Original Article

Mean Arterial Pressure in Very Low Birth Weight (801 to 1500 g) Concordant and Discordant Twins During the First Day of Life

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OBJECTIVE:
To determine retrospectively mean arterial pressure (MAP) for stable and unstable concordant and discordant very low birth weight (VLBW: 801 to 1500 g) twins during the first 24 hours of life.

BACKGROUND:
Morbidity and mortality are much higher for extremely low birth weight (ELBW $\leq$800 g) than for VLBW twins. Recently, we reported MAP trends and reference values in concordant and discordant ELBW twins. No comparable information is available for VLBW infants.

DESIGN:
Retrospective cohort study.

METHODS:
We studied 48 sets of concordant and 40 sets of discordant (birth weight difference $\geq$20%) consecutively born VLBW twins. Stable patients were defined as having umbilical cord hemoglobin $\geq$14 g/dl, nonacidotic blood gases, never treated for hypotension and survived at least 7 days. MAPs (Torr) were measured by oscillometry in 3163 and by transducer via umbilical artery in 2028 instances.

RESULTS:
Concordant and discordant twins were similar in demographics, history of twin–twin transfusion (TTTX), antenatal steroids, chorioamnionitis, preeclampsia, cesarean delivery, cord hemoglobin, normal head ultrasounds or I to II intracranial hemorrhage (97 and 99%) and neonatal mortality (4 and 5%), but were different in incidence of preterm labor (83 and 58%), birth weight (1227 and 1509 g) and gestational age (GA) (30 and 32 weeks). In all, 66 (69%) concordant twins and 61 (76%) discordant twins were stable. Stable concordant twins, whether small or large, had comparable MAP on admission that increased to 24 hours. Twins of $\leq$32 weeks GA had lower MAP throughout than those of $\geq$33 weeks GA. Although their mean birth weights were similar (1262 and 1274 g), 23 stable concordant males had significantly higher MAP than 43 concordant females. Stable discordant twins were divided into 31 small (1241 g) and 30 large (1845 g); their MAPs were different ($p<0.05$): 35 and 39 (admission), 35 and 39 (1 hour), 36 and 46 (6 hours), 38 and 41 (12 hours), 40 and 41 (18 hours) and 42 and 42 (24 hours) Torr. In all, 88% of small discordant twins were IUGR and 91% of large discordant twins had normal growth. TTTX syndrome occurred in 12 monochorionic sets. Nine of 12 donors were IUGR while 10 of 12 recipients had normal growth. Four of 12 donors had grades III to IV intracranial hemorrhage, eight donors and all 12 recipients had normal ultrasounds. Although their cord hemoglobin levels were similar, donor and recipient MAPs were higher than in any other group and, opposite to concordant and discordant twins, their values decreased from birth to 24 hours.

CONCLUSION:
In stable concordant, stable discordant, and small and large discordant twins, MAP correlates with birth weight, GA and postnatal age, and increases during the first 24 hours. In recipient and donor twin–twin transfusion infants, MAP is higher throughout and declines over time.
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INTRODUCTION

Recent advances in maternal – fetal medicine and neonatal care make the survival of premature infants likely.[1] Morbidity and mortality, however, are markedly different between extremely low birth weight (ELBW <800 g) and very low birth weight (VLBW 801 to 1500 g) infants. Twins have higher perinatal mortality and morbidity, especially discordant infants whose risks are associated not only with prematurity but with discordancy itself.[2,3] Twin–twin transfusion syndrome (TTTX) affects a significant number of monochorionic twins and represents a group with unique fetal growth and cardiovascular compromises.[2–6] Arterial pressure monitoring is essential in the management of these critically ill infants because systemic hypotension associates with short- and long-term sequelae and mortality.[7–11] Hypotension that is prevalent in the first 24 hours of life should have timely treatment.[12–14] Unfortunately, treatment is often based on arbitrary blood pressure values with no physiological relevance.[13,15] Furthermore, mean arterial pressure (MAP) reference values for

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specific populations such as twins have not been readily available. We recently reported that MAP for concordant and discordant ELBW infants increases from birth to 24 hours and noted that in this cohort that small discordant twins and twin–twin transfusion donors were intrauterine growth restricted (IUGR) and had MAP commensurable to their gestational age (GA) and not to their birth weight.[16]

The purpose of this retrospective investigation was to determine MAP for concordant and discordant VLBW (801 to 1500 g) twins with and without TTTX syndrome during the first 24 hours of life and to compare trends and reference values with those of ELBW twins reported earlier.[16]

Study Population

A total of 48 sets of concordant VLBW (all 801 to 1500 g) and 40 sets of discordant VLBW twins (at least one infant of each set weighed 801 to 1500 g) born alive between 1998 and 2002 were studied. All infants were considered viable; therefore, in all cases there was intention to treat. For comparison purposes, concordant as well as discordant twins were divided into *stable* and *unstable* groups. Infants were considered stable when the following criteria were met; umbilical cord hemoglobin ≥ 14 g/dl, normal acid–base balance during the first 24 hours, no clinical evidence of a patent ductus arteriosus, no indomethacin, steroids, muscle relaxant or narcotic treatment, no hypotension treatment (packed red blood cells, inotropic agents, colloids) and survival for at least 7 days. The remaining infants were considered unstable.

METHODS

Demographic and clinical data were obtained from medical records. This study was approved by our Institutional Review Board. GA was determined by first trimester ultrasound or by obstetrical dating of the pregnancy and examination of the newborn infant. Discordancy was calculated using the inter-twin birth weight difference expressed as a percentage of the larger twin's birth weight.[2,3,16,17] Discordancy $\geq 20\%$ separated discordant from concordant twins. Zygosity was determined prenatally by ultrasound and postnatally by placental examination.[18] TTTX was diagnosed in identical twins by discordance in fetal weight and ultrasonographic documentation of polyhydramnios in one and oligohydramnios in the other.[2,17,19] Significant differences in umbilical cord hemoglobin, which are indicative of acute but not of chronic TTTX, were not used as diagnostic criteria.[2]

Birth weight and GA for all subgroups described above were plotted in fetal growth nomograms specific for monochorionic and dichorionic twins.[20] Those twins who plotted at the 10th percentile or lower were considered IUGR.

All ELBW infants were treated empirically with ampicillin (100 mg/kg/day i.v. given in two doses every 12 hours) and gentamicin (5 mg/kg/day i.v. given every 48 hours) for 2 days if blood cultures were negative. Mechanical ventilation was performed with a neonatal pressure-limited time-cycled ventilator and, when indicated, with a high-frequency device. Umbilical arterial catheterization was performed for blood gas monitoring, and umbilical or central venous catheters were used for long-term parenteral nutrition. During placement of these lines, no more than 3 ml of saline was used for flushing, followed by a continuous infusion of 100 ml/kg/day D5W. Exogenous surfactant Survanta® (Ross Products Division, Abbott Laboratories, Columbus, OH) was given at the manufacturer's recommended dosage.

Blood Pressure Measurements

On admission to the NICU, systolic, diastolic and mean blood pressures were obtained in all limbs by the oscillometric technique (Dinamap, Criticon, Inc., Tampa, FL until 1995 and Horizon XL, Mennen Medical Corp., Clarence, NY from 1996 to 2002) using a cuff size 1 to 3 (Criticon, Inc., Tampa, FL). Blood pressures were then measured continuously with a disposable pressure transducer (98-4527-RI Abbott Critical Care Systems, Chicago, IL) connected to a single lumen umbilical arterial catheter (Argyle 3.5 F) filled with saline or 5% dextrose in water. The catheter was positioned between T-7 and T-10 into the abdominal aorta. This system was calibrated with zero reference at midchest level.

Statistical Analysis

Comparisons between groups and subgroups were made with Student's *t*-test for interval and χ^2 analysis for categorical data. MAPs obtained by oscillometry in 3163 and by direct transducer in 2028 were reported in mmHg (torr). MAPs recorded during short periods of high-frequency ventilation were not included in the analysis. Stepwise multiple linear regressions were made for prediction of MAP on admission to the NICU and at 2, 4, 6,12,18 and 24 hours of life by gender, race, GA, birth weight, percent of discordancy in birth weight, intrauterine growth restriction, history of preterm labor, chorioamnionitis, pre-eclampsia, antepartum steroids, acute and chronic fetal distress, mode of delivery, Apgar scores, intratracheal epinephrine administration, umbilical cord hemoglobin and skin temperature. Regression analysis was used to determine mean MAP and 80% confidence limits at hourly intervals for concordant, discordant and TTTX twin groups as to condition (stable), gender (male and female) and birth weight (large and small). Values are reported as mean, standard deviation (SD), range and median.

RESULTS

Concordant and discordant twins were similar in demographics, zygosity, history of TTTX, chorioamnionitis, pre-eclampsia, antenatal steroids and incidence of cesarean delivery. They were different in history of preterm labor, mean birth weight (1227 and 1509 g), GA (30 and 32 weeks) and in percent of stable infants (69 and 76%) (Table 1).

Table 1 Study Population

	Concordant	Discordant
No. of twin sets	48	40
Identical (%)	12 (24)	18 (45)
Preterm labor (%)	39 (83)	23 (58)*
Chorioamnionitis (%)	4 (9)	0
Antepartum steroids (%)	38 (81)	36 (90)
Pre-eclampsia (%)	3 (6)	7 (18)
Cesarean section (%)	36 (77)	34 (85)
No. of live births	96	80
Birth weight (g)	1227±244	1509±438*
Gestational age (weeks)	30±2	32±2*
Twin–twin TX (%)	8 (10)	16 (20)
No. of stable pts. (%)	66 (69)	61 (76)*
Neonatal mortality (%)	4 (4)	4 (5)

Mean±SD.
*$p<0.05$.

During the first 24 hours of life, 120 of 176 (68%) infants were conventionally ventilated at rates ranging from 20 to 50 (median 26), peak inflation pressures from 16 to 33 (median 18) cm H_2O and end expiratory pressures from 4 to 6 cm H_2O (median 5). For short periods, four concordant twins and one discordant twin were also treated with high-frequency ventilation. During the first 6 hours of life, arterial blood gases in all patients were normal, with the exception of moderate metabolic acidosis in two concordant twins. Severe respiratory acidosis was noted in one concordant and one discordant twin. In all, 64 of 98 (65%) concordant and 34 of 76 (45%) discordant twins received exogenous surfactant.

Four of 96 (4%) concordant and four of 80 (5%) discordant twins (all but one of less than 30 weeks GA) died during the neonatal period. Of those twins without TTTX, one infant had lung hypoplasia, two had intractable respiratory failure and one had necrotizing enterocolitis. Four infants had TTTX, which associated with pulmonary hemorrhage in one case, with pulmonary hypoplasia in two and with late-onset sepsis in the other. The unique morbidity and mortality of the 24 infants with TTTX syndrome prompted us to treat them as a separate group.

Head ultrasounds were obtained during the first 2 days of life in 172 of 176 (98%) of twins. Normal head ultrasounds were observed in 86 (88%) concordant, 50 (89%) discordant and 18 (75%) of TTTX infants. Intracranial hemorrhage (Papile's classification)[21] grades I to II was noted in nine (9%) concordant, six (11%) discordant and two (8%) TTTX infants. Grades III to IV were found in one (1%) concordant and in four donor (17%) TTTX infants, but none were present among discordant twins or recipient TTTX. Periventricular leukomalacia was observed at 4 weeks of life in one discordant large infant who had a normal ultrasound at birth.

Stable Concordant and Discordant Twins

Stepwise multiple linear regression shows that gender, race, GA, birth weight, percent discordancy in birth weight, intrauterine growth restriction, history of preterm labor, chorioamnionitis, pre-eclampsia, antepartum steroids, acute and chronic fetal distress, mode of delivery, Apgar scores, intratracheal epinephrine administration, umbilical cord hemoglobin and skin temperature did not independently predict MAP on admission to the NICU or at 2, 4, 6, 12, 18 and 24 hours.

From 1 to 24 hours of life, MAP increased from 36 to 41 Torr for 66 stable concordant and from 37 to 42 Torr for 61 stable discordant twins (Figure 1a,b). MAP and 10th percentile values for stable concordant infants at 1, 3, 6, 12, 18 and 24 hours were 36 (25), 36 (26), 37 (27), 38 (28), 39 (29) and 41 (30) Torr, respectively. MAP and 10th percentile values from 61 stable discordant infants at 1, 3, 6, 12, 18 and 24 hours were 37 (25), 37 (25), 38 (26), 39 (27), 40 (29) and 42 (30) Torr, respectively.

Concordant Twins

In all, 66 stable concordant twins were divided according to gender: 23 male and 43 female twins were similar in birth weight, GA and perinatal factors. Concordant stable male twins always had higher MAPs than their female counterparts. These differences were statistically significant at 5, 6, 13, 16, 18 and 22 hours of age (40 and 35*), (40 and 36*), (44 and 37*), (41 and 37*), (44 and 38*) and (43 and 38*) Torr, respectively.

Stable concordant twin pairs, excluding TTTX, were divided according to birth weight into 30 large (1317±242 g) and 30 small (1216±208 g) infants. These birth weight differences were not statistically significant. Comparisons from fetal growth nomograms showed that 61 of 96 (64%) concordant twins were between the 10th and 90th percentiles. Two infants were above the 90th percentile while the remaining 33 (34%) were at or below the 10th percentile. Mean MAP and 10th percentile for selected hours are

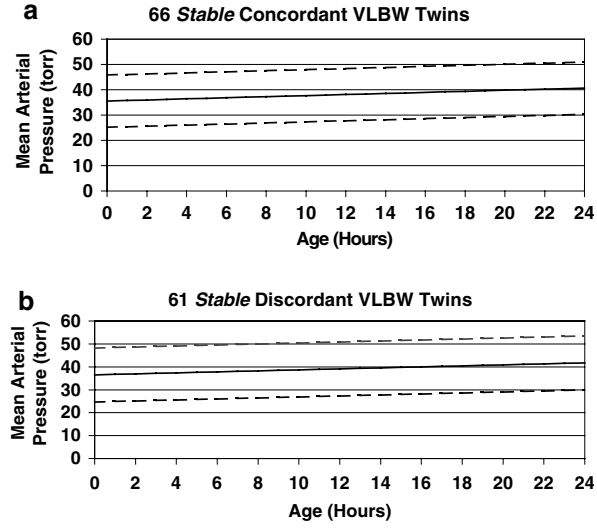

Figure 1. Regression lines and 80% confidence limits: stable concordant MAP = 0.213 × hours+35.55; stable discordant MAP = 0.218 × hours+36.50.

Table 2 Mean Arterial Pressure (Torr): Mean (10th) Percentiles by Diagnosis and Postnatal Age

	No. of pts	Birth weight (g)	GA (weeks)	1 hour	3 hours	6 hours	12 hours	18 hours	24 hours
Small concordant	30	1216±208	30±2	36 (25)	36 (25)	37 (26)	38 (27)	39 (28)	40 (29)*
Small discordant	31	1241±259	32±2	35 (24)	35 (25)	36 (26)	38 (27)	40 (29)	42 (39)*
Small TTTX (donor)	12	1060±261	31±2	40 (19)	40 (19)	40 (19)	40 (19)	40 (19)	40 (19)
Large concordant	30	1317±242	30±2	36 (26)	36 (26)	37 (27)	38 (28)	39 (30)	41 (31)*
Large discordant	30	1845±380	32±2	39 (27)	39 (27)	40 (28)	41 (28)	41 (29)	42 (30)*
Large TTTX (recipient)	12	1480±440	31±2	43 (28)	43 (28)	42 (28)	42 (27)	41 (26)	40 (26)

Mean±SD.
GA: gestational age.
Simple linear regression *$p<0.01$.

presented in Table 2. Large as well as small infants showed a steady increase of MAP from the first hour (35 and 36 Torr) to 24 hours (40 and 41 Torr). In spite of wide individual variations, no differences in MAP were noted between the two groups. MAP values for 48 concordant $\leq$32 weeks and 32 infants $\geq$33 weeks GA at 1, 3, 6, 12, 18 and 24 hours were statistically different at selected times (36 and 36), (36 and 35), (38 and 40*), (40 and 42*), (41 and 43*) and (42 and 43) Torr, respectively.

Discordant Twins

Groups of discordant twins without TTTX syndrome were divided by size into 31 small (1241±259 g) and 30 large (1845±385 g) groups of infants (one infant from the latter group was unstable, therefore the groups remained uneven). Comparison between these subgroups showed similarities in race, gender, GA and neonatal mortality. Among 30 large discordant twins without TTTX, four (13%) plotted above the 90th percentile and 26 (87%) between the 10th and 90th percentiles. In all, 28 of 31 (90%) small discordant twins without TTTX fell below the 10th percentile, while the remaining three were between the 10th and 90th percentiles. MAP regression lines and 80th percentile confidence limits for large discordant and small discordant infants without TTTX are presented in Figure 2a and b. Both groups of infants had a wide range of individual values but still showed steady increases in MAP from 1 to 24 hours. Large discordant infants always had higher MAPs than small discordant twins, and these differences were statistically significant at 1, 2, 4, 5, 8, 9, 11 and 13 hours (Table 2).

A total of 61 stable discordant infants were grouped according to gender: 29 male and 32 female twins were similar in GA and perinatal factors and were significantly different in birth weight. Mean arterial pressure values were similar through the 24-hour observation period.

Twin–Twin Transfusion (TTTX)

The characteristics of the 12 sets of twins that suffered from TTTX syndrome (TTTX) are shown in Table 3. Only eight of 12 sets of twins were noted to be discordant in birth weight by the above-described criteria. In all, 11 of 12 (92%) large TTTX (recipients)

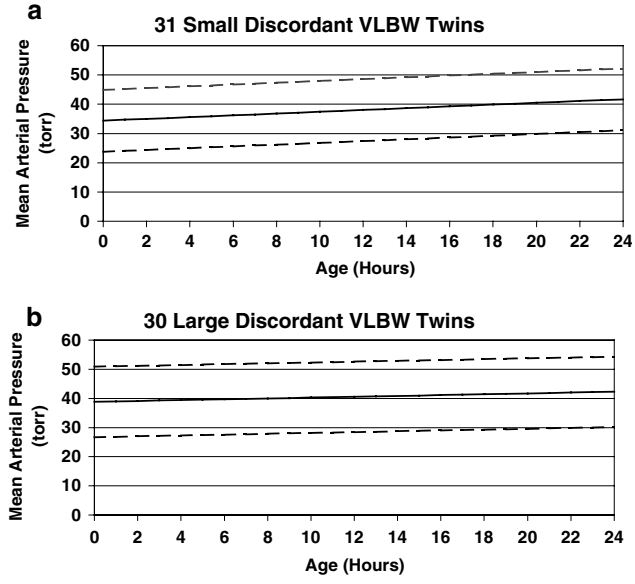

Figure 2. Regression lines and 80% confidence limits: small discordant MAP = 0.30 × hours+34.38; large discordant MAP = 0.143 × hours+38.35.

plotted between the 10th and 90th percentiles, while one nonhydropic infant was above the 90th percentile. Nine of 12 (75%) small TTTX infants (donors) were below the 10th percentile, while three were between the 10th and 30th percentiles.

There were significant differences noted between the donor and the recipient twins in birth weight and incidence of IUGR. No significant differences were found in cord hemoglobin, number of unstable infants and mortality.

Simple MAP regression lines are presented in Figure 3a and b, and selected MAP values are shown in Table 2. Recipient twins in the TTTX syndrome group started at higher initial MAPs than either the large concordant or large discordant twins. MAP declined over the first 24 hours in contrast to the large concordant and large discordant twins for whom there was a sustained increase in MAP. Donor TTTX twins also started at higher initial MAP when

Table 3 Characteristics of 24 VLBW with Twin–Twin Transfusion Syndrome

	Donor	Recipient
No. of infants	12	12
Birth weight (g)	1060±261	1480±420*
Gestational age (weeks)	31±2	31±2
Fetal growth ≤10 percentile	9(75)	0*
Fetal growth 11–89 percentile	3(25)	11(92)
Fetal growth ≥90 percentile	0	1 (8)
Cord hemoglobin (g/dl)	15±5	16±4
Stable (no.)	5 (42)	6 (50)
Head u/s		
Normal or grades I–II	8(67)	12(100)*
Grades III–IV	4(33)	0
Neonatal mortality (%)	3(25)	1(10)

Mean±SD.
u/s=ultrasound.
*$p<0.05$.

compared to the smaller of the concordant and discordant twins, but MAP remained unchanged during the first 24 hours. MAP values are also presented in Table 3 for 1, 3, 6, 12, 18 and 24 hours of life.

DISCUSSION

Oscillometry is easy to use and measures blood pressure well when the correct cuff size is used.[21] Arterial pressure measurements through a 3.5 F umbilical catheter, although reproducible, could be affected by signal dampening.[22,23] To avoid this, we used MAP and not systolic and diastolic measurements. Since many investigators[14,24–27] have documented good correlation between the two methods, we analyzed 3163 oscillometric readings together with 2028 direct pressure determinations.

Our study population was selected by birth weight because it is an objective reference, whereas GA estimates, unless obtained by first trimester ultrasound, are of limited value. We focused on the first 24 hours of life because that is when hypotension is usually diagnosed and treated.[12,14] Later, many variables such as a patent ductus arteriosus preclude recognition of a stable population.[28] In

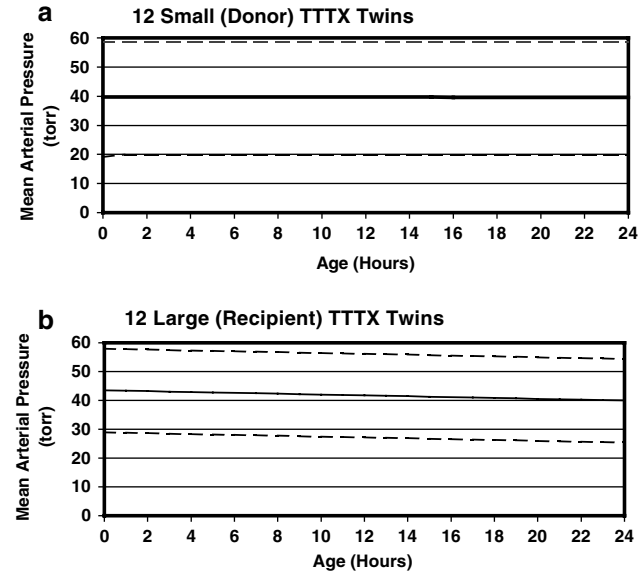

Figure 3. Regression lines and 80% confidence limits: TTTX small MAP = 0.001 × hours+40.01; TTTX large MAP = 0.110 × hours+43.105.

defining our stable group, like others, we excluded factors that affect blood pressure,[8–10] but allowed others, which are now known not to influence MAP in ELBW infants.[11,14,16] As in earlier investigations,[14,16] we found that history of pre-eclampsia, antenatal steroid usage, umbilical cord hemoglobin,[1] intratracheal epinephrine administration and skin temperature on admission did not influence MAP.

Obtaining reference values from stable populations such as concordant and discordant twins of different birth weights is important. ELBW infants, especially those of ≤26 weeks GA, are seldom stable[16] and have a higher mortality than the more mature VLBW infants. Until now, it was not known if MAP trends and correlations noted in ELBW twins were also present in VLBW infants, a group of more stable patients less likely to experience hypotension. We are reporting that, among concordant and discordant VLBW twins without TTTX, birth weight, GA and postnatal age influence MAP during the first 24 hours of life. To highlight the similarities in trend and the differences in MAP values between ELBW and VLBW stable concordant twins, we

Table 4 Mean Arterial Pressure (Torr): Mean (10th) Percentiles by Birth Weight/Postnatal Age in Concordant twins

	No. of pts.	Birth weight (g)	GA (weeks)	1 hours	3 hours	6 hours	12 hours	18 hours	24 hours
Stable ELBW**	14	700±84	25±1	29 (21)	29 (21)	30 (22)	31 (23)	33 (25)	35 (26)*
Stable VLBW	66	1285±250	30±2	36 (25)	36 (26)	37 (27)	38 (28)	39 (29)	41 (30)*

Mean±SD.
GA: gestational age, ELBW: extremely low birth weight, VLBW: very low birth weight.
Simple linear regression *$p<0.01$.
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constructed a table with data from the present and from a previous investigation[16] (Table 4).

By direct observation and by linear regression, several investigators noted a strong correlation between GA and blood pressure for full-term and premature infants[11,22,23,26,27,29,30] and that, at the same birth weight, singletons of older gestation had higher MAP. We corroborated that observation for ELBW[16] and, in the present investigation, for VLBW concordant and discordant twins.

Large discordant VLBW twins without TTTX are appropriate for GA and have been shown to be hemodynamically comparable to normal singletons in utero. Thus, during early neonatal life, their MAP should be similar to those of singletons of comparable GA, postnatal age and birth weight.[5]

Small discordant VLBW twins without TTTX are usually IUGR, and their MAPs during the first 24 hours of life are lower than those of their larger siblings. In utero, small discordant twins have blood flow velocity waveforms, including the descending aorta and cerebral vasculature, similar to those of IUGR singletons.[5] Preferential decrease in organ blood flow may initiate changes on arterial structures[31,32] or prompt the release of vasoconstrictors (i.e. endothelin-1,[33] angiotensin-II[34]) that may ultimately contribute to the pathogenesis of cardiovascular disease in the adult.[35]

We reported that ELBW TTTX recipients, unlike large discordant twins, start with very high MAPs that slowly decline over the first 24 hours of life.[16] This trend, unique to TTTX recipients, was again seen in our present study with VLBW twins. Since most of the recipients in both investigations did not have polycythemia, it is likely that these MAP values are due to a more complex mechanism. TTTX is thought to result from an unbalanced fetal blood supply through placental arteriovenous anastomoses. As a result of acute or chronic transfusions, the recipient becomes hypervolemic, polycythemic, may develop cardiomegaly, right ventricular hypertrophy, decreased right ventricular shortening fractions, triscupid regurgitation, high flow velocities, hydrops, pulsatile venous waveforms and left ventricular involvement.[6,31] Since there is no correlation between cardiac dysfunction in utero and differences in hemoglobin concentration at birth, the traditional explanation of circulatory overload for the recipient is an oversimplification.[36] Hemodynamic abnormalities in the recipient may also result from increased right ventricular afterload.[6,36] Regardless of pathogenesis, ventricular hypertrophy can occur and has been associated with systemic arterial hypertension in some neonates.[31,37–39] Another contributing factor to cardiac dysfunction (i.e. fetal hypertension) may be the higher levels of endothelin-1 and hypertensin-II found in umbilical cords of recipients when compared with donors.[33] In the donor, chronic hypovolemia activates the renin – angiotensin system, and the availability of renin to the recipient may further fetal and perhaps neonatal hypertension.[40]

Our data show that, on average, MAPs for VLBW donors start at higher levels than those of small discordant twins without TTTX, and did not increase or decrease during the 24-hour period. These data conflict with those reported by us earlier[16] where ELBW donors (mean birth weight 617 g, GA 27 weeks and cord hemoglobin 10 g/dl) had lower MAPs than small discordant twins without TTTX at birth and showed similar increasing trends throughout the first day. We interpreted these findings to reflect anemia and hypovolemia. In the current investigation, however, VLBW donor infants (mean birth weight 1060 g, GA 31 weeks and cord hemoglobin 15 g/dl) have higher MAPs than concordant and small VLBW discordant twins without TTTX. Whether differences in MAP between the groups of donors described above are related to different birth weights, GA or, more importantly, hemoglobin concentrations deserve further investigation.

In summary, we present MAP reference values for stable concordant and discordant VLBW twins and note that similar to ELBW twins there is a positive correlation with birth weight, GA and postnatal age. Concordant and large discordant VLBW twins without TTTX behaved like singletons of comparable GA. Small discordant twins and donor TTTX are IUGR, while their large counterparts are appropriate for GA. Recipients and donors have higher MAP values than concordant and discordant twins of comparable birth weights and GA. In TTTX, cardiovascular adaptations rather than fetal growth disorders alone may influence MAP.

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