD twins with sIUGR we reported previously ($r=0.87$, $p<0.0001$) (8). In addition, the levels of NT-pro BNP were similar between larger and smaller twins. This is in accordance with the findings of Hammerer-Lercher et al, even though their study did not distinguish between monozygotic and dizygotic pregnancies (13). The mechanisms of this correlation remain to be elucidated; however, the fact that a weaker correlation was found in DD twins without vascular anastomoses than in MD twins with vascular anastomoses is intriguing.

The main limitation of this study is the relatively small number of patients, as this is a single center retrospective observational study. Moreover, the lower prevalence of DD twins with sIUGR could contribute to this small number of patients (11). Further studies using larger twin patients set are therefore required to validate our findings. Additionally, the significant differences in the clinical backgrounds of DD twins with and without sIUGR meant that we could not determine the significance of DD-sIUGR on increased cardiac load at birth. Thus, it remains to be clarified whether DD-sIUGR itself is an exaggerating factor for postnatal cardiovascular adaptation. In addition, we could not provide specific cut-off values for NT-proBNP, because there were insufficient data about reference values of NT-proBNP levels at birth in premature newborns with complicated pregnancy course except those of cord blood in healthy term newborns [668 pg/ml (range, 281–2,595 pg/ml)](23).

CONCLUSION

This preliminary study has shown that serum NT-pro BNP levels at birth in DD twins with sIUGR were significantly higher than those without, and significantly lower than in MD twins with sIUGR. These results suggest the contribution of vascular anastomoses to the cardiac load in MD twins with sIUGR during the perinatal period. Novel therapeutic strategy during the fetal-neonatal period based on this observation might be preferable.

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