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Pediatric Cardiology

Fetal Cardiovascular Physiology

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Abstract. The cardiovascular system of the fetus is physiologically different than the adult, mature system. Unique characteristics of the myocardium and specific channels of blood flow differentitate the physiology of the fetus from the newborn. Conditions of increased preload and afterload in the fetus, such as sacrococcygeal teratoma and twin-twin transfusion syndrome, result in unique and complex pathophysiological states. Echocardiography has improved our understanding of human fetal cadiovasvular physiology in the normal and diseased states, and has expanded our capability to more effectively treat these disease processes.

Our understanding of fetal cardiovascular physiology has advanced significantly during the past 20 years. Knowledge about the mammalian fetal circulation derives primarily from original work done in sheep. By performance of classical physiological studies, Rudolph and Heymann [44] generated a body of knowledge that has formed the basis for understanding human fetal cardiovascular physiology. With the advent of ultrasonic imaging and fetal echocardiography, direct observation of phenomena occurring during gestation in the normal and diseased human fetus has been possible, further advancing our understanding and knowledge [30].

In this article, I review the elements that distinguish the unique fetal cardiovascular system from that in the developed postnatal human. I also review the physiological response of the fetal cardiovascular system to hemodynamic stress. As examples, I discuss the fetal response to the volume load of arteriovenous malformation and the complex and puzzling disorder known as twin–twin transfusion syndrome.

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The Fetal Myocardium

The fetal myocardium differs from the adult myocardium in a number of ways. First, the fetal myocardium is composed of a greater proportion of noncontractile elements than in the adult. Up to 60% of fetal myocardium is composed of noncontractile elements versus 30% in the adult myocardium [15], Second, myocardial cellular replication is different in the fetus than in the adult. Cardiomyocytes contain the contractile elements of the heart. Primitive mesodermal cells differentiate into cardiomyocytes and then receive a signal to exit the cell cycle at approximately the time of birth. Whereas early fetal cardiomyocytes may divide and increase in number (hyperplasia), mature adult cardiomyocytes can only grow in size (hypertrophy). In fact, the left ventricular myocyte increases in volume 30- to 40-fold during the neonatal to adolescent period. Third, relaxation properties of the fetal myocardium differ from those of the adult. Experimental animal studies in the fetus have demonstrated a difference in the process of rapid removal of calcium from troponin C, the mechanism responsible for myocardial relaxation [33]. This may be due to diminished sarcoplasmic reticulum function and greater dependence on the sodium–calcium exchanger process to remove cytosolic calcium in the fetus [3]. Fourth, differences exist in the fuel used for myocardial cell metabolism. Long-chain fatty acids are the preferred fuel in adults, whereas lactate is the primary agent metabolized in the immature myocardium [13]. In the fetus, this is due to a deficiency in the enzyme carnitine palmitoyl transferase-*1*, responsible for transporting long-chain fatty acids into the mitochondria.

Stiffness and impaired relaxation of the fetal myocardium are reflected in the pattern of Doppler echocardiography-derived flow signals obtained across the atrioventricular valves. In the adult, early diastolic filling predominates with an E wave (early passive filling) to A wave (active atrial contraction)

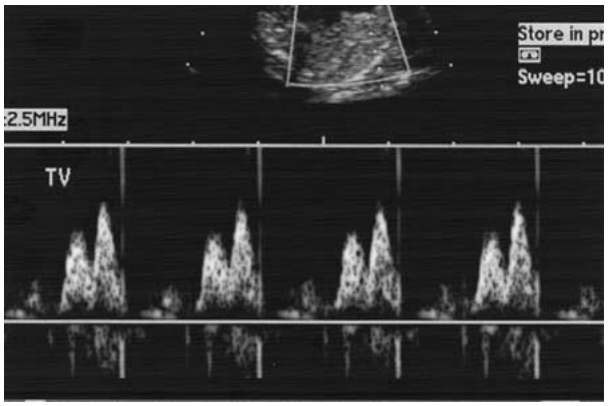

Fig. 1. Doppler flow pattern across the normal fetal tricuspid valve. Note the A wave (second peak) is taller than the E wave.

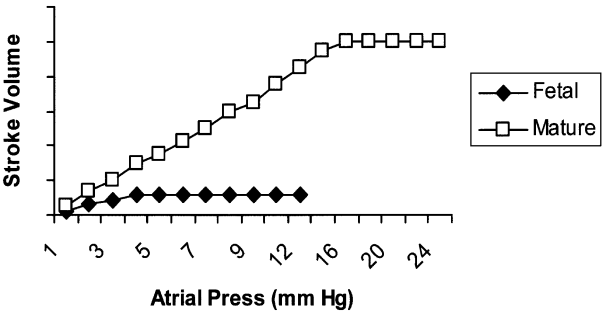

Fig. 2. Increase in ventricular stroke volume as atrial pressure rises with increasing preload. The fetal heart cannot increase its stroke volume beyond a small incremental increase in atrial pressure, with peak stroke volume occurring at approximately 4 or 5 mmHg. The mature adult heart can continue to increase its stroke volume as preload increases up to atrial pressure 16–18 mmHg.

velocity ratio (E:A ratio) that exceeds 1. In the fetus, passive early filling is impaired and active atrial contraction is primarily responsible for emptying the atrium [40]. Hence, the E:A ratio will typically be less than 1 (Fig. 1).

Increased myocardial stiffness may explain some of the limitations in stroke volume augmentation uniquely present in the fetus. Fetal myocardium follows the Frank–Starling law, which predicts an increase in stroke volume with increasing preload. Ultimately, a point is reached after which any increase in preload with increasing atrial pressure will result in a plateau without any further increase in stroke volume [17]. Whereas normal adult myocardium may have significant potential for augmentation of stroke volume based on increasing preload, the fetal myocardium functions near the "break point" of the curve and can only increase stroke volume to a small degree in response to an increase in preload (Fig. 2). Hence, the fetal myocardium has very little preload reserve [49].

Some investigators have argued that the limitation in ability to increase stroke volume in the fetus is due to properties inherent within the fetal myocardium and that the immature myocardial architecture exhibits poor compliance. An intriguing alternative theory advocated by Grant and colleagues [18] is that fetal stroke volume is limited not by intrinsic properties of the fetal myocardium but by ventricular constraint due to extrinsic compression of the fetal heart. These investigators argue that acute cardiovascular changes take place immediately at birth resulting in a sudden doubling of fetal stroke volume. Ventricular constraint arising from the tissues that surround the fetal heart, such as the chest wall, the lungs, and the pericardium, limits fetal ventricular preload and thus determines the limits of fetal cardiac function. Relief of this constraint at birth, with aeration of the lungs and clearance of the lung liquid associated with fetal lungs, may be the key mechanism responsible for an increase in left ventricular (LV) preload and thus the increase in stroke volume seen in the newborn infant [19–21].

Distinct differences exist between the right and left ventricles in the fetal heart. Due to the parallel circuit setup and specific blood pathways of the fetal circulation, right ventricular stroke volume exceeds left ventricular stroke volume, with the right ventricle delivering approximately 60–70% of the total cardiac output to the circulation. Right ventricle output is directed across the main pulmonary artery and patent ductus arteriosus, with a small portion going to the vasoconstricted pulmonary vascular bed. Right ventricular output perfuses the descending aorta, lower part of the body, and placental circulation. Left ventricular output is directed toward the coronary and cerebral circulations, with a small portion crossing the aortic isthmus to perfuse the lower body. Intracardiac streaming across the foramen ovale results in the relatively high degree of oxygenated blood returning via the ductus venosus to be directed to the organs in greatest need of oxygen delivery for development—the heart and head.

At a common filling pressure due to an unobstructed interatrial communication (foramen ovale), if right ventricular stroke volume exceeds left ventricular stroke volume, then the right ventricular cavity chamber must be larger than the left. Echocardiographic evaluation of the human fetal heart confirms this to be the case. In addition, imaging the human fetal heart reveals the right and left ventricular wall thicknesses to be approximately equivalent, resulting in a greater radius-to-wall thickness ratio for the right ventricle than for the left. This results in a greater wall stress for the right ventricle, as per Laplace's law, where wall stress is directly

proportional to transmural pressure and radius but inversely proportional to wall thickness. One can therefore predict that the right ventricle will exhibit greater sensitivity to changes in afterload, such as an increase in vascular resistance, than the left ventricle [41]. Although physiological stressors, such as increased systemic arterial pressure, affect both ventricles, the right ventricle is affected to a greater degree than the left in the developing fetus [39]. Hence, under conditions of undue afterload or increased preload, the right ventricle will manifest hypertrophy, dilatation, or dysfunction before the left ventricle.

Uniqueness of the Fetal Circulatory System

Fetal circulatory patterns differ markedly from circulatory patterns of the mature adult. A number of intracardiac and vascular passages exist that allow for blood streaming patterns that are unique to fetal life [43]. Fundamentally, the right and left ventricles function in parallel in order to perfuse the body as well as a richly vascularized, low-resistance circuit—the placenta. The placenta is the organ responsible for metabolic exchange and receives 50% of the combined cardiac output of the fetal heart. Placental vascular resistance continues to decrease during gestation; however, it can be altered either primarily or secondarily due to disease states. Alteration of placental resistance can have profound effects on the developing circulatory systems within the fetus and on the developing myocardium.

Doppler echocardiography allows for the ability to examine blood flow patterns in various segments of the fetal cardiovascular system [1]. Well-defined patterns of flow for normal and abnormal states have been identified [23]. Alterations in normal patterns may signify important changes in physiology; hence, understanding the basis of these patterns is important.

Ductus Arteriosus

The ductus arteriosus connects the main pulmonary artery to the descending aorta and is responsible for carrying the majority of blood flow to the lower body and placenta. The normal flow pattern in the ductus arteriosus consists of a predominant systolic peak and a second low-velocity diastolic wave of continuous flow up until the next beat. Systolic flow is related to ventricular systolic thrust, whereas diastolic flow is related to the combined lower extremity and placental resistances and signifies runoff into the placental circulation. A measure of flow across the ductus arteriosus is the pulsatility index, calculated as the Doppler-derived peak systolic velocity minus the end diastolic velocity divided by the velocity–time integral of the entire beat. Elevated diastolic velocity and hence a low pulsatility index can be seen in the presence of ductal constriction, as may occur after maternal administration of indomethacin for tocolysis [36]. Sacrococcygeal teratoma or lower body arteriovenous malformation may also cause an increase in ductal diastolic velocity, leading to an abnormally low pulsatility index.

Aortic Isthmus

The aortic isthmus is the region of the aorta between the take-off of the left subclavian artery and the insertion of the ductus arteriosus. Fouron and colleagues [14] studied the flow patterns across this region and consider it a unique site since it straddles the outputs of the two fetal cardiovascular ejection systems, the right and left ventricles. Normally, flow is anterograde across the isthmus in both systole and diastole. However, in disease states such as in impaired left ventricular output, due to either congenital LV hypoplasia or acquired LV dysfunction, flow across the aortic isthmus may be retrograde in systole. In addition, conditions that reduce upper body vascular resistance such as a cerebral arteriovenous malformation may result in retrograde flow in the aortic isthmus in diastole [38]. In a compensatory protective manner, the stressed fetus may exhibit a profound autoregulatory diminution in cerebrovascular resistance in order to preserve cerebral perfusion. In such a circumstance, abnormal retrograde diastolic flow in the aortic isthmus may be seen.

Middle Cerebral Artery

Doppler echocardiographic assessment of middle cerebral artery (MCA) flow patterns can be performed to assess the effects of pathological states on overall fetal cerebrovascular flow [24, 28, 51]. In the normal state, resistance is relatively high with low diastolic velocity [28]. Under conditions of fetal anemia, peak systolic velocities are elevated [51]. Under conditions of fetal stress, cerebrovascular resistance decreases and diastolic flow increases [37]. It is useful to compare resistances between the MCA and the umbilical artery, with the resistance in the latter normally being much lower than that in the former. Hence, identification of elevated diastolic velocity in the MCA and a calculated MCA pulsatility index that is lower than the umbilical artery pulsatility index suggest that the cerebral circulation is abnormally vasodilated. This phenomenon, known as brainsparing, is a compensatory response seen under adverse conditions [10].

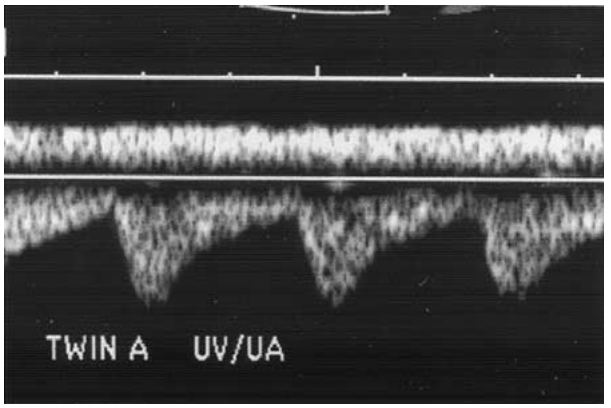

Fig. 3. Umbilical cord Doppler tracing in a normal twin. Flow above the baseline is continuous nonphasic flow of the umbilical vein, and flow below the baseline is umbilical arterial flow. Note thepresence of a systolic peak and continuance of flow into systole up until the next beat.

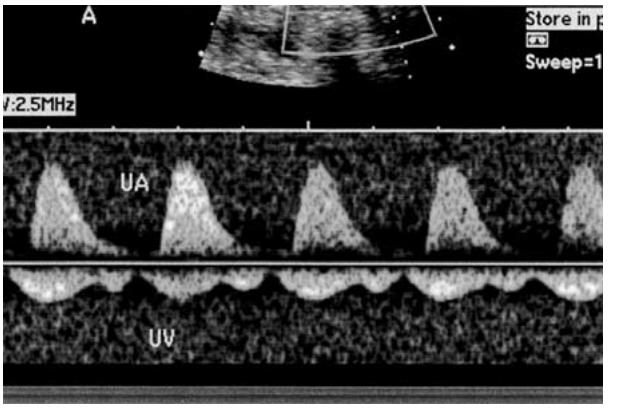

Fig. 4. Umbilical cord Doppler tracing in an abnormal fetus with twin–twin transfusion syndrome (recipient). Note the diminished umbilical arterial (*UA*) diastolic flow suggestingelevated vascular resistance. The umbilical vein (*UV*) exhibits pulsations, with diminution of flow in ventricular diastole, as determined by looking at the UA flow above. Diminished UV flow in diastole suggests impaired forward flow during ventricular diastole, likely related to abnormal ventricular compliance.

Umbilical Arteries

The placenta has the unique characteristic of having the lowest vascular resistance of any normal structure in the human body. Hence, the two arterial vessels arising from the iliac arteries traveling to the placenta carry a significant amount of blood in both systole and diastole. The normal umbilical arterial pulsatility index is low and progressively decreases during gestation (Fig. 3) [2]. Abnormalities of placental resistance, such as occurs in diseases of placental insufficiency or the twin–twin transfusions syndrome, are reflected as a diminution in diastolic flow and increase in pulsatility index [24]. In severe cases of placental vascular disease, reversal of diastolic flow can be seen. This signifies the presence of marked inequity in regional vascular resistances, with an impetus toward flow away from the placenta in diastole to a region within the fetus of vascular resistances that is lower than the placenta.

Umbilical Vein

The umbilical vein carries oxygenated blood back from the placenta to the fetus. Umbilical venous flow is normally low velocity, continuous flow without the presence of any significant phasic components [22]. Pulsations or phasic flow suggest a physiological abnormality. Simultaneous recording of both umbilical artery and umbilical vein flow patterns can help elucidate the etiology of the hemodynamic derangement by identifying the timing of events. Diminution of umbilical venous flow during the systolic wave of umbilical arterial flow suggests impairment of forward flow during systole. This can be due to severe tricuspid regurgitation with transmittal of pressure proximally toward the inferior vena cava and umbilical vein. Diminution of umbilical venous flow during the diastolic portion of umbilical arterial flow suggests impaired diastolic filling of the right ventricle. This can be seen under conditions of a stiff, noncompliant right ventricle (Fig. 4).

Ductus Venosus

The ductus venosus connects the umbilical vein, after its entry into the fetal abdomen, with the inferior vena cava just as it enters the right atrium. Flow in the ductus venosus is normally phasic but all anterograde toward the heart (Fig. 5). This is in contradistinction to the inferior vena cava, in which there is normally a small amount of reversal of flow during atrial systole. Phasic periods of absent forward flow, or reversal of flow in the ductus venosus, are considered abnormal and may be due to impaired relaxation of the heart (Fig. 6) [25, 29]. Many investigators consider abnormal flow patterns of the ductus venosus a very sensitive marker of fetal unwellness, particularly under conditions of intrauterine growth retardation [23].

The Fetal Cardiovascular System during Physiological Stress

The fetal cardiovascular system exhibits a unique set of physiological responses to the stress of hypoxia. Fetal hypoxia can be due to maternal hypoxemia,

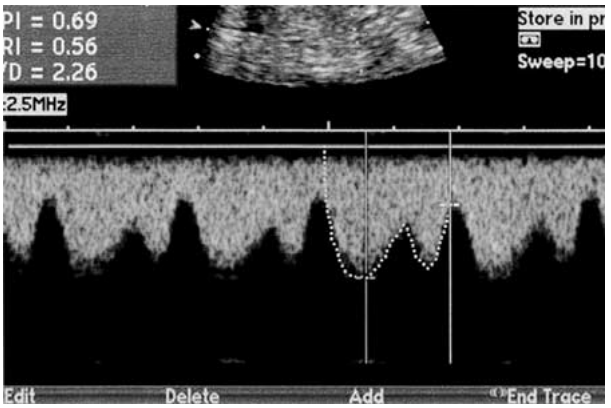

Fig. 5. Normal flow in the ductus venosus. Note that the flow is phasic and all anterograde. Pulsatility index (*PI*) calculations reveal a low value.

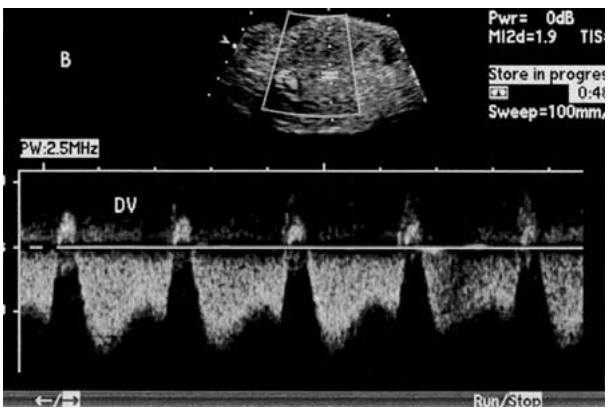

Fig. 6. Abnormal flow pattern in the ductus venosus (*DV*) with reversal of flow, as noted above the baseline. This is likely due to transmission of flow back to the DV during atrial systole and suggests markedly abnormal ventricular compliance.

restriction of uterine blood flow, impaired placental function, or restriction of umbilical blood flow via cord compression. Unlike the adult circulation, which responds to hypoxia by increasing heart rate, the fetal heart responds with bradycardia. Our knowledge concerning these responses is derived from the sheep model [42]. Chemoreceptors in the fetal aorta respond to ascending aortic blood pO_2 values below 18 or 19 Torr by inducing bradycardia. Fetal hypoxia due to maintenance of flow but with decreased oxygen content, such as with maternal hypoxemia or impaired placental gas exchange, results in maintenance of fetal combined cardiac output but with remarkable changes in blood distribution. Blood flows to the myocardium and the adrenal glands are increased dramatically, cerebral flow is moderately increased, and renal and gastrointestinal flows are moderately reduced. Flows to the lungs and peripheral circulation of muscle, skin, and bones are markedly reduced. Using microspheres, Rudolph and colleagues [11] demonstrated increased preferential streaming of ductus venosus and left hepatic venous flow across the foramen ovale, resulting in an increased blood oxygen content for blood volumes reaching the left ventricle and subsequent coronary and cerebral circulations.

Fetal Cardiovascular Stress

Undue Preload

The fetal cardiovascular system can be perturbed by a variety of disorders that impose undue loading conditions. As mentioned earlier, the fetal heart has little preload reserve; hence, once beyond a mild increase in filling pressures, further augmentation of cardiac output cannot be achieved and fetal heart failure and hydrops ensue. Quantifying fetal blood flow volumes and output can be helpful. Cardiac output for the left and right heart in the fetus has been documented by a number of investigators using echocardiography [9, 27, 35]. Combined cardiac output in the normal fetus is in the range of 425–550 ml/min/kg and is maintained at this level throughout gestation.

Anomalies such as large artreriovenous malformation or sacrococcygeal teratoma (SCT) may result in a progressive increase in preload with consequential changes in the fetal myocardium. These anomalies are interesting in that they not only result in an increase in preload by virtue of a low-resistance circuit but also in the same manner reduce afterload on the fetal heart initially, with progressive increase in ventricular cavity wall stress over time. Silverman and Schmidt [45, 47] studied fetuses with SCT and performed serial Doppler echocardiography to assess changes in fetal cardiac output over time. They reported dramatic increases in combined cardiac output, beyond that believed to be achieved by the fetal heart, prior to the onset of hydrops.

At The Children's Hospital of Philadelphia, we have been studying fetuses with arteriovenous malformation-type anomalies prior to fetal surgical intervention. Serial Doppler echocardiography has been useful in monitoring these fetuses and has been a helpful guide for determining the timing of intervention prior to the onset of heart failure and hydrops. We evaluated 27 fetuses with 72 echocardiograms at 20–37 weeks of gestation; 18 with SCT, 7 with vascular neck mass, and 2 with cerebral arteriovenous malformation (unpublished data). Cardiothoracic ratio, combined cardiac output, and atrioventricular valve regurgitation as assessed by color Doppler echocardiography were recorded. Patients were categorized as either well throughout gestation (group 1)

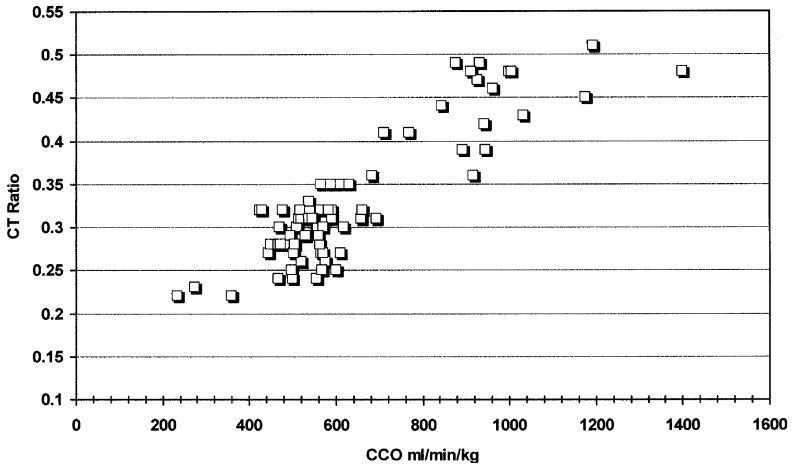

Fig. 7. Relationship of combined cardiac output (*CCO*) to cardiothoracic (*CT*) ratio in 27 fetuses with anomalies of ventricular volume overload. As CCO increases, the fetalheart compensates by a linear increase in size ($r = 0.82$).

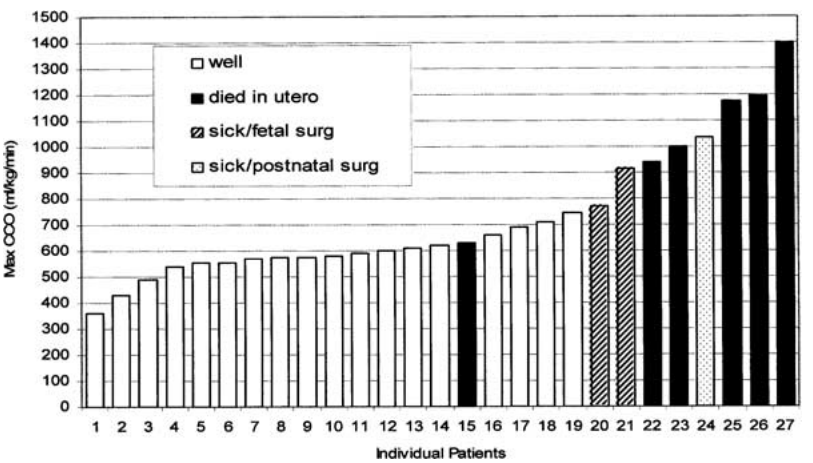

Fig. 8. Graph of maximal combined cardiac output (*CCO*) achieved for each of the individual 27 fetuses studied. Fetal surgical resection of the SCT was performed in patients 20 and 21 due to progressive symptoms. All patients with CCO less than 750 cc/kg/min did well except for patient 15. This patient exhibited a rapid increase in CCO over a short period of time as well as reversal of flow in the umbilical artery.

or unwell (group 2), defined as exhibiting signs of hydrops such as ascites, pleural or pericardial effusion, or experienced fetal demise. A close association was present between combined cardiac output as a reflection of degree of preload and cardiothoracic ratio (Fig. 7). In addition, the maximum combined cardiac output achieved for any individual patient predicted outcome (Fig. 8). The maximal combined cardiac output ranged from 370 to 1400 ml/min/kg. Most fetuses did well without evidence for hydrops until reaching 700–800 ml/min/kg combined cardiac output. Only 1 fetus with combined cardiac output of less than 750 ml/kg/mm died *in utero*. This fetus exhibited an extremely rapid increase in combined cardiac output and had evidence of reversal of diastolic flow in the umbilical artery, suggesting a steal phenomenon from the placental circulation. The grade of atrioventricular valve regurgitation, as a consequence of progressive ventricular dilatation due to increasing preload, was higher in group 2 than in group 1 (Fig. 9).

Twin–Twin Transfusion Syndrome

Twin–twin transfusion syndrome (TTTS) occurs in the presence of diamniotic, monochorionic twin gestation. Although the pathophysiology is not fully understood, it is believed that vascular connections deep within the placental mass cause an unstable equilibrium with shift of blood volume from the donor twin to the recipient [5]. The donor twin manifests impaired growth and oligohydramnios, whereas the recipient twin exhibits increased somatic growth

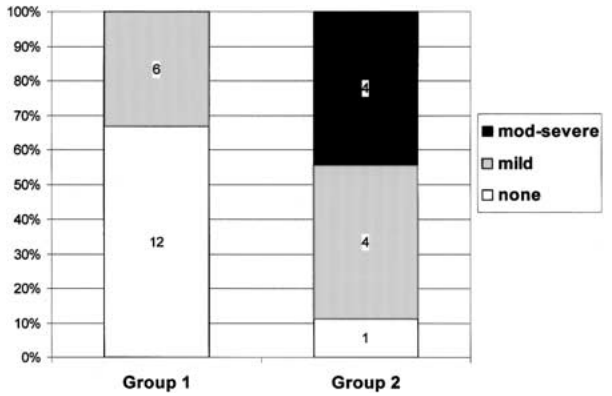

Fig. 9. Graphical display of the degree of atrioventricular valve regurgitation for group 1 (well) fetuses and group 2 (unwell) fetuses. No patient in group 1 had hemodynamically significant regurgitation, whereas four of nine patients in group 2 had hemodynamically significant regurgitation.

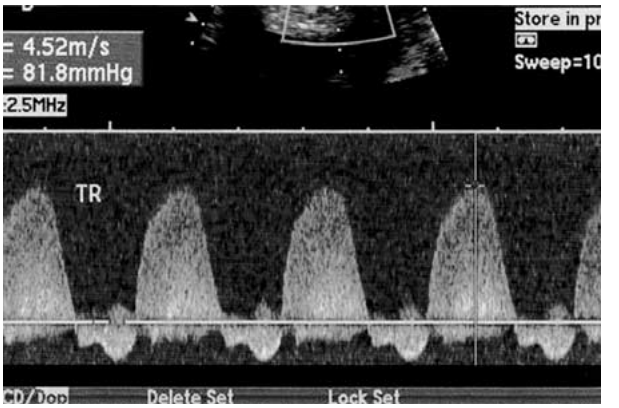

Fig. 10. Continuous-wave Doppler tracing across the tricuspid valve in a 21-week gestation recipient fetus of the twin–twin transfusion syndrome. Peak velocity is 4.5 m/sec, consistent with a severely elevated systolic right ventricular cavity pressure of more than 80 mmHg.

and manifests polyhydramnios. Fetal mortality in TTTS is high and neurological damage is common [6, 52] The syndrome is the most common cause of death in twin gestations.

Most interesting are the cardiovascular perturbations that take place in the donor and recipient partners of this condition [12, 48, 53]. The donor twin exhibits findings of volume depletion with nephrosclerosis. Investigators have documented elevated levels of endothelin-1 in the donor fetus in TTTS [4] as well as evidence for a stimulated renin–angiotensin system with increased levels of angiotensin II [32]. Doppler echocardiographic sampling in the umbilical artery of the donor twin commonly reveals evidence of markedly increased vascular resistance with diminished diastolic flow and elevated pulsatility index. Although the donor twin heart likely experiences an overall increase in total vascular resistance, myocardial changes are rare. Ventricular function is typically preserved, as is atrioventricular valve competence. Investigators have found abnormalities in vascular compliance with increased pulse-wave velocity in surviving postnatal donor twins [7]. This finding suggests that the prenatal pathophysiology of TTTS influences the developing donor fetal vascular system, resulting in a programmed postnatal abnormality that may be lifelong. Abnormal vascular compliance may predispose to hypertension and atherosclerotic disease. Long-term outcome studies in these patients are needed to better understand the implications of this fetal cardiovascular derangement.

The most dramatic cardiovascular changes in TTTS occur in the recipient twin. The recipient twin manifests a cardiomyopathy that is progressive and can be observed in its evolution. At first, ventricular dilatation and hypertrophy can be identified as a consequence of the increased volume load. Curiously, many recipient fetuses display marked degrees of ventricular hypertrophy, with only mild evidence of dilatation. Atrioventricular valve regurgitation is common and can be severe. Estimation of right ventricular cavity systolic pressure by measurement of tricuspid regurgitant jet velocity reveals pressures that may be two or three times normal (Fig. 10). The right ventricle is typically affected first and to a greater degree than the left ventricle; however, as the process progresses LV hypertrophy and hemodynamically significant mitral regurgitation can be seen. A possible explanation as to why ventricular hypertrophy out of proportion to the degree of dilatation is seen may relate to hormonal factors crossing placental connections from the donor twin. Not only is there a shift in blood volume from donor to recipient but also the mediators released by the donor in response to its hypovolemia are transported across as well. Hence, the recipient twin experiences an increase in blood volume and is also exposed to mediators that result in vasoconstriction and ventricular hypertrophy. Specifically, angiotensin II has been identified as a potent stimulant for myocardial hypertrophy [26]. Angiotensin II production is under the control of angiotensin converting enzyme activity, for which a genetic polymorphism has been identified [8]. It is conceivable that this polymorphism, and hence variably expressed angiotensin converting enzyme activity, may explain some of the variability in frequency and severity of myocardial hypertrophy seen in the TTTS. Segar and colleagues, [46] demonstrated a direct increase in left ventricle mass in fetal sheep infused with angiotensin II, independent of increase in systolic afterload, suggesting a direct hormonal effect on the developing heart.

Further investigation in this intriguing area is warranted.

In some cases, the recipient fetus continues to develop progressive ventricular hypertrophy, ventricular dysfunction, and valvar regurgitation, ultimately leading to hydrops and demise despite therapeutic maneuvers. In a small fraction of recipient twins, the cardiomyopathy evolves toward progressive right ventricular hypertrophy with development of pulmonary infundibular stenosis and even pulmonary atresia [31]. When this occurs, the recipient twin has transmogrified into an anomaly that is identical to the congenital form of pulmonary stenosis/atresia with intact ventricular septum. We, as have others, have observed the process in which a hypertrophied, poorly functioning right ventricle of a recipient twin at 18–20 weeks of gestation progresses in its hypertrophy toward cavity diminution with impaired pulmonary annular growth. This phenomenon can best be described as development of an ''acquired'' form of ''congenital'' heart disease and supports the notion that some forms of congenital heart disease may in fact be a consequence of early gestational changes in loading conditions and flow.

Outcome of the recipient twin cardiomyopathy of TTTS can vary. No completely successful therapeutic intervention has been developed, although amnioreduction in the polyhydramniotic twin has been shown to halt progression and reduce mortality [34]. In addition, placental laser therapy in which vascular anastomoses between donor and recipient are interrupted has shown promise, with cessation of progression and even regression of cardiomyopathy seen [50]. A randomized multicenter National Institutes of Health sponsored trial between amnioreduction and placental laser therapies is under way. Gardiner and colleagues [16] reported on improved vascular mechanics and arterial distensibility in survivor children after intrauterine laser photocoagulation therapy for TTTS. This suggests that vascular programming can perhaps be altered by fetal intervention (i.e., reprogramming).

Conclusion

The fetal cardiovascular system exhibits a unique and complex physiology. The tools of echocardiography have tremendously enhanced exploration of this system. However, much remains to be learned about the progression of disease processes and the physiological events that take place in early gestation, with the goal to develop a continuum of understanding between the earliest molecular and cellular events at conception and full maturation of the cardiovascular system. Of growing interest is the potential impact of fetal events on the programming of cardiovascular phenomenon that become manifest only later in life. Of great promise is the possibility that prenatal intervention may alter the development of detrimental physiological phenomenon, thereby improving both fetal and mature adult outcomes.

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