Early Changes in Vascular Dynamics in Relation to Twin-Twin Transfusion Syndrome

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A clearer understanding of the early determinants of normal and abnormal vascular development is pivotal in order to identify those at increased risk of later vascular disease, and perhaps to prevent it by early intervention. Measurement of pulse wave velocity(PWV) has been used in the postnatal evaluation of the monochorionic(MC) twins. They are genetically identical and those with twin-twin transfusion syndrome(TTTS) provide an ideal natural model in whom to study the influence of differing haemodynamic stresses on the developing vascular tree. We investigated firstly whether surviving twin pairs with TTTS have altered arterial distensibility in childhood by comparing PWV in the radial arteries of surviving MC twin pairs with TTTS and in two control groups, one cohort of MC twins without TTTS and another dichorionic group (DC) Secondly, we tested a cohort of TTTS twin pair survivors treated with laser photocoagulation. The co-twin pairs in the group managed palliatively with amnioreduction showed increased PWV in the donor and reduced PWV in the recipient twins. This was neither seen in the laser-treated, nor in the control groups . Our studies suggest that a period of haemodynamic imbalance gives rise to changes in a muscular conduit artery that persist at least into infancy and it seems that by correcting the abnormal haemodynamics relatively soon after the disease process had begun, the alterations in elasticity are prevented. These studies are the first to demonstrate fetal programming of the vascular bed in humans, and prevention or reversal of this programming by an intervention in mid-gestation.

There is long-standing evidence that vascular development is influenced by abnormalities of flow during development, with or without additional structural cardiac abnormalities. Histology of the common iliac artery at postmortem in subjects with single umbilical artery confirmed that the artery on the side where umbilical arterial flow was absent was small and muscular whilst that on the opposite side was large, elastic in nature with marked calcification and atherosclerotic changes, implying marked flow-dependent differences in development (Meyer & Lind, 1974). These morphological differences have been reflected in studies of the compliance in iliac arteries in middle-aged individuals who had single umbilical arteries documented at birth. The discordant compliance reported in their iliac arteries (Berry et al., 1976) supports histological evidence that decreased flow in a vessel may initiate permanent changes in arterial structure detectable by physiological testing. The fetal origins hypothesis proposes that fetal adaptation to its environment may have life-long consequences, which may account for at least some of the morbidity and mortality in the adult population. Consistent with this hypothesis is the observation that "normalisation" of flow in a vessel after birth, for example by repairing isolated coarctation of the aorta in the neonatal period, does not necessarily ensure normal arterial function even in normotensive young adults. The finding of reduced distensibility in the brachial arteries of these individuals suggests that abnormalities of flow during development may produce life-long alterations in arterial responses (Gardiner et al., 1994).

A clearer understanding of the early determinants of normal and abnormal vascular development is pivotal in order to identify those at increased risk of later vascular disease, and perhaps to prevent it by early intervention. Many studies to date have been observational and retrospective and so by their nature contain certain deficiencies and assumptions. In studying the aetiology of disease processes complex interactions between genetic, haemodynamic, hormonal and nutritional influences occur. The use of well characterised monozygotic twin cohorts, characterised antenatally, constitute a valuable resource in furthering our understanding of the determinants of vascular disease, thus permitting us to identify the influences on fetal vascular growth and function, free from many potential confounders.

Normal Vascular Development and Modeling

Morphology of the Vessel Wall

The ideal vessel wall is required to have a relatively high tensile strength but the ability to extend adequately, but not excessively. It should be able to distribute stress uniformly and have appropriate visco-elastic responses to pulsatile oscillations. The functional unit of the aortic media has been termed the laminar unit and is composed of the elastin lamella and circumferentially orientated smooth muscle fibres with collagen fibres uniformly dispersed. In the chick embryo new lamellae are formed at the adventitial boundary,

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https://doi.org/10.1375/twin.4.5.371 Published online by Cambridge University Press

at the zone of maximum tension gradient, and cross species studies have shown remarkable similarities in vessel wall structure. In smaller species (< 20 Kg) there is a linear relationship between weight and aortic diameter, specifically with the thickness of the media. There is a close relationship between the thickness of the media and aortic diameter (0.05 mm increase for each 1 mm increase in aortic diameter) and the number of laminar units in relation to the size of the animal so that the stress per unit remains relatively constant across species (Wolinsky & Glagov, 1967).

The vascular tree of the early fetus is composed predominantly of collagen and lacks sufficient elastin to enable the aorta to function as a capacitor. This is essential to store energy during systole and release it during diastole thus maintaining the resting diameter of the vessel wall in the mature aorta (Roach & Burton, 1957) and allowing the aorta to function as a Windkessel, permitting continuous flow (Belz, 1995). Scanning electron microscopy has revealed elastin to be formed of branched lamellae that are seen from as early as 8 weeks of gestation in the human aorta. In contrast to the rapid increases in aortic length (from 25 mm to 105 mm in humans from 10 to 32 weeks gestation) the increase in elastin in the media occurs more slowly and appears to be determined by the increasing hydrodynamic forces and pressures of the fetal circulation with a decrease in distribution with increasing distance from the ascending aorta (Song & Park, 1992). The observation that elastin is deposited at an exponential rate during the second half of pregnancy, and in particular around the perinatal period, has given rise to the hypothesis that abnormalities of nutrition occurring at this time may affect elastin deposition and account for later cardiovascular pathophysiology (Martyn & Greenwald, 1997).

Developmental Physiology of the Vessel Wall

Developmental changes in the behaviour of the arterial wall of the fetus have been described following a series of animal experiments and observations of the human fetus using a wall-tracking device developed by the team of Professor Karel Maršál in the University of Lund, Sweden (Gustafsson et al., 1989; Lindström et al., 1987; Sonesson et al., 1993). These studies have described changes in the biophysical properties of the aorta of the human fetus during normal development and associated with growth restriction (Stale & Gennser, 1991; Gardiner, Brodszki, & Marsal, 2001; Gardiner et al., 1998). A more recent development has included a synchronized wall-tracking and pulse wave Doppler device to enable assessment of volume flow taking into account changes in diameter of the aorta during the cardiac cycle (Brodszki et al., 1998).

Longitudinal studies of aortic function in normally growing fetuses show changes in arterial wall pulsations that reflect not only improved ventricular function and increasing cardiac output but also the effects of the decreasing placental impedance found in the fetal circulation during normal pregnancy. Measurement of compliance or elastance of a blood vessel may be determined from the speed of propagation of a pulse traveling in its wall, the pulse wave velocity (PWV): the faster the velocity, the stiffer the wall. PWV has been shown to increase by about 1 metre per second in chick embryos from stage 18 to 29 (Zahka et al., 1987) and by a similar amount in the human fetus from 20 weeks to term (Gardiner et al., 2001). PWV depends on the mean distending pressure of the vessel and the composition of the vessel wall. Mean aortic blood pressure increases during gestation, as does the thickness of the aortic wall relative to the lumen and the supporting adventitial tissue. The composition of the wall changes with an accelerated deposition of elastin during the last weeks of gestation. This continues during the first months of life, and confers increased distensibility to the aorta (Berry et al., 1972); (Martyn et al., 1997).

Aortic PWV increases in the fetus with gestational age (Gardiner et al., 2001) and throughout life (Avolio et al., 1985) reflecting a progressive age-related reduction in arterial distensibility. It may be an earlier indicator than blood pressure of reduced arterial compliance. Pulse wave velocity in middle age is inversely correlated with birthweight even when corrected for the confounding effect of blood pressure (Martyn et al., 1995) consistent with the fetal origins hypothesis. However this relationship has not been confirmed in growth restricted fetuses in the third trimester, nor in infancy or in young adults (Montgomery et al., 2000; Styczynski et al., 2000), perhaps suggesting that a period of amplification of the initial stimulus is required to produce demonstrable pathophysiological effects (Gardiner et al., 2001). Nonetheless, the velocity of the pulse wave is an important determinant of coronary arterial flow and left ventricular function (Lehmann et al., 1997) and has been shown to correlate with atherosclerosis and to be increased in coronary arterial disease (Hopkins et al., 1994).

Measurement of pulse wave velocity using a photoplethysmographic technique has been used in the postnatal evaluation of the monochorionic twin cohorts discussed in this review. This is a non-invasive technique using two probes, each containing an infra-red emitting diode and a photo-transistor, that are placed over the artery of interest, a known distance apart, to measure the pulse transit time (Figure 1; Greenwald et al., 1997). The PWV is derived by dividing the distance between the two probes, measured to the nearest millimetre, by the transit time.

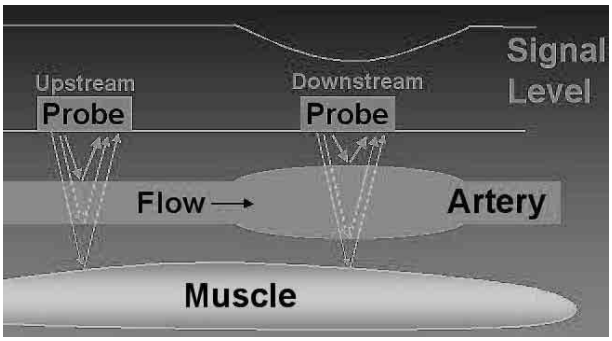

Figure 1

Cartoon illustrating the photoplethysmographic method of measuring pulse wave velocity.

https://doi.org/10.1375/twin.4.5.371 Published online by Cambridge University Press

Vascular Studies in Monochorionic Twins

Monochorionic twins are genetically identical and those with twin-twin transfusion syndrome provide an ideal natural model in whom to study the influence of differing haemodynamic stresses on the developing vascular tree.

Prevalence & Aetiology of Twin-twin Transfusion Syndrome

Monozygotic twins account for about 4/1000 liveborn infants in European countries with about 70% sharing a placenta who therefore have the potential to develop TTTS. It is a relatively common complication, occurring in 10–15% of monochorionic (MC) twins (Sebire, 1997) therefore affecting approximately 1 in 3200 pregnancies, or 1 in 1600 fetuses. Twin-twin transfusion syndrome is not a new disease. One of the first possible recorded cases is documented in a painting by an unknown artist of two swaddled children (De Wikkelkinderen) in 1617 who are thought to have died soon after birth (Berger et al., 2000). This continued to be a condition with an extremely high mortality, approaching 100% until effective management strategies were developed over the last decade. Even now dual survivors of TTTS are infrequent, forming only a third of surviving infants in many series.

The condition usually presents in the mid-trimester with gross discordance in amniotic fluid volume. Polyhydramnios and oligohydramnios are defined as deepest vertical pools of amniotic fluid of > 8 cm and < 1 cm, respectively measured sonographically. The triggering mechanism for TTTS is unknown. The pathophysiological substrate is thought to be due to unbalanced inter-twin transfusion via deep arterio-venous anastomoses that permit unidirectional flow from the "donor" to the "recipient" fetus in combination with a relative paucity of the superficial artery to artery anastomoses (AAA) that allow bi-directional flow and thus are able to redress any haemodynamic imbalance (Figure 2; Taylor et al., 2000). However, it is not known whether the fetus is a passive bystander in this process or whether the disease may be initiated or sustained by fetal factors that have yet to be determined.

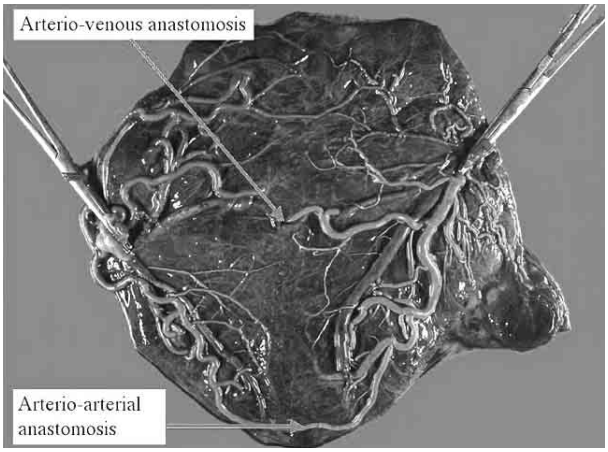

Figure 2

Placental anastomoses from a monochorionic pregnancy demonstrated by postnatal injection techniques.

Clinical Characteristics of TTTS

TTTS may be staged for severity with Stage I defined as oligo-poly-hydramnios sequence only, with Stage II also including absent visible bladder on ultrasound examination of the donor fetus, Stage III having in addition abnormal umbilical arterial, venous or ductus venosus Doppler recordings. Stage IV included the presence of hydrops in either fetus and Stage V when a single intrauterine death is diagnosed (Quintero et al., 1999).

The significant haemodynamic disturbances resulting from TTTS can be monitored sonographically. The hypervolaemic recipient fetus has cardiomegaly, polyuria, polyhydramnios, and may develop hydrops. Fetal echocardiography has demonstrated ventricular hypertrophy, tricuspid regurgitation and right ventricular outflow obstruction in the recipient heart that may persist postnatally requiring treatment (Zosmer et al., 1994), although there is spontaneous resolution in most recipient survivors during the first weeks of life (Fesslova et al., 1998). In contrast the donor fetus shows little cardiac pathophysiology but there is often absent or reversed end-diastolic flow (AREDF) for weeks in the umbilical artery (UA) and descending aorta, and evidence of chronic hypovolaemia, with poor renal perfusion resulting in oliguria and oligohydramnios. Venous Doppler waveforms may be abnormal in the recipient with pulsatile changes seen in the umbilical vein (UV) and reversal of flow with atrial contraction in the venous duct (DV) indicating a high central venous pressure.

Therapy

Perinatal mortality has been greatly reduced over the last decade by intrauterine management strategies consisting of palliative therapies such as serial amnioreduction or amniotic septostomy, and definitive treatment such as laser photocoagulation of placental anastomotic vessels. Selective fetocide using occlusive cord photocoagulation is also an alternative management option when the disease is severe (Duncan et al., 1997). The primary aim of amnioreduction is to reduce amniotic fluid volume and pressure, thereby reducing the risk of preterm labour or ruptured membranes. Laser therapy reduces or abolishes intertwin transfusion by destroying chorionic plate anastomoses, producing functionally dichorionic pregnancies (Hecher et al., 1999).

Following laser treatment there is an immediate and permanent restoration of AREDF in the donor UA along with acute reversal of AREDF in the DV, which resolves within a few days (Zikulnig et al., 1999). These Doppler findings are consistent with an increase in circulating blood volume in the formerly hypovolaemic donor. Indeed, the changes in the DV probably reflect acute volume overload in the usually chronically vasoconstricted donor, that resolves as the fetus adapts to its new haemodynamic load.

Studies of Vascular Development in TTTS

Modern technology allows us to make non-invasive observations on vascular physiology and to monitor the rate of fetal growth. Disease processes that alter normal development can be studied in these twin pair cohorts with each

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pair acting as its own case-control. Queen Charlotte's and Chelsea Hospital is a tertiary referral centre for twin-twin transfusion syndrome (TTTS) as well as being the headquarters of the Multiple Birth Foundation Group. The clinical data presented in this review comes from some of the large cohort of monochorionic twins who have been monitored at 2 weekly intervals throughout their pregnancies and followed into childhood.

Our observation of the fetal haemodynamics in TTTS, superimposed on studies strongly suggesting that fetal haemodynamic abnormalities could cause persistent vascular abnormalities, prompted our group to develop two hypotheses for further study. Firstly, that differences in volume loading during fetal life produce measurable effects during infancy which remain even though the disease process ceases at birth. Secondly: that definitive treatment of the disease in its early stages by laser photocoagulation of placental anastomoses prevents or reverses discordant vascular stiffness in MC twin pairs.

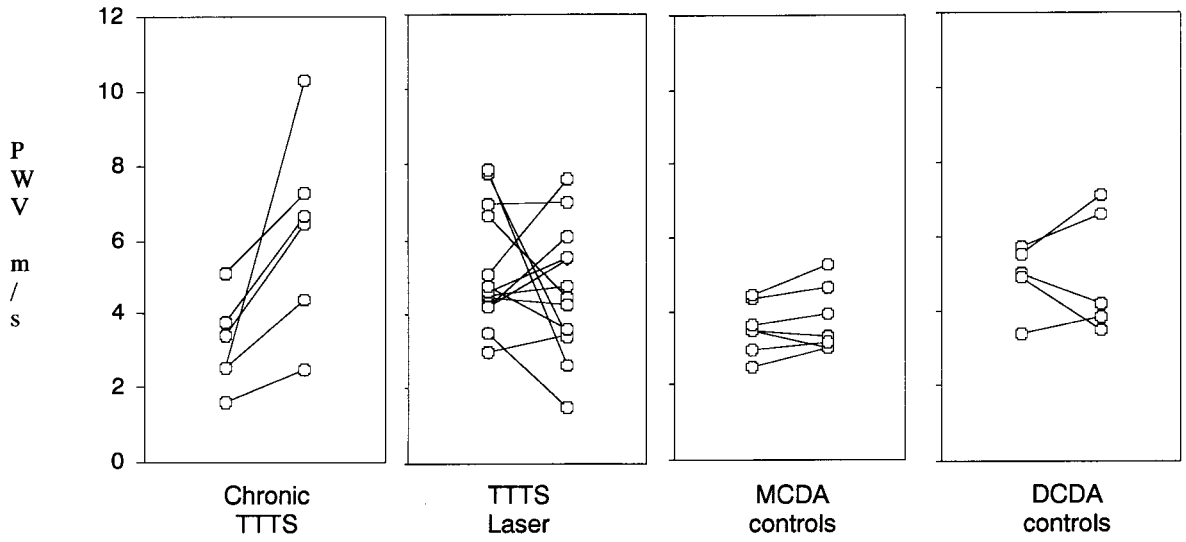
We investigated firstly whether surviving twin pairs with TTTS have altered arterial distensibility in childhood by comparing PWV in the radial arteries of surviving MC twin pairs with TTTS and in two control groups, one cohort of MC twins without TTTS and another dichorionic group (DC)(Cheung et al., 2000). To test the second hypothesis a cohort of TTTS twin pair survivors treated with laser photocoagulation were recruited in Hamburg and studied in collaboration with Dr K Hecher (Gardiner et al., submitted). Full details of these studies may be found in the published reports.

The important findings were those of marked discordance in PWV between the donor and recipient co-twins in the TTTS group treated palliatively that was neither seen in the laser-treated, nor in the control groups (Figure 3). The co-twin pairs in the group managed palliatively with amnioreduction showed increased PWV in the donor and reduced PWV in the recipient twins. In those treated with laser, the estimated duration of disease process was much shorter with a median of 2 compared with 10 weeks. Postnatal age at time of examination, donor status and duration of TTTS were significant determinants of arterial distensibility. There were no significant differences in blood pressure nor in birth weight Z scores between the lighter and the heavier twins in inter-group analysis (using analysis of variance) to account for the observed differences in PWV.

The results of the first study suggested that a period of haemodynamic imbalance gives rise to changes in a muscular conduit artery that persist at least into infancy, whilst no intertwin differences in vessel stiffness were seen in the two control groups. In the second study it seemed that by correcting the abnormal haemodynamics relatively soon after the disease process had begun, the alterations in elasticity are prevented. Thus the destruction of intertwin placental anastomoses by laser appears protective against vascular sequelae following TTTS. These studies are the first to demonstrate fetal programming of the vascular bed in humans, and prevention or reversal of this programming by an intervention in mid-gestation (Cheung et al., 2000); Gardiner et al., submitted).

Vascular Responses to TTTS

The potential mechanisms underlying these observations are made easier to explore because of the study design. Genetically identical pairs of subjects were recruited who were studied at 2 weekly intervals throughout pregnancy



Chronic TTTS cases treated palliatively and TTTS laser: cases treated using laser photocoagulation of placental anastomoses. PWV m/s=pulse wave velocity in metres per second; TTTS = twin to twin transfusion service; MCDA = monochorionic control twins without TTTS; DCDA = dichorionic control twins.

Figure 3

Plot of paired co-twin PWV values (m/s).

https://doi.org/10.1375/twin.4.5.371 Published online by Cambridge University Press

thus removing many potential confounders and ensuring that the individuals are well characterised in terms of fetal biometry and blood flow.

Vascular responses to changes in haemodynamic stress have been described using animal models. Wolinsky and Glagov (1967) have described a uniformity of composition of the vessel wall, regardless of species, that is optimal for the stress experienced by the vessel. The vascular response to hypertension in the adult human is that of an increase in the diameter of the artery, reduced compliance and an increase in pulse pressure to reduce wall stress. Evidence from animal studies suggests that the immediate response to a rapid increase in intravascular pressure is dominated by a change in vascular smooth muscle contractile state and that over a period of a week this increased resistance is maintained by remodelling (Fridez et al., 2001). These adaptive changes remain when blood pressure is reduced experimentally in animal experiments. It may be postulated that the adaptive response of the wall is due to the effects of the pulsatility of the blood pressure rather than the mean pressure. Increasing stiffness of the vessel wall reduces baroreceptor activity and may lead to an increase in sympathetic tone (Andresen, 1984; Boutouyrie et al., 1994). In the mature animal, neurohormonal feedback is important but this is not evident in the human fetus until the latter half of gestation.

Vascular modeling in the fetal and neonatal period forms an essential response to growth, and to changes in intravascular pressure. The importance of remodelling in response to stress is perhaps most dramatically exemplified when one considers the medial thickness of human pulmonary arteries. These have appearances similar to the aorta in fetal life but the vessel wall responds to the normal physiological drop in pressure after birth with a reduction in medial thickness. Failure of this adaptive response results in persistent pulmonary hypertension. Peterson has described the modulus of elasticity or tension per unit of wall thickness as the most important physiological measure (Peterson et al., 1960). In the canine model the aortic radius to wall thickness is 6 in the thoracic aorta compared to 22 in the normally adapted pulmonary artery.

Factors that may influence vascular development in TTTS are the fetal responses to differences in circulating volume (increased in the recipient and reduced, with absence or reversal of diastolic flow, in the donor), viscosity and discordant nutritional status due to the smaller placental share of the donor twin.

Although growth restriction may play a role in reduced arterial distensibility in early life, it is unlikely that it alone can account for the decrease in arterial distensibility seen in the donor fetuses in this study as the absence of similar findings in the lighter twins in the other three groups (whose gestational-age adjusted birth weights were similar) would suggest that it is the donor status in the palliated group that confers additional risk to decreased arterial distensibility. Furthermore, in our study, the longer the duration of circulatory imbalance, unrelated to the ultimate fetal size, the greater the discordance in PWV between the donor and recipient (Cheung et al., 2000).

The effect of nutrition on the developing vessel wall has been studied in animal models. In a study by Berry and Looker (Berry & Looker, 1973), transient growth inhibition of the rat aortic wall was effected using methotrexate with folinic acid rescue and resulted in altered number of cells in many organs. Whilst the numbers of lamellar units did not change in relation to the size of the animal there were transient abnormalities of elastin deposition and an overall reduction in scleroprotein (collagen and elastin) content but not balance. Little is known of the effects on vascular development of the more subtle changes in nutrition seen in the human fetus during nutritional deprivation.

Vascular physiology may be affected by blood viscosity. However data from our series show only 25% of twins with TTTS had > 5 g/dl (25% discordancy) in haemoglobin either from cord blood at delivery or at fetal blood sampling at 28 weeks' gestation, a level that is unlikely to produce significant differences in physiological measures (Fisk et al., 1998).

Raised endothelin concentrations at birth (Bajoria et al., 1994) and transient neonatal hypertension (Tolosa et al., 1993) in the recipient fetus provide indirect evidence of increased systemic vascular resistance, paradoxical in the face of the observations of a lower PWV and normal BP in recipients studied later in childhood. The mechanism responsible for this lower PWV in infancy may be due to increased shear stress secondary to increase volume flow during development. It has been shown that increased sheer stress inhibits vascular smooth muscle cell (VSMC) proliferation in vessels both with a healthy and damaged endothelium. In vitro studies suggest that Transforming Growth Factor _1 [TGF_1] and tissue-type plasminogen activator [TPA] inhibit VSMC proliferation directly (Ueba et al., 1997) and may play a role in the response of the developing vessel to changing haemodynamic stress.

The response of the donor fetus to low flow situations is uncertain but examination of the aorta in fetuses with restricted intrauterine growth due to placental insufficiency has shown that the resultant decrease in flow of aortic blood in combination with increased impedance is manifest in an alteration of the properties of pulsation of the fetal aortic wall (Gardiner et al., 1998) that may have long-lasting effects such as those seen in studies of human carotid arteries that have shown early plaque formation in arteries where there was reduced and oscillating flow (Ku et al., 1985).

Adaptive responses to reduced flow in animals include compensatory vasoconstriction, important to maintain satisfactory systemic and placental perfusion, and neurohormonal activation of the renin-angiotensin system (Segar, 1997; Wood et al., 1989).

There is evidence that neurohormonal responses are active in the fetal donor twin as increased renin gene and protein expression has been detected in donor kidneys with virtually absent expression in recipient kidneys (Kilby et al., 2001; Mahieu-Caputo et al., 2001). Increased angiotensin II increases collagen synthesis, induces smooth muscle hypertrophy and causes vascular medial hypertrophy in sheep (Kato et al., 1991; Morishita et al., 1994; Robillard et al., 1982) and may play an important role in the vascular abnormalities we have described in the donor fetus.

Increased aortic stiffness in response to generalised vasoconstriction may decrease baroceptor activity, similar to that

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shown to happen with ageing and result in feedback mechanisms that reset the baroreceptor reflex and result in persistent elevation of basal sympathetic tone, which is known to reduce arterial compliance (Boutouyrie et al., 1994). Alteration in baroreceptor activity has yet to be confirmed in children following TTTS.

A reduction in the arterial characteristic impedance results in increased pulse pressure and the pulsatile cardiac workload is accentuated. Furthermore, the resultant increase in the velocity of the pulse wave results in early return of the reflected wave and further augments the systolic pressure, shown to be a cardiovascular risk factor (Blacher et al., 1999).

Conclusions

The finding of markedly decreased arterial distensibility in the donor twin treated by amniodrainage or conservative methods but not in those treated by laser has significant implications for the future management of this disease as reduced arterial distensibility contributes to the pathogenesis of hypertension.

References

Andresen, M. C. (1984). Short- and long-term determinants of baroreceptor function in aged normotensive and spontaneously hypertensive rats. *Circulation Research, 54*(6), 750–759.

Avolio, A. P., Deng, F. Q., Li, W. Q., Luo, Y. F., Huang, Z. D., Xing, L. F., & O'Rourke, M. F. (1985). Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: Comparison between urban and rural communities in China. *Circulation, 71*(2), 202–210.

Bajoria, R., Sullivan, M., & Fisk, N. M. (1994). Endothelin concentration in monochorionic twins with severe twin-twin transfusion syndrome. *Human Reproduction, 14*, 1614–1618.

Belz, G. G. (1995). Elastic properties and Windkessel function of the human aorta. *Cardiovascular Drugs and Therapy, 9*, 73–83.

Berger, H. M., de Waard, F., & Molenaar, Y. (2000). A case of twin-to -twin transfusion in 1617. *Lancet, 356*, 847–848.

Berry, C. L., Gosling, R. G., Laogun, A. A., & Bryan, E. (1976). Anomalous iliac compliance in children with a single umbilical artery. *British Heart Journal, 38*(5), 510–515.

Berry, C. L., & Looker, T. (1973). An alteration in the chemical structure of the aortic wall induced by a finite period of growth inhibition. *Journal of Anatomy, 114*(1), 83–94.

Berry, C. L., Looker, T., & Germain, J. (1972). Nucleic acid and scleroprotein content of the developing human aorta. *Journal of Pathology, 108*(4), 265–274.

Blacher, J., Asmar, R., Djane, S., London, G. M., & Safar, M. E. (1999). Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. *Hypertension, 33*(5), 1111–1117.

Boutouyrie, P., Lacolley, P., Girerd, X., Beck, L., Safar, M., & Laurent, S. (1994). Sympathetic activation decreases medium-sized arterial compliance in humans. *American Journal of Physiology, 267*(4 Pt 2), H1368–H1376.

Brodszki, J., Gardiner, H. M., Eriksson, A., Stale, H., & Marsal, K. (1998). Reproducibility of ultrasonic fetal volume blood flow measurements. *Clinical Physiology, 18*(5), 479–485.

Cheung, Y. F., Taylor, M. J. O., Fisk, N. M., Redington, A. N., & Gardiner, H. M. (2000). Fetal origins of reduced arterial distensibility in the donor twin in twin-twin transfusion syndrome. *Lancet, 355*, 1157–1158.

Duncan, K. R., Denbow, M. L., & Fisk, N. M. (1997). The aetiology and management of twin-twin transfusion syndrome. *Prenatal Diagnosis, 17*(13), 1227–1236.

Fesslova, V., Villa, L., Nava, S., Mosca, F., & Nicolini, U. (1998). Fetal and neonatal echocardiographic findings in twin-twin transfusion syndrome. *American Journal of Obstetrics & Gynecology, 179*(4), 1056–1062.

Fisk, N. M., Denbow, M. L., Taylor, M., Cox, P., & Talbert, D. (1998). Scientific basis of TTTS and its relevance to treatment strategies. *Fetal Diagnosis and Therapy, 13*(1), 49.

Fridez, P., Makino, S., Miyazaki, H., Meister, J. J., Hayashi,K., & Stergiopulos, N. (2001). Short-term biomechanical adaptation of the rat carotid to acute hypertension: Contribution of smooth muscle. *Annals of Biomedical Engineering, 29*, 26–34.

Gardiner, H. M., Brodszki, J., Eriksson, A., & Marsal, K. (2001). Ventriculo-vascular interaction in the normal development of the fetal circulation. *Early Human Development* (in press).

Gardiner, H. M., Brodszki, J., & Marsal, K. (2001). Ventriculovascular physiology of the growth restricted fetus. *Ultrasound in Obstetrics & Gynecology*, *18*, 47–53.

Gardiner, H. M., Celermajer, D. S., Sorensen, K. E., Georgakopoulos, D., Robinson, J., Thomas, O., & Deanfield, J. E. (1994). Arterial reactivity is significantly impaired in normotensive young adults after successful repair of aortic coarctation in childhood. *Circulation, 89*(4), 1745–1750.

Gardiner, H. M., Kopecka, J., Stale, H., & Marsal, K. (1998). Fetal vascular programming: Aortic biophysical properties differ in growth restriction. *Proceedings of the Second World Congress in Paediatric Cardiology and Cardiac Surgery,* 110–111.

Greenwald, S. E., Denyer, H. T., & Sobeh, M. S. (1997). Non-invasive measurement of vascular compliance by a photoplethysmographic technique. *SPIE proc., 2970,* 89–97.

Gustafsson, D., Stale, H., Bjorkman, J. A., & Gennser, G. (1989). Derivation of hemodynamic information from ultrasonic recordings of aortic diameter changes. *Ultrasound in Medicine and Biology, 15*(3), 189–199.

Hecher, K., Plath H., Bregenzer Y., Hansmanll & Hackeloer B.J. (1999). Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. *American Journal of Obstetrics & Gynecology, 180*, 717–724.

Hopkins, K. D., Lehmann, E. D., & Gosling, R. G. (1994). Aortic compliance measurements: A non-invasive indicator of atherosclerosis? *Lancet, 343*(8911), 1447.

Kato, H., Suzuki, H., Tajima, S., Ogata, Y., Tominaga, T., Sato, A., & Saruta, T. (1991). Angiotensin II stimulates collagen synthesis in cultured vascular smooth muscle cells. *Journal of Hypertension, 9*(1), 17–22.

Kilby, M. D., Platt, C., Whittle, M. J., Oxley, J., & Lindhop, G. B. (2001). Renin gene expression in fetal kidneys of pregnancies complicated by twin-twin transfusion syndrome. *Pediatric and Developmental Pathology, 4*, 175–179.

Ku, D. N., Giddens, D. P., Zarins, C. K., & Glagov, S. (1985). Pulsatile flow and atherosclerosis in the human carotid bifurcation: Positive correlation between plaque location and low and oscillatory shear stress. *Arteriosclerosis, 5*, 293–302.

https://doi.org/10.1375/twin.4.5.371 Published online by Cambridge University Press

Lehmann, E. D., Riley, W. A., Clarkson, P., & Gosling, R. G. (1997). Non-invasive assessment of cardiovascular disease in diabetes mellitus. *Lancet, 350*(Suppl 1), SI14–SI19.

Lindström, K., Gennser, G., Sindberg Eriksen, P., Benthin, M., & Dahl, P. (1987). An improved echo-tracker for studies on pulse waves in the fetal aorta. In P. Rolfe (Ed.), *Fetal Physiological Measurements* (pp. 217–226). London: Butterworths.

Mahieu-Caputo, D., Dommergues, M., Delezoide, A. L., Lacoste, M., Cai, Y., & Narcy, F. (2001). Twin-to-twin transfusion syndrome. Role of the fetal renin-angiotensin system. *American Journal of Pathology, 156*, 629–636.

Martyn, C. N., Barker, D. J. P., Jespersen, S., Greenwald, S., Osmond, C., & Berry, C. (1995). Growth in utero, adult blood pressure, and arterial compliance. *British Heart Journal, 73*(2), 116–121.

Martyn, C. N., & Greenwald, S. E. (1997). Impaired synthesis of elastin in walls of aorta and large conduit arteries during early development as an initiating event in pathogenesis of systemic hypertension. *Lancet, 350*(9082), 953–955.

Meyer, W. W., & Lind, J. (1974). Iliac arteries in children with a single umbilical artery. Structure, calcifications, and early atherosclerotic lesions. *Archives of Disease in Childhood, 49*(9), 671–679.

Montgomery, A. A., Ben-Shlomo, Y., McCarthy, A., Davies, D., Elwood, P., & Smith, G. D. (2000). Birth size and arterial compliance in young adults. *Lancet, 355*(9221), 2136–2137.

Morishita, R., Gibbons, G. H., Ellison, K. E., Lee, W., Zhang, L., & Yu, H. (1994). Evidence for direct local effect of angiotensin in vascular hypertrophy: In vivo gene transfer of angiotensin converting enzyme. *Journal of Clinical Investigation, 94*, 978–984.

Peterson, L. H., Hensen, R. E., & Parnell, J. (1960). Mechanical properties of arteries in vivo. *Circulation Research, 8*, 622.

Quintero, R. A., Morales, W. J., Allen, M. H., Bornick, P. W., Johnson, P. K., & Kruger, M. (1999). Staging of twin-twin transfusion syndrome. *Journal of Perinatology, 19*, 550–555.

Roach, M. R., & Burton, A. C. (1957). The reason for the shape of the distensibility curves of arteries. *Canadian Journal of Biochemistry and Physiology, 35*, 681–690.

Robillard, J. E., Gomez, R. A., Meernik, J. G., Kuehl, W. D., & Van Orden, D. (1982). Role of angiotensin II on the adrenal and vascular responses to hemorrhage during development in fetal lambs. *Circulation Research, 50*(5), 645–650.

Sebire, N. J. (1997). The hidden mortality of monochorionic twin pregnancies. *British Journal of Obstetrics and Gynaecology, 104*, 1203–1207.

Segar, J. L. (1997). Ontogeny of the arterial and cardiopulmonary baroreflex during fetal and postnatal life. *American Journal of Physiology, 273*, 457–471.

Sonesson, B., Hansen, F., Stale, H., & Lanne, T. (1993). Compliance and diameter in the human abdominal aorta — the influence of age and sex. *European Journal of Vascular Surgery, 7*, 690–697.

Song, S. H., & Park, H. W. (1992). Development of elastin layers in the aortic wall of human fetuses. *Yonsei Medical Journal, 33*(4), 337–343.

Stale, H., & Gennser, G. (1991). Fetal aortic diameter pulse wave response to changes in maternal position after membrane rupture. *Ultrasound in Obstetrics and Gynaecology, 1*, 261–265.

Styczynski, G., Abramczyk, P., Szmigielski, C., Placha, G., & Gaciong, Z. (2000). Birth size and arterial compliance in young adults. *Lancet, 356*(9232), 855–856.

Taylor, M. J., Denbow, M. L., Tanawattanacharoen, S., Gannon, C., Cox, P. M., & Fisk, N. M. (2000). Doppler detection of arterio-arterial anastomoses in monochorionic twins: Feasibility and clinical application. *Human Reproduction, 15*, 1632–1636.

Tolosa, J. E., Zoppini, C., Ludomirsky, A., Bhutani, V., Weil, S. R., & Huhta, J. C. (1993). Fetal hypertension and cardiac hypertrophy in the discordant twin syndrome. [Abstract]. *American Journal of Obstetrics and Gynecology, 168,* 292

Ueba, H., Kawakami, M., & Yaginuma, T. (1997). Shear stress as an inhibitor of vascular smooth muscle cell proliferation. *Arteriosclerosis, Thrombosis and Vascular Biology, 17*, 1512–1516.

Wolinsky, H., & Glagov, S. (1967). A lamellar unit of aortic medial structure and function in mammals. *Circulation Research, 20*, 99–111.

Wood, C. E., Chen, H. G., & Bell, M. E. (1989). Role of vagosympathetic fibers in the control of adrenocorticotropic hormone, vasopressin, and renin responses to hemorrhage in fetal sheep. *Circulation Research, 64*, 515–523.

Zahka, K. G., Hu, N., & Clark, E. B. (1987). Pulse wave velocity in the stage 18 to 29 chick embryo. *Circulation, 76*(IV), 454.

Zikulnig, L., Hecher, K., Bregenzer, T., Bäz, E., & Hackelöer, B. J. (1999). Prognostic factors in severe twin-twin transfusion syndrome treated by endoscopic laser surgery. *Ultrasound in Obstetrics and Gynecology, 14*, 380–387.

Zosmer, N., Bajoria, R., Weiner, E., Rigby, M., Vaughan, J., & Fisk, N. M. (1994). Clinical and echographic features of in utero cardiac dysfunction in the recipient twin in twin-twin transfusion syndrome. *British Heart Journal, 72*(1), 74–81.

https://doi.org/10.1375/twin.4.5.371 Published online by Cambridge University Press