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Cardiomegaly of the larger twin in monochorionic twin pregnancies warrants neonatal intensive care even without twin-to-twin transfusion syndrome

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ABSTRACT

Objectives: Some monochorionic twin pregnancies need intensive cardiac management even in the absence of twin-to-twin transfusion syndrome after birth. The purpose of this study was to investigate risk factors related to persistent hypotension requiring cardiotonic agent use among monochorionic twin pregnancies without twin-to-twin transfusion syndrome.

Study design: This was a retrospective study of 316 monochorionic twin pregnancies without twin-to-twin transfusion syndrome (632 babies). All cases were treated in the neonatal intensive care unit. Hypotension was defined as mean arterial blood pressure below the norm for gestational age. Decreased left ventricular ejection fraction was defined as a value <60%. Dopamine, dobutamine and phosphodiesterase III inhibitor were used as cardiotonic agents for hypotension persisting even after adequate infusion.

Results: Among the 632 cases, 33 (5.2%) needed cardiotonic agents for persistent hypotension. The frequency of persistent hypotension with decreased left ventricular ejection fraction was significantly higher among larger twins (4.4%) than among smaller twins (0.6%, $p = 0.0038$). In larger twins, multivariate analysis showed that Z-score for cardiothoracic area ratio (odds ratio, 2.31; $p < 0.001$), tricuspid regurgitation (odds ratio, 6.34; $p = 0.015$) and gestational age at delivery (odds ratio, 0.66; $p < 0.001$) correlated with persistent hypotension. In smaller twins, univariate analysis showed gestational age at delivery, birth weight, Z-score for birth weight and Z-score for cardiothoracic area ratio of the larger twin were related to persistent hypotension. Concentration of brain natriuretic peptide in the umbilical vein in larger and smaller twins were significantly correlated (coefficient of correlation = 0.792, $p < 0.001$).

Conclusions: In monochorionic twin pregnancies, attention needs to be given to cardiac size along with amniotic fluid and fetal growth. Both larger and smaller twins carry risks of persistent hypotension after birth. Close observation is needed, especially in cases where the larger twin displays cardiomegaly despite absence of twin-to-twin transfusion syndrome.

Introduction

Monochorionic (MC) twins are reported to show significantly higher mortality and morbidity rates compared with dichorionic (DC) twins [1–3]. Chorionicity-related complications are thought to be based on vascular anastomoses on the shared placenta, and severely imbalanced flow causes twin-to-twin transfusion syndrome (TTTS). Both TTTS and selective intrauterine growth restriction with abnormal Doppler findings are recognized as risk factors for poor perinatal outcomes [4–6]. Twin anemia-polycythemia sequence may also represent a predictor of poor perinatal prognosis [7].

Hypotension, kidney failure, cardiac hypertrophy and cardiac dysfunction are observed in some TTTS cases treated without fetoscopic laser photocoagulation [8–11]. Increased fetal blood levels of brain natriuretic protein (BNP) reportedly correlate with recipient cardiac dysfunction in TTTS.[12] Both donors and recipients may experience hemodynamic problems in TTTS cases. On the other hand, several reports have also described cardiomegaly and

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cardiac insufficiency in neonates requiring catecholamine despite the absence of TTTS [13,14]. Such reports suggest that these fetuses had been under the influence of fetal blood communication via vascular anastomosis even without TTTS. We have also encountered MC twin cases needing cardiotonic agents for persistent hypotension in the neonatal period despite not having TTTS. Hypotension in the neonatal period should be carefully managed, because of the associations with short- and long-term adverse effects such as neonatal death, severe intraventricular hemorrhage, ischemic cerebral lesions and neurodevelopmental complications [15–17]. If MC twin neonates are treated without close observation because TTTS is not present, some cases may be at risk of such complications due to the hypotension described above. No reports have described the prediction of hemodynamic instability in the neonatal period of twin pregnancies. The purpose of this study was to investigate prenatal risk factors for persistent hypotension that requires cardiotonic agent use after birth in MC twin pregnancies without TTTS.

Materials and methods

The medical records of all twin pregnancies delivered at National Hospital Organization Nagara Medical Center, Gifu, Japan, were reviewed for the period from April 2005 until August 2017. During this study period, 705 pairs of twins (1410 babies) were delivered. Chorionicity was determined on the basis of ultrasound assessment of the dividing membrane in the first trimester. We excluded pregnancies with dichorionic twins (332 pregnancies), unknown chorionicity (8 pregnancies), single fetal death (10 pregnancies), major fetal anomaly (4 pregnancies), TTTS (26 pregnancies), selective intrauterine growth restriction with abnormal Doppler findings (3 pregnancies), twin anemia-polycythemia sequence (3 pregnancies), and incomplete data (2 pregnancies). Septic cases in the neonatal period (2 infants) were excluded because infection has been reported as a cause of neonatal hypotension [18]. All cases were delivered by Cesarean section and treated in the neonatal intensive care unit (NICU), regardless of birth weight and gestational age (GA) at delivery. Neonatal echocardiography was performed in cases of neonatal pathological condition on Day 0. If the condition of the newborn remained unstable, echocardiography was also performed after Day 1. Risk factors for persistent hypotension in the neonatal period immediately after birth were investigated. Ultrasound examinations were performed at least twice a week for MC twins. If abnormal signs (growth restriction, abnormal amniotic fluid volume, Doppler abnormality, ascites or cardiac enlargement) were seen, ultrasound examinations were performed more closely. Ultrasound measurements at the last examination were used for analysis. Fetal cardiac size was measured in all cases, and was expressed as the cardiothoracic area ratio (CTAR). Determination of CTAR was made from measurements on a good four-chamber view in which the ribs of both sides were completely visualized on the screen in the diastolic phase. Heart and chest areas were measured using the ellipse method. Reference points for the chest were the anterior thoracic wall and posterior edge of the fetal vertebral body, including the skin [19]. Z-score for CTAR was calculated as previously reported [20]. Hypotension was defined as a mean arterial blood pressure below the norm for GA (in weeks) based on the recommendations of The Joint Working Group of the British Association of Perinatal Medicine [21]. Persistent hypotension was defined as hypotension that continued even after adequate volume expansion and required use of a cardiotonic agent (dopamine, dobutamine and/or phosphodiesterase 3 inhibitor). Control cases were defined as those cases that had not needed any administration of cardiotonic agents for hypotension. Left ventricular ejection fraction (LVEF) was used to evaluate neonatal cardiac function, measured with M-mode on the parasternal long-axis view. The maximum minor axis of the left ventricle was measured at end-diastole and end-systole. Left-ventricular volume in each cardiac cycle was calculated using the Teichholz method as: volume = 7.0 / (2.4+dimension) * dimension [3]. LVEF was calculated as: (left ventricular end-diastolic volume – left ventricular end-systolic volume) / left ventricular end-diastolic volume * 100 (%) [22]. Decreased LVEF was defined as a value <60%. The larger twin was defined as the infant with higher birth weight than the co-twin. Inter-twin birth weight discordance was expressed as the discordance rate: (larger twin body weight - smaller twin body weight) / larger twin body weight. TTTS was diagnosed antenatally by ultrasound using Quintero's criteria [23]. Selective intrauterine growth restriction was defined as a growth restriction (estimated fetal growth <-1.5 standard deviations below the mean for GA) in one fetus with an interfetal weight discordance (discordance rate <0.25) [24]. Twin anemia-polycythemia sequence was diagnosed antenatally by ultrasound and confirmed after birth, in accordance with previously reported criteria [25,26].

In the mid-course of the study period, we encountered some MC twin neonates showing cardiac failure even without TTTS. BNP concentration in the umbilical vein at delivery was measured in the

Table 1
Profiles of larger and smaller twins in all monochorionic twin pregnancies.

	larger	smaller	P
No of cases	316		
Maternal age (years)	32 (19–44)		
GA at delivery (weeks)	36 + 6 (27 + 2–38 + 5)		
Birth weight (g)	2365 (838–3421)	2128 (730–3133)	<0.001
Z score of Birth weight (SD)	−0.58 (−2.54 to 2.25)	−1.44 (−4.05 to 1.58)	<0.001
Discordant rate	0.097 (0.0016–0.42)		
CTAR (%)	33.7 (19.1–52.0)	32.0 (17.0–46.0)	0.001
Z score of CTAR (SD)	1.42 (−3.5 to 7.9)	0.96 (−4.0 to 5.4)	0.0015
UAAREDF	1(0.32), N=312	0(0.0), N=310	1
DVAREDF	1(0.32), N=306	0(0.0), N=307	0.5
TR	36 (14.0), N=257	11 (4.3), N=258	<0.001
Cardiotonic agent for persistent hypotension	22 (7.0)	11 (3.5)	0.072
Cardiotonic agent for persistent hypotension with decreased left ventricle ejaction fraction	14(4.4)	2(0.6)	0.0038
MVP before birth (cm)	4.5 (1.8–12.7)	4.3 (1.0–12.7)	0.026
pH of umbilical artery	7.27 (7.14–7.37)	7.27 (7.10–7.44)	0.113
BE of umbilical artery	−4.3 (−15 to 4.0)	−4.2 (−20.8 to 4.3)	0.28
Neonatal death	1 (0.32)	0 (0)	1.0

Data are given as median (range) or n (%). GA = gestational age; CTAR = cardio-thoracic area ratio; UAAREDF = absent or reversed end diastolic flow in umbilical artery; DVAREDF = absent or reversed end diastolic flow in ductus venosus; TR = tricuspid regurgitation; MVP = maximum vertical pocket; BE = base excess.

last 95 MC pregnancies (from January 2013 to August 2017). BNP was measured by chemiluminescent immunoassay; the normal range based on the institutional standard was ≤18.4 pg/ml.

Continuous variables were analyzed using Student's *t*-test or the Mann-Whitney *U* test Categorical variables were analyzed using Fisher's exact test. Binary logistic regression analysis was used for multivariate analysis. Coefficient of correlation was analyzed with Spearman's rank method. A value of $p < 0.05$ was considered significant. Data analysis was performed using Dr. SPSS II for Windows software (IBM, Armonk, NY). The institutional review board at Nagara Medical Center evaluated and approved the study.

Results

Among the 1410 twin babies, 632 MC twin babies were included in this investigation. Median gestational age at delivery was 36 + 6 weeks (range, 27 + 2–38 + 5 weeks). Median birth weight was 2245 g (range, 730–3421 g). Median pH in the umbilical artery was 7.27 (range, 7.10–7.44). At least one type of cardiotonic agent was administered to manage persistent hypotension for 33 cases (5.2%). The incidence of persistent hypotension was higher in the larger twin (7.0%) than in the smaller twin (3.5%), but the difference was not significant ($p = 0.072$). The incidence of persistent hypotension with decreased LVEF was significantly higher in the larger twin (4.4%) than in the smaller twin (0.6%; $p = 0.0038$). Significant differences in birth weight, Z-score of birth weight, CTAR, incidence of tricuspid regurgitation (TR) and maximum vertical pocket before birth were evident between larger and smaller twins (Table 1).

The clinical characteristics and postnatal course of persistent hypotension cases in MC twin cases are presented in Table 2. No cases displayed abnormal Doppler findings in umbilical artery (UA) and ductus venosus (DV) before birth. Median age in days at initiation of cardiotonic agent was 1 day (range, 0–2 days) and duration of cardiotonic agent use was 4 days (range, 1–17 days). All except one case (97%) were discharged without cardiac complications. In the remaining case (3%), neonatal death due to heart failure occurred at 2 days old despite intensive cardiac care (Table 2).

Table 2
Clinical characteristics and postnatal course of the persistent hypotension cases in MC tiwn cases.

No of cases	33
Maternal age mean (years)	31 (21–44)
GA at delivery (weeks)	33 + 3 (27 + 2–37 + 3)
Larger twin	22 (66.7)
Discordant rate	0.18 (0.02–0.42)
CTAR	38.1 (19.3–52.0)
UAAREDF	0 (0.0)
DVAREDF	0 (0.0)
TR	11 (36.7)$^{N=30}$
Birth weight (g)	1809 (730–2976)
Z-score of the birth weight	−1.0 (−3.9 to 1.9)
Pretherapeutic systolic bood pressure (mmHg)	40 (27–56)
Pretherapeutic diastolic bood pressure (mmHg)	20 (12–32)
Pretherapeutic mean blood pressure (mmHg)	26 (18–40)
Lowest LVEF (%)	54.5 (20.0–75.1)
Age in days of lowest LVEF (days)	1 (0–4)
Age in days of starting of cardiotonic agent (days)	1 (0–2)
Duration of using cardiotonic agent (days)	4 (1–17)
Discharge without cardiac complications	32 (97.0)
Neonatal death	1 (3.0)

Data are given as median (range) or n (%). GA = gestational age; BE = base excess; CTAR = cardio thoracic ratio; UAAREDF = absent or reversed end diastolic flow in umbilical artery; DVAREDF = absent or reversed end diastolic flow in ductus venosus; TR = tricuspid regurgitation; LVEF = left ventricle ejection fraction.

In larger twins, univariate analysis showed that the persistent hypotension was related to CTAR, Z-score for CTAR, incidence of TR, GA at delivery, birth weight and discordant rate. Multivariate analysis showed that Z-score for CTAR (odds ratio (OR), 2.31; 95% confidence interval (CI), 1.46–3.66; $p < 0.001$), incidence of TR (OR, 6.34; 95%CI, 1.44–27.9; $p = 0.015$) and GA at delivery (OR, 0.66; 95% CI, 0.52–0.84; $p < 0.001$) correlated independently with persistent hypotension of the larger twin (Table 3). The cut-off CTAR and Z-score that predicted persistent hypotension were 36.6% (75.0% sensitivity, 76.1% specificity, area under the curve (AUC) 0.82) and 2.58 SD (85.0% sensitivity, 79.2% specificity, AUC 0.84), respectively.

In smaller twins, univariate analysis showed that persistent hypotension was related to CTAR of the (larger) co-twin, Z-score for CTAR of the co-twin, GA at delivery, birth weight and Z-score for birth weight. Multivariate analysis could not be performed owing to the small number of cases in the persistent hypotension group (Table 4).

BNP in the umbilical vein was significantly higher in the persistent hypotension group of larger twins (517.0 pg/ml) than in the control group of larger twins (33.0 pg/ml; $p < 0.001$). BNP in the umbilical vein was significantly higher in the persistent hypotension group of smaller twins (404.0 pg/ml) than in the control group of smaller twins (33.5 pg/ml; $p = 0.0015$) (Fig. 1). BNP in the umbilical vein in larger and smaller twins showed a significant correlation (coefficient of correlation = 0.792; $p < 0.001$) (Fig. 2).

Discussion

In this study, cardiomegaly in the larger twin correlated with persistent hypotension in both larger and smaller twins. Endocrinological communications were suspected of being the key to the complex pathophysiology of complications in MC twin pregnancies.

Hypotension in the neonatal period is more common in premature infants because of the delays in circulatory transition from intra- to extrauterine life and immature myocardium. Perinatal asphyxia, infection and myocardial dysfunction are reportedly related to neonatal hypotension in singleton pregnancy [18]. The frequency of neonatal hypotension is significantly higher in TTTS cases treated by amnioreduction than in TTTS cases treated by fetoscopic laser photocoagulation or in DC twin cases [8]. Those findings suggest that inter-twin anastomoses affect neonatal hypotension in the twin pregnancy. Although persistent hypotension occurred in both larger and smaller twins, incidence of persistent hypotension with decreased LVEF was significantly higher among larger twins than among smaller twins in the present study. These findings suggest that larger twins were more likely to have persistent hypotension with myocardial dysfunction, while smaller twins had persistent hypotension based on causes other than myocardial dysfunction. Since persistent hypotension in larger and smaller twins was suspected to involve differences in contributing mechanisms, we divided subjects into larger and smaller twins and investigated each associated factors.

Among larger MC twins, not only GA at delivery, but also cardiomegaly and TR correlated independently with neonatal persistent hypotension. Decreased LVEF was observed in more than half of persistent hypotension cases and BNP in the umbilical vein was significantly higher in the persistent hypotension group than in the control group. These findings suggested that neonatal hypotension in the larger twin relates to not only prematurity, but also to decreased cardiac function. Increased heart size and increased BNP suggested volume overload before birth that caused cardiac dysfunction in the neonatal period. Similar findings have also been shown in previous reports. Cardiac hypertrophy and cardiac dysfunction have been reported in both TTTS and non-TTTS

Table 3
Univariate and multivariate analysis of clinical variables for presistent hypotension in larger twins of monochorionic twin pregnancies.

	persistent hypotension	control	Univariate analysis	Multivariate analysis		
	(N = 22)	(N = 294)	p	OR	95% CI	p
Maternal age (years)	31 (21–40)	32 (19–44)	0.96			
CTAR (%)	41.0 (19.3–52)	33.2 (19.1–49)	<0.001			
Z-score of CTAR (SD)	4.0 (−2.9 to 7.9)	1.3 (−3.5 to 6.6)	<0.001	2.31	1.46–3.66	<0.001
CTAR of Co-twin (%)	30.8 (26.6–46.0)	32.0 (17.0–44.2)	0.27			
Z-score of CTAR of Co-twin (SD)	0.76 (−0.7 to 5.4)	0.98 (−4.0 to 4.)	0.71			
UAAREDF	0 (0.0)	1 (0.34)$^{N=290}$	1.00			
DVAREDV	0 (0.0)$^{N=21}$	1 (0.35) $^{N=285}$	1.00			
TR	11 (55)$^{N=20}$	25 (0.14)$^{N=237}$	<0.001	6.34	1.44–2.79	0.015
MVP	4.6 (2.2–11.5)	4.5 (1.8–12.7)	0.48			
GA at delivery (weeks)	33 + 6 (27 + 2 to 37 + 3)	36 + 6 (27 + 5 to 38 + 5)	<0.001	0.66	0.52-0.84	<0.001
birth weight (g)	2072 (838–2976)	2401 (935–3421)	<0.001			
Z-score ob birth weight	−0.62 (−1.80 to 1.86)	−0.58 (−2.54 to 2.25)	0.41			
Discordant rate	0.18 (0.017–0.417)	0.094 (0.002–0.40)	0.004	0.02	0.0001–10.0	0.36
pH of umbilical artery	7.26 (7.14–7.33)	7.27 (7.15–7.37)	0.66			
BE of umbilical artery	−4.4 (−9.0 to -1.7)	−4.3 (−15.0 to 4.0)	0.89			

Data are given as median (range) or n (%). CTAR = cardio-thoracic area ratio; UAAREDF = absent or reversed end diastolic flow in umbilical artery; DVAREDF = absent or reversed end diastolic flow in ductus venosus; TR = tricuspid regurgitation; MVP = maximum vertical pocket; GA = gestational age; BE = base excess; 95% CI:95% confidence intervals.

Table 4
Univariate analysis of clinical variables for presistent hypotension in smaller twins of monochorionic twin pregnancies.

	persistent hypotension (N = 11)	control (N = 305)	Univariate analysis p
maternal age (years)	28 (26–44)	32 (19–43)	0.62
CTAR (%)	33.0 (26.6–43)	32.0 (17.0–46.0)	0.85
Z-score of CTAR (SD)	1.35 (−0.44 to 4.6)	0.95 (−4.0 to 5.4)	0.37
CTAR of Co-twin (%)	36.3 (19.3–43.0)	33.5 (19.1–52.0)	0.038
Z-score of CTAR of Co-twin (SD)	2.82 (−2.88 to 4.82)	1.40 (−3.51 to 7.90)	0.015
UAAREDF	0 (0.0)	0 (0.0) $^{N=302}$	1.00
DVAREDF	0 (0.0) $^{N=10}$	0 (0.0) $^{N=297}$	1.00
TR	0 (0.0) $^{N=10}$	11 (4.4) $^{N=248}$	1.00
MVP	5.4(2.6–7.9)	4.3(1.0–12.7)	0.093
GA at delivery (weeks)	33 + 0 (27 + 3 to 36 + 1)	36 + 6 (27 + 5 to 38 + 5)	<0.001
birth weight (g)	1422 (730–2049)	2138 (801–3133)	<0.001
Z-score of birth weight	−2.31 (−3.92 to 0.26)	−1.42 (−4.05 to 1.58)	0.009
Discordant rate	0.15 (0.03–0.35)	0.095 (0.002–0.42)	0.065
pH of umbilical artery	7.24 (7.17–7.37)	7.27 (7.10–7.44)	0.37
BE of umbilical artery	−5.5 (−10.0 to −2.0)	−4.2 (−20.8 to 4.3)	0.109

Data are given as median (range) or n (%). CTAR = cardio-thoracic area ratio; UAAREDF = absent or reversed end diastolic flow in umbilical artery; DVAREDF = absent or reversed end diastolic flow in ductus venosus; TR = tricuspid regurgitation; MVP = maximum vertical pocket; GA = gestational age; BE = base excess.

cases. Simpson et al. reported that eight of 12 recipients of TTTS cases managed with amnioreduction showed cardiac chamber dilation and decreased ventricular contractility [10]. Catherine et al. reported that among the recipients of TTTS cases managed with amnioreduction, diastolic dysfunction appeared from the initial stage, and systolic dysfunction was seen in progressive cases [11]. On the other hand, Kondo et al. reported a case of MC twins in which the larger fetus showed cardiac hypertrophy even without TTTS. The neonate in that report needed catecholamine to manage hypotension and oliguria immediately after birth [13]. Cardiac enlargement is not considered rare among TTTS cases and should be noted even in non-TTTS cases. Increased fetal blood and amniotic fluid levels of BNP are reportedly related to recipient cardiac dysfunction in TTTS [12,27]. Several larger twins in this study did not have TTTS, but were considered to have hemodynamics similar to recipients of TTTS. Despite the suspected similar hemodynamics, the reason why TTTS did not develop is uncertain, but the endocrinological paradox may have provoked this situation. Mahieu-Caputo et al. reported a recipient of TTTS in whom umbilical cord blood levels of renin and aldosterone were increased, although renal secretion of renin was down-regulated [28]. This report suggested that MC twins show endocrinological communication, which may cause a paradoxical endocrinological environment counteracting the feedback that should originally occur. In this study, BNP in the umbilical vein in larger and smaller twins showed a strong correlation. This finding suggested that communication of endocrinological factors and a paradoxical endocrinological environment might have occurred in the cases. Assuming transmission of the renin-angiotensin system, a conflicting endocrine environment from the co-twin may inhibit urine production, which should originally be increased. Despite TTTS-like hemodynamics, a contradictory endocrine environment may lead to a situation that does not satisfy the diagnostic criteria for TTTS. There is a possibility that MC twins receive chronic cardiac load in the fetal period even in the absence of TTTS.

In MC twins, neonatal persistent hypotension in the smaller twin was unrelated to cardiomegaly in that individual, but was related to cardiomegaly in the co-twin. Decreased LVEF in smaller twins was rare. These findings suggest that the cause of persistent hypotension in the smaller twin was not cardiac dysfunction in the individual, but was affected by cardiac dysfunction in the larger twin. The reason blood pressure in the smaller twin was affected by cardiac dysfunction in the larger twin was uncertain, but may be related to endocrinological communication through the inter-twin

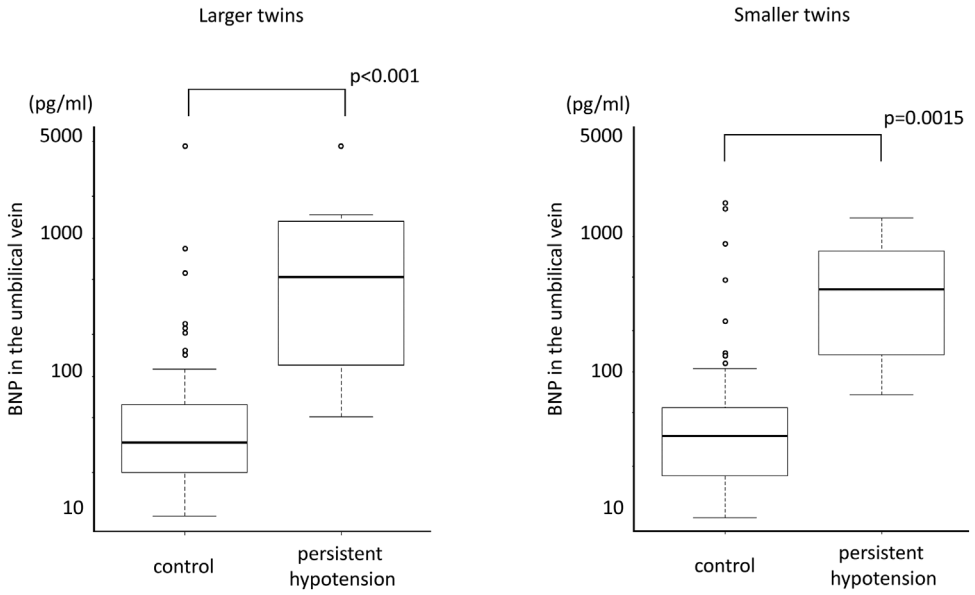

Fig. 1. Comparison of BNP values in the umbilical vein between Control and Persistent Hypotension groups.
BNP was significantly higher in the umbilical vein in the Persistent Hypotension group of larger twins (517.0 pg/ml) than in the Control group of larger twins (33.0 pg/ml, $p < 0.001$). BNP in the umbilical vein was significantly higher in the Persistent Hypotension group of smaller twins (404.0 pg/ml) than in the Control group of smaller twins (33.5 pg/ml, $p = 0.0015$).

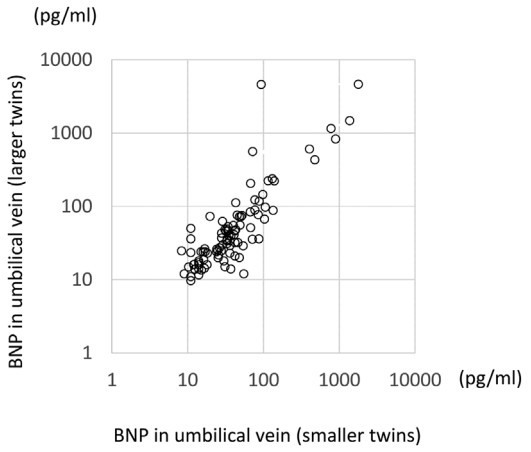

Fig. 2. Correlation between BNP concentrations in the umbilical veins of larger and smaller twins.
BNP concentrations in the umbilical veins of larger and smaller twins showed a significant correlation (coefficient of correlation = 0.792, $p < 0.001$).

anastomoses. In our study, BNP in the umbilical vein of the larger and smaller twins was significantly correlated. Assuming that BNP secreted by a larger twin undergoing volume overload had been transported to the smaller twin via a vascular anastomosis, this may have caused diuresis or vasodilatation that would not occur in the smaller twin. Cardiomegaly in the larger twin was suggested to be related to neonatal hypotension in the smaller twin.

Two main limitations need to be considered for this study. The first limitation was the shortage of cases of persistent hypotension among smaller twins. Because of the small number of positive cases, multivariate analysis for smaller twins was impossible. The second limitation was that no data were available regarding the renin-angiotensin system. Endocrinological proof is needed to explain the pathophysiology of persistent hypotension in both larger and smaller twins that occurred even without TTTS. A prospective study should be planned to cover endocrinological analyses in detail.

Hypotension in the neonatal period should be treated carefully, because of the relationships with short- and long-term outcomes of premature babies [15–17]. This phenomenon may occur in all twins that have inter-twin anastomoses. Careful observation and management are warranted for all MC twins even without TTTS and abnormal Doppler findings. In conclusion, not only the amount of amniotic fluid and estimated body weight, but also fetal heart size should be surveyed when managing MC twins. When cardiomegaly in a larger twin is observed, careful neonatal management is needed not only for the larger twin, but also for the smaller twin.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Lee YM, Wylie BJ, Simpson LL, D'Alton ME. Twin chorionicity and the risk of stillbirth. Obstet Gynecol 2008;111:301–8.
[2] Adegbite AL, Castille S, Ward S, Bajoria R. Neuromorbidity in preterm twins in relation to chorionicity and discordant birth weight. Am J Obstet Gynecol 2004;190:156–63.
[3] Hack KE, Derks JB, Elias SG, et al. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. BJOG 2008;115:58–67.
[4] Berghella V, Kaufmann M. Natural history of twin-twin transfusion syndrome. J Reprod Med 2001;46:480–4.
[5] Gratacós E, Lewi L, Muñoz B, et al. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. Ultrasound Obstet Gynecol 2007;30:28–34.
[6] Ishii K, Murakoshi T, Takahashi Y, et al. Perinatal outcome of monochorionic twins with selective intrauterine growth restriction and different types of umbilical artery Doppler under expectant management. Fetal Diagn Ther 2009;26:157–61.

[7] Robyr R, Lewi L, Salomon LJ, et al. Prevalence and management of late fetal complications following successful selective laser coagulation of chorionic plate anastomoses in twin-to-twin transfusion syndrome. Am J Obstet Gynecol 2006;194:796–803.
[8] Lenclen R, Paupe A, Ciarlo G, et al. Neonatal outcome in preterm monochorionic twins with twin-to-twin transfusion syndrome after intrauterine treatment with amnioreduction or fetoscopic laser surgery: comparison with dichorionic twins. Am J Obstet Gynecol 2007;196(450):e1–7.
[9] Zosmer N, Bajoria R, Weiner E, Rigby M, Vaughan J, Fisk NM. Clinical and echographic features of in utero cardiac dysfunction in the recipient twin in twin-twin transfusion syndrome. Br Heart J 1994;72:74–9.
[10] Simpson LL, Marx GR, Elkadry EA, D'Alton ME. Cardiac dysfunction in twin-twin transfusion syndrome: a prospective, longitudinal study. Obstet Gynecol 1998;92:557–62.
[11] Barrea C, Alkazaleh F, Ryan G, et al. Prenatal cardiovascular manifestations in the twin-to-twin transfusion syndrome recipients and the impact of therapeutic amnioreduction. Am J Obstet Gynecol 2005;192:892–902.
[12] Bajoria R, Ward S, Chatterjee R. Natriuretic peptides in the pathogenesis of cardiac dysfunction in the recipient fetus of twin-twin transfusion syndrome. Am J Obstet Gynecol 2002;186:121–7.
[13] Kondo Y, Hidaka N, Yumoto Y, Fukushima K, Tsukimori K, Wake N. Cardiac hypertrophy of one fetus and selective growth restriction of the other fetus in a monochorionic twin pregnancy. J Obstet Gynaecol Res 2010;36:401–4.
[14] Fujioka K, Mizobuchi M, Sakai H, et al. N-terminal pro-brain natriuretic peptide levels in monochorionic diamniotic twins with selective intrauterine growth restriction. J Perinatol 2014;34:6–10.
[15] Miall-Allen VM, de Vries LS, Whitelaw AG. Mean arterial blood pressure and neonatal cerebral lesions. Arch Dis Child 1987;62:1068–9.
[16] Watkins AM, West CR, Cooke RW. Blood pressure and cerebral haemorrhage and ischaemia in very low birthweight infants. Early Hum Dev 1989;19:103–10.
[17] Goldstein RF, Thompson [119_TD$DIFF]Jr RJ, Oehler JM, Brazy JE. Influence of acidosis, hypoxemia, and hypotension on neurodevelopmental outcome in very low birth weight infants. Pediatrics 1995;95:238–43.
[18] Shead SL. Pathophysiology of the cardiovascular system and neonatal hypotension. Neonatal Netw 2015;34:31–9.
[19] Awadh AM, Prefumo F, Bland JM, Carvalho JS. Assessment of the intraobserver variability in the measurement of fetal cardiothoracic ratio using ellipse and diameter methods. Ultrasound Obstet Gynecol 2006;28:53–6.
[20] Chaoui R, Heling KS, Bollmann R. Sonographische Messungen am fetalen Herzen in der Vierkammerblick-Ebene. Geburtshilfe Frauenheilkd 1994;54(2):92–7.
[21] Development of audit measures and guidelines for good practice in the management of neonatal respiratory distress syndrome. Report of a Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians. Arch Dis Child 1992;67:1221–7 No authors listed.
[22] Terminology and Diagnostic Criteria Committee of The Japan Society of Ultrasonics in Medicine. Standard measurement of cardiac function indexes. J Med Ultrason 2006;33(2):123–7.
[23] Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. J Perinatol 1999;19:550–5.
[24] Gratacós E, Lewi L, Carreras E, et al. Incidence and characteristics of umbilical artery intermittent absent and/or reversed end-diastolic flow in complicated and uncomplicated monochorionic twin pregnancies. Ultrasound Obstet Gynecol 2004;23:456–60.
[25] Slaghekke F, Kist WJ, Oepkes D, et al. Twin anemia-polycythemia sequence: diagnostic criteria, classification, perinatal management and outcome. Fetal Diagn Ther 2010;27:181–90.
[26] Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Vandenbussche FP, Walther FJ. Hematological characteristics in neonates with twin anemiapolycythemia sequence (TAPS). Prenat Diagn 2010;30:251–5.
[27] Habli M, Cnota J, Michelfelder E, et al. The relationship between amniotic fluid levels of brain-type natriuretic peptide and recipient cardiomyopathy in twin-twin transfusion syndrome. Am J Obstet Gynecol 2010;203(404):e1–7.
[28] Mahieu-Caputo D, Meulemans A, Martinovic J, et al. Paradoxic activation of the renin-angiotensin system in twin-twin transfusion syndrome: an explanation for cardiovascular disturbances in the recipient. Pediatr Res 2005;58:685–8.