Ultrasound studies in monochorionic twin pregnancies : results of TULIPS: Twins and ultrasound in pregnancy studies

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Chapter 7

Fetal cardiac output in monochorionic twins

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Abstract

Objective To compare fetal cardiac output (CO) in donor and recipient twins of TTTS pregnancies after fetoscopic laser therapy to monochorionic twins without TTTS and to normal singletons.

Methods In a longitudinal, prospective study, we sonographically assessed fetal CO in donors (n=10) and recipients (n=10) with TTTS after fetoscopic laser therapy, in monochorionic twins without TTTS (n=20) and in 20 normal singleton pregnancies. The fetal CO of TTTS twins was determined 1 day and 1 week after laser treatment, and from then on every 2 to 4 weeks until birth. Twins without TTTS were examined biweekly until birth. Singletons were examined twice with an 8-week interval at different gestational ages between 17 and 35 weeks.

Results Absolute CO increased exponentially with advancing gestational age ($p<0.001$), and was significantly related to fetal weight for all groups ($p<0.0001$). The median CO/kg in donors after laser therapy, recipients after laser therapy, and non-TTTS monochorionic twins was significantly higher compared to singletons (all p-values <0.001). Median CO/kg in donors after laser therapy, recipients after laser therapy, and non-TTTS monochorionic twins was not significantly different from each other.

Conclusion Monochorionic twins with TTTS have an increased CO/kg after laser treatment as compared to normal singletons. These results may be of importance in view of the increasing awareness of fetal origins of adult disease.

Introduction

Before birth, the circulations of monochorionic diamniotic twins are almost invariably connected by vascular placental anastomoses[1]. With two hearts serving one circulation, continuous intertwin transfusion is standard during monochorionic twin pregnancy. Twin-to-twin transfusion syndrome (TTTS) develops when uncompensated unidirectional blood flow from one twin ("donor") to the other ("recipient") causes circulatory imbalance[2]. The donor twin then becomes volume depleted and oliguric, while the recipient twin becomes volume overloaded, polyuric, and eventually hydropic. TTTS complicates 15% of monochorionic twin pregnancies in the second and early third trimester[3] and is associated, if left untreated, with a fetal mortality rate of >80%[4]. Repeated amniodrainage has been used as symptomatic therapy[5]. The causal and more effective treatment consists of fetoscopic laser coagulation of vascular anastomoses[6]. Even after laser therapy, perinatal mortality and morbidity remain high[6].

Two recent studies report cardiac malformation rates of 6.9 and 11.2% in TTTS-survivors[7,8], significantly higher than in the general population (0.56%)[9]. The recipient fetuses are most commonly affected[7,8,10,11], but an increased incidence of congenital heart disease in donors has been reported as well[8]. Monochorionic twins without TTTS also show an increased frequency (2.3%) of cardiac disease[7]. Cardiac pathology most frequently diagnosed includes cardiomegaly, biventricular hypertrophy, tricuspid regurgitation, and right ventricular outflow tract obstruction (RVOTO)[8,10-20]. The mechanisms behind this increased rate of cardiac disease in both monochorionic twins with and without TTTS remain unraveled. To gain more insight in these mechanisms, we aimed to compare fetal CO in donor and recipient twins of TTTS pregnancies treated with laser therapy to CO in monochorionic twins without TTTS and to CO in normal singletons.

Methods

Population

Leiden University Medical Center (LUMC) is the tertiary referral center for fetoscopic laser treatment in the Netherlands. On average, 40 cases of TTTS are referred annually to our center for laser treatment. Uncomplicated monochorionic twin pregnancies from our region are also followed sonographically for early detection of TTTS symptoms. All monochorionic diamniotic twin pregnancies referred to our obstetrical unit between July 2003 and June 2004 were studied in a longitudinal, prospective manner. Criteria for inclusion were: monochorionic diamniotic twinning confirmed by first-trimester ultrasound showing a twin pregnancy with absent lambda sign and thin dividing membrane, and informed consent to the study. Exclusion criteria were: no confirmatory placental pathological examination after birth, cardiac (n=1) and other fetal

malformation (n=1), miscarriage (n=1) or intrauterine death of one or both fetuses (n=6). One patient refused to continue participating in the study.

Twins with TTTS were scanned and echocardiography was performed 1 day after laser, 1 week after laser, and from then on biweekly until birth. Twins without TTTS underwent biweekly ultrasound examination including echocardiography from inclusion until birth. In all cases, gestational age was based on the first day of last menstrual period and confirmed by ultrasound examination in the first or early second trimester. TTTS was diagnosed by the presence of oligo/polyhydramnios sequence in the absence of other causes. Polyhydramnios was defined as deepest vertical pocket (DVP) of amniotic fluid of >8 cm and oligohydramnios as a DVP of <2 cm. TTTS severity was assessed according to Quintero's established criteria[21]. All TTTS cases were treated by selective fetoscopic laser coagulation of the placental anastomoses[22-26] combined with a single amniodrainage procedure after laser coagulation. Patients with unreliable identification of former donor and recipient due to iatrogenic intertwin membrane perforation during laser were excluded from the study (n=2).

Twenty twin pairs remained available for analysis. Twin fetuses were divided into three groups: donors (n=10), recipients (n=10), and non-TTTS monochorionic twins (n=20). Three TTTS pregnancies were classified as Quintero Stage 1 (30%), four as Stage 2 (40%), and three as Stage 3 (30%). Values obtained in monochorionic twins were compared to values obtained in 20 normal singletons that were examined twice with an 8-week interval at different gestational ages between 17 and 35 weeks. A systematic ultrasound examination of fetal anatomy, including echocardiography, was initially performed to exclude any structural abnormality. Routine ultrasound scan measurements of each fetus included biparietal diameters, head and abdominal circumferences, and femur lengths that were used to calculate estimated fetal weight (EFW)[27]. The institutional review board approved the study.

Echocardiography

Doppler flow velocity waveforms from the ascending aorta were obtained in the five-chamber view of the fetal heart while Doppler flow velocity waveforms from the main pulmonary artery were obtained in the short axis of the right ventricle[28]. Doppler tracings were obtained with the sample volume placed immediately distal to the free-floating tips of the aortic and pulmonary valve leaflets in the center of the lumen[28-30]. An angle of <20° between the vessel and Doppler beam was used[28,31], and angle correction was applied.

Vessel diameters were measured from inner wall to inner wall at the level of valve insertion immediately after valve opening[28,32]. Both outlet valves were imaged with the aorta and pulmonary artery viewed in long axis, and diameter measurements were performed perpendicular to the luminary long axis. All measurements were achieved in periods of fetal rest and apnea and stored electronically for later analysis. In all cases, an Acuson Sequoia (Acuson, Mountain View,

California, USA) ultrasound machine with a 4.0 or 6.0 MHz-probe was used. All measurements were performed by one of two experienced sonographers (MS or KAT).

Doppler waveforms were obtained from three different cardiac cycles. In each cycle, as a minimum, three consecutive waveforms with similar appearance and a narrow band of frequencies were recorded, and one of these was analyzed. The peak flow velocity of the ascending aorta and pulmonary artery were determined. The maximum envelopes of the Doppler waveforms of the ascending aorta and pulmonary artery were automatically integrated from opening to closure of the valve and along the zero line during the no flow period until opening of the valve indicating the beginning of the next cardiac cycle (time averaged maximum velocity, TAMX; in cm/sec). The TAMX values of three different cardiac cycles were averaged and used to calculate CO. Heart rate (HR, in beats per minute) was measured from Doppler velocity signals obtained from the ascending aorta.

Vessel diameter measurements were performed three times. The averaged diameter value (d; in cm) was used for computing valve cross-sectional areas ($\pi \times d^2/4$), assuming a circular configuration unaffected by systole[33]. Left CO and right CO were determined using the aortic and pulmonary Doppler TAMX and vessel diameters, respectively. Biventricular CO was computed by the sum of left CO and right CO, and referred to as CO. CO (in milliliters per minute (mL/min)) was calculated with the following formula: $CO = TAMX \times 60 \times \pi \times d^2/4$[28].

Statistical Analyses

Differences in gestational age at delivery between TTTS twins and non-TTTS monochorionic twins were analyzed with the Mann Whitney test. To study the relations between the CO parameters and gestational age and to study differences between the four subgroups, linear regression models were used with gestational age and group as independent variables. The dependent variables were: absolute CO, CO per kg EFW (CO/kg), ratio of right to left CO, and the components of CO/kg: heart rate, TAMX and diameter of ascending aorta and pulmonary artery. All dependent variables were transformed on a logarithmic scale. Parameters in the regression models were estimated using Generalized Estimation Equations (GEE)[34] to take into account that repeated measurements on the same fetus were taken and that dependency between the outcomes within a twin pair could exist. A test for interaction between group and gestational age in the regression model was performed to see whether the pattern over time was similar in the groups (equivalent to testing if the regression slopes were equal in the four groups). If there was no significant interaction, testing for a linear relation between the dependent variable and gestational age was done by testing if the regression coefficient for gestational age was equal to zero. If needed, correcting for EFW was done by adding the logarithm of fetal weight as independent variable in the model. When the dependent variable was log transformed, results were transformed back to the original scale. This implies that differences between mean

values on the log scale were transformed back as ratios between median (geometric mean) values on the original scale.

Results

In total, 418 ultrasound examinations of twin pairs were performed. Successful recordings could not be obtained in all subjects (through maternal discomfort, duration of examination, and fetal position). Left CO could be determined in 60% (252/418 ultrasound examinations), right CO in 60% (251/418) and biventricular CO in 56% (234/418). Median gestational age of TTTS twins at laser treatment was 18.2 weeks (range, 15.6-23.9).

Figure 1 shows the estimated median absolute biventricular fetal CO across gestation in donors and recipients of TTTS twin pregnancies treated with laser, non-TTTS monochorionic twins, and singletons. CO increased exponentially with advancing gestational age ($p<0.001$). The pattern of increase of CO in relation to gestational age was not significantly different between the four groups ($p=0.19$).

Absolute CO was significantly related to EFW for all groups ($p<0.0001$). Donor twins had significantly lower EFW compared to recipients ($p<0.0001$), non-TTTS monochorionic twins

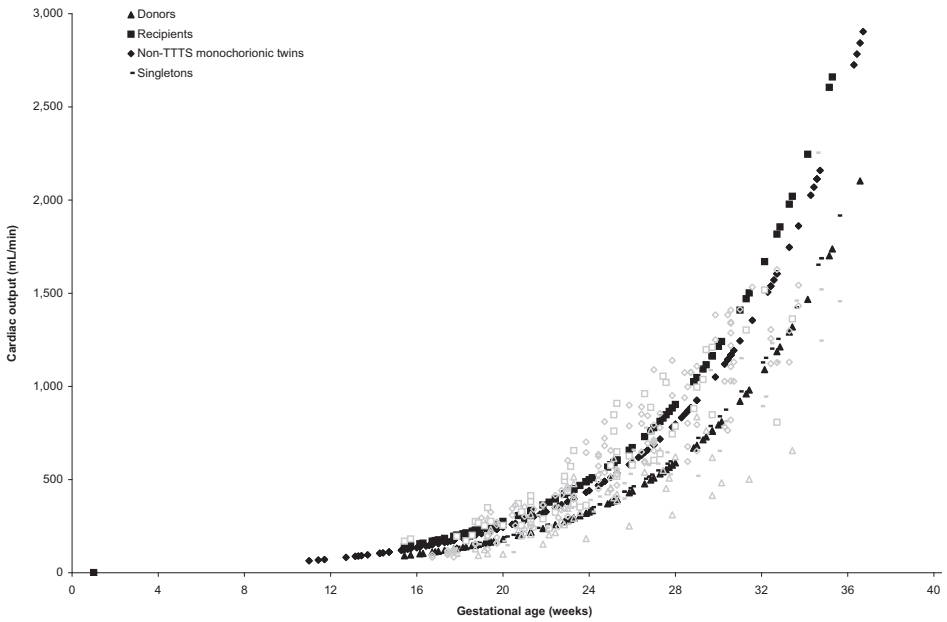

Figure 1 Estimated median absolute fetal biventricular cardiac output (CO) during gestation in donors and recipients of TTTS twin pregnancies treated with laser, of non-TTTS monochorionic twins, and of singletons

Black symbols represent the estimated median absolute fetal biventricular CO; open and gray symbols represent the individual values of fetal biventricular CO.

Table 1 Median cardiac output per kg estimated fetal weight (CO/kg) in donors and recipients of TTTS twin pregnancies treated with laser therapy, in non-TTTS monochorionic twins, and in singletons

	Median cardiac output in mL/min/kg* (95% CI)
Donors (n=10)	696 (623 – 778)
Recipients (n=10)	756 (686 – 834)
Non-TTTS monochorionic twins (n=20)	705 (670 - 742)
Singletons (n=20)	548 (509 - 590)

* Median CO/kg remained constant between 17 and 35 weeks' gestation in all groups. Median CO/kg in donors and recipients treated with laser and non-TTTS monochorionic twins was significantly higher compared to singletons (all p-values <0.001). Median CO/kg in donors, recipients and non-TTTS monochorionic twins was not significantly different from each other. TTTS, twin-to-twin transfusion syndrome.

(p=0.03), and singletons (p=0.001). Non-TTTS monochorionic twins had significantly lower EFW compared to singletons (p=0.02) and recipients (p=0.01). Fetal weights of recipients and singletons were not significantly different (p=0.60). Table 1 shows CO/kg in donors and recipients treated with laser, non-TTTS monochorionic twins, and singletons. The median CO/kg did not change significantly throughout pregnancy for any of the groups (p=0.59). Median CO/kg in donors, recipients, and non-TTTS monochorionic twins was significantly higher compared to singletons (all p-values <0.001). Median CO/kg in donors, recipients, and non-TTTS monochorionic twins was not significantly different from each other.

Table 2 shows the differences in components that determine CO/kg in donors and recipients treated with laser and in non-TTTS monochorionic twins compared to singletons. All values were corrected for EFW and gestational age. Heart rate did not differ significantly between the four groups. Pulmonary artery TAMX of donors was significantly decreased. Pulmonary artery TAMX of recipients was significantly increased. Diameters of ascending aorta and pulmonary artery of donors and recipients, and non-TTTS monochorionic twins were both significantly increased compared to singletons.

Table 2 Components used to calculate cardiac output in donors and recipients of TTTS twin pregnancies treated with laser therapy and in non-TTTS monochorionic twins, expressed as a ratio to measurements in singletons

Measurement	Donors*	Recipients*	Non-TTTS monochorionic twins*
Heart rate	0.99 (0.96-1.02)	0.99 (0.96-1.02)	1.01 (0.98-1.03)
Ascending aorta TAMX	0.99 (0.90-1.09)	1.05 (0.99-1.11)	0.99 (0.94-1.05)
Pulmonary artery TAMX	0.91 (0.84-0.98)	1.08 (1.00-1.17)	1.04 (0.97-1.10)
Ascending aorta diameter	1.13 (1.06-1.21)	1.11 (1.04-1.18)	1.10 (1.05-1.15)
Pulmonary artery diameter	1.14 (1.07-1.23)	1.15 (1.07-1.24)	1.14 (1.09-1.19)

* The effect measures given are ratios with 95% confidence interval (CI), using the value of singletons as reference category. TTTS, twin-to-twin transfusion syndrome; TAMX, time averaged maximum velocity.
For the purpose of statistical analysis, all values were log transformed, and results were transformed back to the original scale. This implies that differences between median values on the log scale were transformed back as ratios between median values on the original scale.

Discussion

This study focused on the longitudinal evaluation of fetal CO in monochorionic twins with and without fetoscopic laser treatment for TTTS. We found that median CO/kg in donors and recipients after laser treatment, and in non-TTTS monochorionic twins was significantly higher as compared to singletons.

The comparability of CO of donors and recipients after laser therapy is in line with expectations. Since laser treatment aims at the interruption of intertwin transfusion, volumes of both fetuses are expected to equalize afterwards, which has been shown before by the disappearance of intertwin differences in venous blood flow volume in donors and recipients after laser ablation[35,36]. Our findings confirm results described by Karatza *et al.*[7]. A striking aspect of our results, though, is the rise in CO of donors and recipients, despite laser ablation, compared to singletons.

Increased CO has been observed in several fetal pathological conditions. In fetal anemia, CO rises probably due to decreased blood viscosity leading to increased venous return and cardiac preload[28,37,38]. Fetuses with intrauterine growth restriction show a relative increase of LCO, probably due to cerebral vasodilatation and consequently decreased cardiac afterload[39,40]. Certain types of fetal arteriovenous shunts, such as in fetal teratoma or placental chorioangioma, are also known to be associated with high fetal CO and even cardiac failure as a result of increased preload[41,42]. Our findings of an increased CO in twin fetuses after laser may therefore be explained by either increased preload or decreased afterload, or a combination of both. However, since we found an increased CO after successful laser treatment, which should normalize fetal volumes[35,36], the model of increased preload as causal factor for the rise in CO seems less likely.

It seems more plausible to link the rise in CO after laser therapy with decreased afterload. Theoretically, in view of the common single monochorionic placenta with intertwin vascular connections, it could be argued that monochorionic twinning is not only associated with increased volume loading, but is also related to a greater number of placental vessels as compared to singletons. From around 28 days after fertilization, vascular communication between the two embryos via the placenta is possible[43]. It has been acknowledged, that blood flow plays a critical role in the development of heart valves, chambers, and arteries[44]. For example, ascending aorta and pulmonary artery stenosis are known to be caused, at least partly, by diminished blood flow[45,46]. Simultaneously, the accompanying great vessel often shows an increased diameter as a result of redistribution, meaning increase of contralateral intracardiac flow[47], suggestive of accelerated growth of the great arteries in case of abnormal and chronic rise in CO. In this view, assuming that an increased amount of blood volume is pumped through all placental vessels starting very early in pregnancy, it would possibly lead to enhanced growth of these placental vessels. Additionally, this may be an explanation for the enlarged great artery diameters in monochorionic twins compared to singletons found in this study. It may even be speculated that tiny arteries and veins on the placental surface that otherwise

remain closed would now be opened. The shared placental resistance of monochorionic twins may therefore be much lower than for normal singletons, resulting in decreased afterload and a rise in CO of both donors and recipients as well as in uncomplicated monochorionic twins. The fact that the increased CO is not neutralized after laser ablation, may be explained by the very early onset of cardiovascular remodeling. Irreversible fetal changes may already have occurred before laser therapy and may have resulted in severely altered fetal circulations that are beyond regulatory control.

This model of decreased afterload, however, seems not compatible with the results of studies on changes in fetal hormones in TTTS. Secondary to chronic volume overload and increased sheer stress, endothelin-1, a potent vasoconstrictor, has been shown to be increased in recipients[48]. Furthermore, the renin-angiotensin system has been shown to be upregulated in the donor twin in response to its hypovolemia. Transfer of angiotensin II from donor to recipient may also result in fetal hypertension and increased afterload[49-51]. In view of the results of our study, we speculate that raised concentrations of circulating peptides are present, however, apparently without immediate effect on the fetal CO. If the released hormones would act properly in TTTS fetuses, all recipients would show systemic hypertension. Although fetal and neonatal hypertension have been described anecdotically[50,52], a recent study at our institution could not detect significant differences in systolic blood pressure of donors and recipients born after laser therapy[53].

The increased CO in monochorionic twinning may play a role in the development of cardiac disease. Since cardiac malformations occur generally in only one of two genetically identical twins[54], the increased prevalence of cardiac defects in monochorionic twins is likely to be determined by non-genetic factors. It is conceivable that the twinning process itself with post zygotic unequal division of the inner cell mass may contribute to the development of cardiac abnormalities. Disturbances of laterality could also have a major influence on the embryo genesis of the heart and may contribute to the development of congenital heart defects in twins[55]. In addition, fetal flow fluctuations during early cardiogenesis are suggested to be the cause of congenital heart defects[44,56]. Some cardiac malformations, such as RVOTO that typically occurs in recipients of TTTS, may however develop at a later stage in pregnancy and are possibly more closely linked to disturbed hemodynamics at a more advanced gestational age, as shown in our study[57-60].

The finding of increased CO in donors and recipients after laser therapy is of particular interest in view of the growing awareness that adult diseases like hypertension and coronary heart disease may find their origins in impaired fetal development[61-63]. A recent paper on intrauterine programming states that the timing, duration, and exact nature of suboptimal intrauterine conditions are highly relevant and potentially disturbing the physiological programming of tissue development and may lead to abnormalities in the cardiovascular system, particularly with increasing age[64]. The permanent increase in CO despite laser therapy for TTTS may well be considered as a suboptimal intrauterine condition. It has already been shown that

the hostile *in utero* environment in TTTS pregnancies may result in fetal vascular remodeling causing increased vascular stiffness and raised cardiac afterload in the surviving donor[65,66]. Attention should be given to the hemodynamic impact of monozygotic twinning on the fetal cardiovascular system[67].

We do realize that our study population is relatively small. Another concern in obtaining measurements of CO is the technical challenge due to the small diameters of the outflow tracts. As a consequence, successful recordings may not be obtained in all subjects. In the literature, the percentage of successful recordings varies from 60-78% in singleton pregnancies[68,69]. We succeeded to measure both LCO and RCO in both twins in 56% of the cases. This should be considered an acceptable rate, especially since different fetal positions were required to perform measurements properly. For this latter reason, CO measurements are hardly possible to be performed in TTTS before laser therapy. The donor twin is stuck to the uterine wall and does not move, which hampers to perform measurements in all required positions. This is in contrast to the recipient twin that obviously is moving too much to perform measurements properly. Moreover, the polyhydramnios hamper detailed imaging. Reliability decreases if the quality of the obtained images is not optimal; therefore we decided to measure CO only after laser therapy. We are aware of the fact that the comparison between CO before and after laser therapy would have provided more valuable information on fetal hemodynamics in TTTS. However, as outlined before, CO measurements before laser therapy were not feasible.

Furthermore, technical aspects of the methods to estimate CO are important to consider. Mielke *et al.*[70], who established gestational-age specific reference ranges for fetal biventricular CO of singletons, found an exponential increase in absolute CO with advancing gestational age, which was confirmed in our study. The median CO/kg in singletons in their study (425 mL/min/kg) was lower, though, than what we found. This may well be explained by the angle correction that we used. At increased angles, correction causes higher, but also more accurate estimations of Doppler flow velocities. Nevertheless, since we were consistent and used the same technique in singletons to obtain our own reference values, differences in our technique from other research groups are unlikely to have any influence on our main findings and conclusions.

In conclusion, our study shows that CO in monochorionic twins after laser coagulation of communicating vessels in the placenta is higher than in singletons. Our findings emphasize the significant effect of monochorionic twinning in general on fetal cardiac hemodynamics, and provide more insight in the possible mechanisms leading to cardiac pathology. Further preferably prospective longitudinal studies are needed to completely understand the etiology of cardiac abnormalities.

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