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Invited Lecture†

Fetal cardiac function and circulatory dynamics—the impact of Doppler echocardiography

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In but a few years, clinical fetal cardiology has become a well-established discipline of fetal medicine. This rapid development was essentially due to the advent of fetal echocardiography, combined with Doppler technology—techniques which gave clinicians and researchers the means to verify on humans the fundamental concepts of fetal circulatory physiology and pathophysiology that were based on the pioneer works performed mostly on fetal sheep. It is my intention to review these basic experimental concepts as they pertain to human ultrasonographic observations. The review will be divided into three parts. First, the contractile characteristics of the fetal myocardium will be briefly discussed, underscoring its reaction to changes in loading conditions. Second, fetal cardiac performance and circulatory dynamics will be considered. Third, the balance between fetal cephalic and subdiaphragmatic vascular impedances, as assessed by Doppler flow velocity waveforms through the aortic isthmus, will be addressed.

Contractile characteristics of the fetal myocardium

Myocardial contractility

By definition, myocardial contractility is the intrinsic ability of muscle to generate force, independent of changes in preload, afterload and rate of contraction. When isolated fetal muscular strips are studied, the force generated by the fetal myocardium is consistently lower than that of the adult.[1] At all lengths along the length-tension curve, the active tension generated by the fetal myocardium is significantly lower than that observed in the adult. Conversely, the resting tension is lower with the adult myocardium. This, according to Friedman, would be due to the significantly greater proportion of non-contractile protein in the fetal myocytes (60% in the fetal myocardium in comparison to 30% in the adult),[1] along with the difference in activity of ATPase of the fetal and adult myosin isoforms.[2]

It must be emphasized that significant maturational changes are observed in the structure of the myocardium prior to birth.[3] In the more immature myocardial cells, the myofibrils are chaotically organized, and often are not oriented in the same direction as the long axis of the cell. Progressively, a maturational increase in the myofilamentous content of the myocyte is observed along with the process of formation of sarcomeres. All three events (organization of the myofibrils, increase in the proportion of myofilaments within the cell, and completion of the process of sarcomerogenesis) have been related to the maturational increase in the ability of the myocardium to contract during the fetal and neonatal periods.

The proportion of sarcoplasmic reticulum in the myocardium, and its ability to take up calcium, also increase with development.[4,5] The counterpart to this observation is that the more immature cells rely heavily on transsarcolemmal movement of calcium for their increase in cytosolic calcium. This relatively greater importance of transsarcolemnal movement of calcium in the immature myocardium could explain the greater effect of alterations in extracellular calcium concentration on the contractile response of the immature myocardium, and its high sensitivity to drugs that would decrease this transfer through the membrane.

Effect of changes in loading condition on the fetal myocardium

CHANGES IN PRELOAD—THE FRANK-STARLING PRINCIPLE

According to the Frank-Starling principle, as the length

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Table 1. The Frank-Starling principle and the fetal heart: points of discussion.

- Experiences with the isolated myocardium
- Experiences with the intact heart (dp/dt max)
- Problem with volume infusion
- Problem with the index of preload
- Diastolic ventricular interaction

of the sarcomere increases, there is an increase in the force of contraction, up to a maximal length. In the intact mature heart, this relationship translates to the well-known observation that an increase in end-diastolic volume causes an increase in stroke volume. The accepted concept that the fetal heart is stiff[6] was the basis for the controversy concerning the application of the Frank-Starling relationship during fetal life. In response to the question—does the Frank-Starling relationship play any role in the regulation of fetal cardiac output?—the answer had been mostly negative. It was felt that variations in fetal cardiac output were essentially linked to changes in heart rate.[7] The lack in the ability of the fetal heart to respond to the Frank-Starling mechanism was also supported by the observation that infusion of vascular fluid to fetal sheep did not result in any significant increase in either right or left ventricular output.[8,9] In later investigations, however, Kenny and collaborators showed, using echo-Doppler technology, that variations in fetal heart rate were not necessarily associated with alterations in cardiac output.[10]

Without delving into too many details, the following comments can be made on this controversial aspect of fetal myocardial function (Table 1). First, one must remember that the Frank-Starling relationship has been demonstrated in the isolated myocardium of the fetal heart.[1] As would be anticipated, however, when the relationships between fiber tension and both extent and velocity of shortening are plotted, the resultant lines for the fetus always fall below those of the adult myocardium. Second, in the intact fetal heart the Frank-Starling mechanism has also been observed when the maximum rate of rise of left ventricular pressure (dp/dt max) was used to assess the effect of changes in end-diastolic volume. In this circumstance, dp/dt max increased when end-diastolic volume increased.[3] Third, infusion of large volumes in the fetal circulation is required to achieve a significant change in venous return because of the large compliance of the umbilical placental circulation. This could cause a significant increase in afterload which, in turn, would limit any increase in stroke volume achieved by an increase in preload.[11]

Another element, which is probably the main reason for this controversy, is the index used to evaluate preload. Because end-diastolic volume is difficult to measure in life, end-diastolic pressure has been substituted. The most appropriate alternative would be the end-diastolic diameter. This is especially true in the fetus because of the stiff nature of the myocardium.[6] In fact, when ventricular dimensions are used in the fetal heart to assess the effect of preload on ventricular stroke volume, a significant positive relationship between end-diastolic volume and stroke volume is found.[3] Post-ectopic increase in stroke volume is another example of this relationship, which is frequently observed during fetal echocardiography.

Finally, during fetal life, the diastolic interaction between ventricles must be taken into account. Because of the widely patent oval foramen, any increase in right ventricular end-diastolic pressure should be transmitted to the left ventricle. The simultaneous increase in diastolic pressure on both sides of the ventricular septum should limit the possibility of expansion of volume in one ventricle and, by the same token, should impose limitations to the Frank-Starling principle. In this respect, although Kirkpatrick et al[12] reported that fetal left ventricular end-diastolic dimension was an important determinant of stroke volume, they could only induce a small increase in ventricular output by raising filling pressures. It is interesting to note that, after birth, left ventricular filling and stroke volume capabilities may be rapidly and significantly enhanced through the decrease in neonatal right ventricular afterload and endocavitary pressure. Thus, blood infusion to newborn lambs a few hours after birth causes a marked increase in atrial pressures related to low myocardial compliance, but also results in a significant rise in left ventricular output.[13] This point must be kept in mind to explain the poor cardiac performance of neonates with persistent pulmonary hypertension.

It can be concluded, therefore, that the fetal myocardium has the ability, albeit limited, to respond positively to the Frank-Starling mechanism. To understand more clearly the diastolic performance of the fetal heart, nonetheless, it is important to clarify the physiological components of cardiac preload during intrauterine life. Each ventricle must be considered separately.

COMPONENTS OF LEFT VENTRICULAR PRELOAD

The components of left ventricular preload during fetal life are shown in Table 2. In a normal fetus, left ventricular preload is greatly influenced by the size of the oval foramen. Although the primary role of an insufficient opening between the two atriums in the development of left ventricular hypoplasia is frequently difficult to establish, there are documented cases in the literature where no other anomaly could be found other than a small foramen. It must be remembered that interference with the right-to-left atrial shunting could

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Table 2. Components of preload and afterload of the fetal heart.

	Left ventricle	Right ventricle
Preload	Oval fossa	The flow from superior caval vein
	Fraction of flow from inferior caval vein	Fraction of flow from inferior caval vein
	Pulmonary venous return	Diastolic function of the left ventricle
	Diastolic function of the right ventricle	
Afterload	Vascular resistance	Vascular resistance
	Head and arms	Subdiaphragmatic circulation
	Partly, in the sudiaphragmatic circulation	Through the arterial duct

occur either at the foramen itself, or at the level of the flap valve guarding this opening (Figure 1 A-B). In view of the presumed importance of the foramen for the development of the left cardiac cavities, it is amazing to observe the great variability of its size on echocardiography (Figure 1 C-D). The value at which the foramen should be considered abnormally small is not known. In this regard, Atkins and associates[14] proposed the ratio of the area of the foramen ovale to the area of the atrial septum, measured on pathological specimens, as a sensitive marker of transatrial shunting. It is then crucial, of course, to define accurately the atrial septum! Most fetal echocardiographers will rely on the size of the left cardiac cavities to diagnose indirectly a functionally insufficient oval foramen. One can speculate that a significant proportion of transient tachypnea of the newborn could be transient left ventricular dysfunction due to a small oval foramen causing a reduction in transatrial shunting during fetal life.

Left ventricular preload is also dependent upon blood drained by the inferior caval vein. It is well known that inferior caval venous blood divides into two unequal parts, one part crossing the oval foramen towards the left atrium (approximately 30 to 40%) while the other part flows into the right atrium and ventricle. Preferential streaming of the blood from the venous duct toward the left atrium has been reported in fetal sheep.[15,16] This partitioning can be well documented on Doppler-color mapping of the flow velocities of blood coming from the inferior caval vein, which can be seen filling both the left and the right atriums.[17] It must be kept in mind that a decrease in the absolute value of volume flow in the vein does not necessarily mean a decrease in left ventricular preload. Indeed, as has been demonstrated by many investigators, conditions that decrease umbilical blood flow and cardiac output, such as placental circulatory impairment, increase the proportion of blood crossing through the oval foramen while maintaining within normal limits the absolute value of the better oxygenated blood going to the brain.[18]

A third element of left ventricular preload is the volume of flow coming from the pulmonary veins. Based on data gathered from experiments on lambs, it has been accepted that no more than 7 to 10% of the combined cardiac output goes to the lungs, a phenomenon explained by the elevated pulmonary vascular resistance during fetal life.[19,20] These previously undisputed data were challenged recently by a report stating that pulmonary arterial flow, measured by Doppler technique on 38 normal human fetuses, increased by almost fourfold over the period of gestation studied, and amounted to a mean of 22% of the combined ventricular output.[21] Many factors such as species differences, gestational age and methodology could explain such a wide discrepancy between the two sets of data. I must say that I have always been puzzled by the normal development of the pulmonary veins in view of the accepted concept of a very low pulmonary flow during intrauterine life. Moreover, at birth, the entire cardiac output, which can be significantly increased by the transitory left-to-right ductal shunt, is well accommodated by the pulmonary vascular network without any sign of venous obstruction. This certainly is an aspect of fetal hemodynamics which deserves clarification.

Diastolic function of the right ventricle should also influence the left ventricular preload, via the widely patent oval foramen, which allows transmission of flow and pressure from the right to the left atrium.

COMPONENTS OF FETAL RIGHT VENTRICULAR PRELOAD

The volume load on the right ventricle consists of not only blood from the superior caval vein, but also the fraction of the inferior caval venous return that did not go through the oval foramen. Approximately 65% of blood ejected by the left ventricle returns through the superior caval vein entirely to the right ventricle. This represents 21% of the total venous return.[20] On the other side, most of the blood ejected by the right ventricle, plus about 40% of the ejectate from the left ventricle, returns to the heart via the inferior caval vein, which carries 70% of the total venous return. This significant difference in volume flow between the superior and inferior caval veins is reflected by their respective Doppler flow profile (Figure 2). Any changes in the

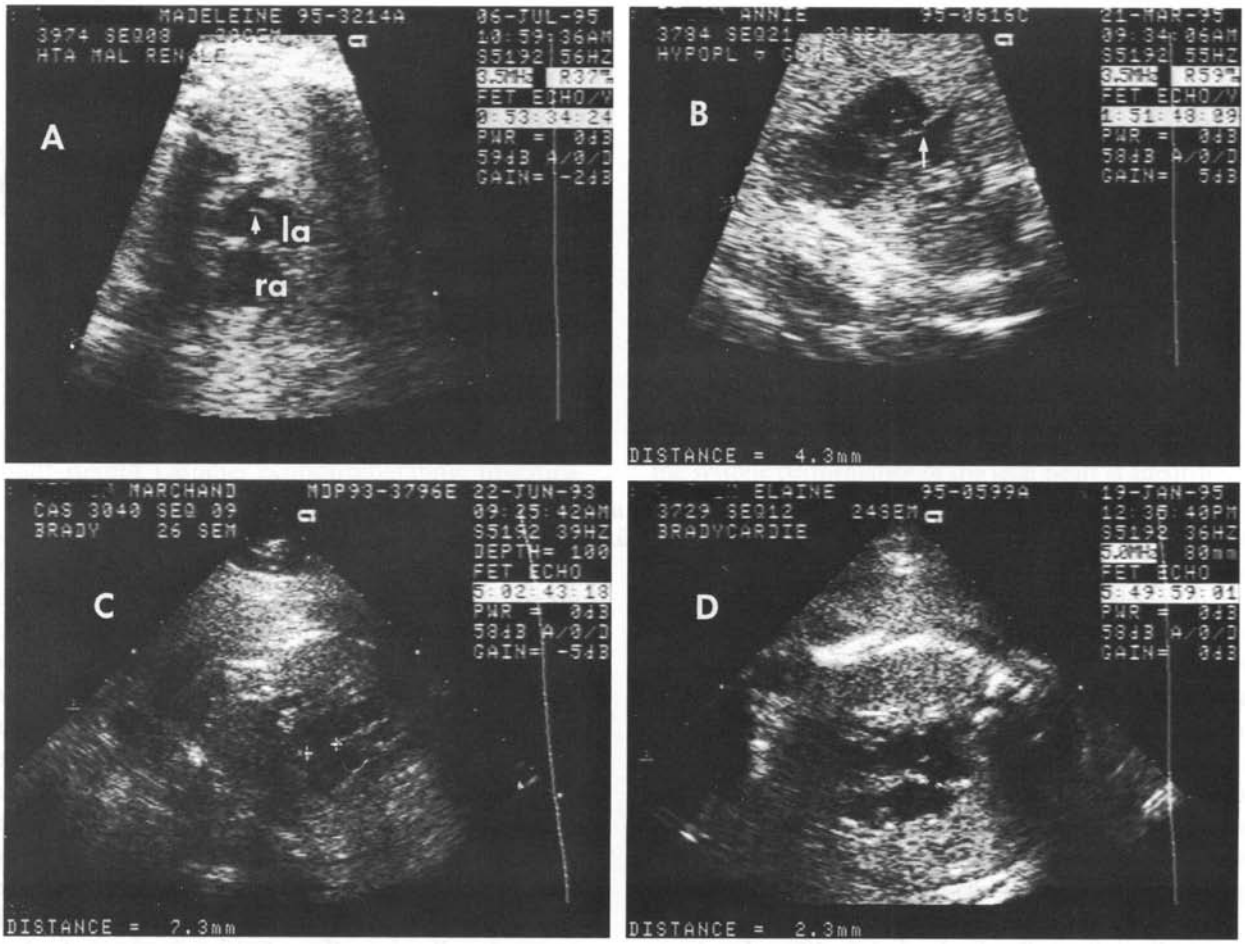

Figure 1. *(A-B) Two examples of the shape and mobility of the flap valve (primary septum) of the oval foramen. (A) The valve is redundant and nonobstructive (arrow); gestational age: 29 weeks (la: left atrium; ra: right atrium). (B) In this 30-week-old fetus, an interatrial opening of 4.3 mm is obstructed by a small valve with very little mobility (straight arrow). Coarctation of the aorta was diagnosed and confirmed after birth. (C-D) The difference in the size of the oval foramen (limited by stars) of these two fetuses is obvious. (C) 7.3 mm at 26 weeks and (D) 2.3 mm at 24 weeks. The development of the left cardiac cavities was normal in both instances.*

distribution of blood toward the brachiocephalic and subdiaphragmatic circulations should alter the flow relationship between the two caval veins. This point is well illustrated in Doppler flow velocity recordings from fetuses suffering intrauterine growth retardation, in whom a decrease in umbilical blood flow causes a fall in inferior caval venous return, while cerebral vasodilation is responsible for an increase in superior caval venous flow. In these circumstances, a reciprocal shift is observed, and flow velocity waveforms in the superior caval vein resemble those of the inferior vein and vice versa.[22]

Left ventricular diastolic performance should also influence right ventricular preload. It is known that the flap valve of the oval foramen behaves in one-way fashion, allowing blood only to go from right-to-left. Consequently, an increase in left atrial pressure, such as that observed in left ventricular diastolic dysfunction, should tend to close the oval foramen, and should have very little repercussion on the right atrial pressure, but should certainly cause significant volume overload of the right ventricle. Figure 3 is an example of such a case. Primary fibroelastosis of the left ventricle in this fetus caused marked diastolic left ventricular dysfunction. The flap valve of the oval foramen can be seen bulging into the right atrium. Obviously, based on the paradoxical position of this structure, a gradient is present between the two atriums, favoring the left atrium. In such a case, the volume load of the right ventricle is increased since the blood from the inferior caval vein should go entirely into the right ventricle.

CHANGES IN AFTERLOAD

The resistance against which the ventricles must eject blood encompasses their ventricular mass, the inertia of blood and the resistance of the peripheral vascular bed. A reliable measure of ventricular afterload should, therefore, consider factors both internal and external to the

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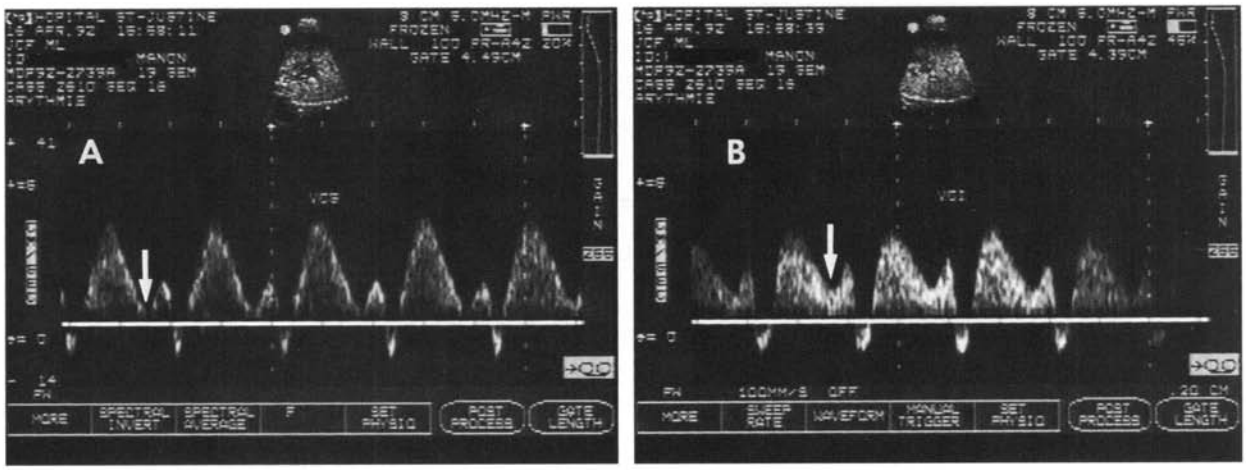

Figure 2. *Illustration of the difference between the flow velocity waveforms of the superior (A) and inferior (B) canal veins. Between ventricular systoles and diastoles (arrow), the velocities fall almost to zero in the superior canal vein, reflecting the smaller volume of flow in this vessel.*

myocardium. In the clinical setting, however, the most commonly used index of afterload is the peripheral vascular resistance. As with the adult heart, the ability of the fetal myocardium to shorten is decreased as afterload is increased.[1] When the relationship between shortening velocity and afterload of the fetal myocardium is compared to that of the adult, the fetal myocardium shortens more slowly than does the adult myocardium against the same relative load.[1]

Interestingly, studies on fetal sheep have shown that, for a similar increase in afterload, a significantly greater reduction in right ventricular stroke volume was observed compared to the left.[23] This difference in ventricular response is well illustrated by the result of a series of experiments on sheep fetuses done in our laboratory.[24] In these studies, resistance to placental flow was created by compression of both umbilical veins. At basal state, normal right ventricular preponderance was observed, the right ventricle contributing approximately 60% to the combined cardiac output. With a progressive increase in resistance to placental flow, the contribution from the right ventricle progressively decreased, while the left ventricular contribution increased proportionally. One explanation offered for this difference was that the right ventricle normally had a higher workload than the left, and would therefore be proportionally more affected with a change in afterload. Another explanation could also be the difference in morphology of these two cavities.[25]

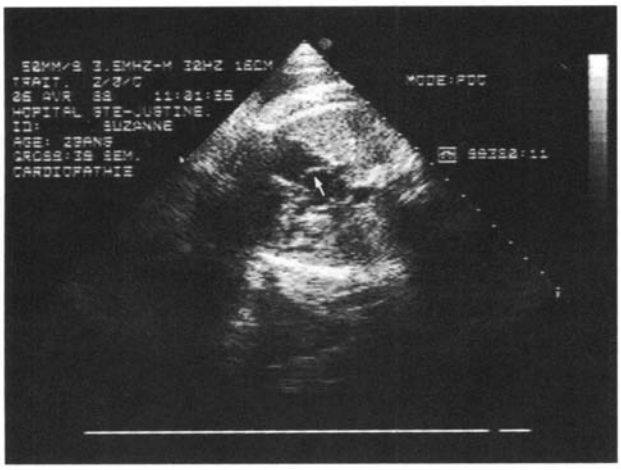

Figure 3. *Real-time echocardiographic imaging of the interatrial septum and the flap valve of the oval foramen of a fetus with left ventricular fibroelastosis. An abnormal bulging of the septum towards the right atrium is observed (arrow).*

COMPONENTS OF FETAL VENTRICULAR AFTERLOAD

As previously mentioned, during fetal life approximately 65% of the blood ejected by the left ventricle perfuses the upper body. For a given ventricular mass, therefore, any change in resistance or pressure in these vascular beds will specifically influence the afterload of the left heart. On the other hand, the right ventricular outlet during intrauterine life consists of a large main pulmonary trunk from which branch smaller left and right arteries at very sharp angles. The widely patent arterial duct forms a natural prolongation of the pulmonary trunk toward the descending thoracic aorta. Somewhere between 80 to 90% of the blood ejected by the right ventricle goes through the duct into the descending thoracic aorta with minimal resistance. Because of this arrangement, fetal right ventricular afterload is essentially dictated by the resistances of the various vascular beds distal to the thoracic descending aorta. The significantly lower resistance and higher volume flow of the umbilical circulation confers to the placental vessels a dominant role in establishing the level of the peripheral vascular component of right ventricular

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afterload. There are well known clinical situations in fetal cardiology where an increase in afterload could be responsible, at least in part, for fetal myocardial dysfunction. One can think of the recipient fetus in the twin-to-twin transfusion syndrome. Another example by far more frequent is the rise in placental vascular impedance observed in certain cases of intrauterine growth retardation.

Fetal cardiac performance and circulatory dynamics

Cardiac performance

With all these elements taken into account, how does the fetal heart perform its primary role, which is to eject blood? Recent Doppler echocardiographic investigations have allowed assessment of flow of blood in the human fetus as early as 18 weeks of gestation. When the combined right and left ventricular outputs/min normalized for fetal body weight are used to examine the ability of the developing human heart to eject blood, very little difference is noted from 18 weeks of gestation to term. There is an exponential relationship between stroke volume and gestational age for both ventricles corresponding to a concomitant increase in ventricular weights.[26,27] Of interest is the fact that, at term, the combined ventricular output of approximately 450 ml/kg/min calculated by Doppler echocardiography in the human fetus[26,27] is also the same as the one found in fetal lambs using radioactive microsphere techniques.[20] Furthermore, right ventricular preponderance as previously described in the sheep, expressed by a stroke volume approximately 20% greater than that of the left ventricle, has been observed in the human fetus,[26,28] despite speculations concerning the discrepancy between the cerebral mass of the two species. Besides cardiac output measurements, the use of other conventional ultrasonographic means of assessing intrauterine ventricular performance is hampered by technical difficulties including the small size of the heart, the distance between the transducer and the target organ and, for M-mode measurements, the absolute need for a perpendicular approach to the free walls. Peak velocity and acceleration time of the Doppler velocity waveforms through both arterial valves have also been used. In normal fetuses, acceleration time is known to be shorter in the pulmonary trunk than in the aorta.[29] This finding has been explained by the higher resistance of the pulmonary vascular bed in the fetus. As previously mentioned, however, the right ventricle is ejecting blood towards the placenta through a widely patent arterial duct. The possibility that the shorter acceleration time may be due to a better right ventricular performance with a higher stroke volume and a lower afterload deserves investigation.

In extrauterine life, ultrasound studies have been used to assess development of ventricular force using Newton's equation, which states that force is the product of mass and acceleration.[30] Based on this formula, it has been demonstrated that the fetal left ventricle develops significantly less force than the adult left ventricle.[31] It is worth mentioning, however, that development of pressure in the fetal left ventricle appears similar to that of the adult. For example, the peak first derivative of the left ventricular pressure (dp/dt max) has the same range in the fetal lamb as it does in the adult ewe, namely between 1500-3000 mm Hg/sec.[3] This range is the same as that observed in the child and adult. Based on flow, and despite the lower indices of contractility in the immature myocardium, it can be concluded that the systolic performance of the fetal heart is adequate.

The main limitations are more in the diastolic performance of the fetal heart. With the advent of Doppler ultrasound, it is possible to study the patterns and velocity of flow through the fetal atrioventricular valves. While, in extrauterine life, the E wave is predominant, it is now well established that the fetal profile is characterized by a higher peak A than E wave.[32] This has been interpreted as a reflection of the low compliance of the fetal myocardium. The fact that the E/A ratio increases progressively, and approaches unity towards the end of gestation, has also been considered as a sign of progressive improvement in myocardial compliance. There are, however, many factors that can influence the flow velocity profile through the atrioventricular valves. Basically, the E and A waves are the reflection of two different events. The E wave occurs early in diastole, and is caused by ventricular relaxation. The A wave is the result of the atrioventricular gradient created by atrial contraction late in diastole. For a given pressure, the amount of blood going across the atrioventricular orifices during atrial contraction is influenced, among other factors, by the ease at which the myocardial fibers can be distended. This, by definition, is ventricular compliance. We have recently shown that, throughout pregnancy, the peak velocity of the A wave does not change significantly, while that of the E wave steadily increases and is entirely responsible for the increase in the E/A ratio.[33] This observation would support the concept of a progressive maturational change involving almost exclusively the active process of ventricular relaxation.

Despite these maturational diastolic limitations, clinical conditions necessitating some adaptation of fetal ventricular diastolic performance are not necessarily associated with fetal death. Pediatric cardiologists with some experience in fetal echocardiography have all seen cases of congenital atrioventricular block with a heart rate of about 60 beats/min associated with a dilated end-diastolic ventricular diameter and no signs of myocardial failure (Figure 4). The same phenomenon can be observed in chronic fetal anemia, most frequently due

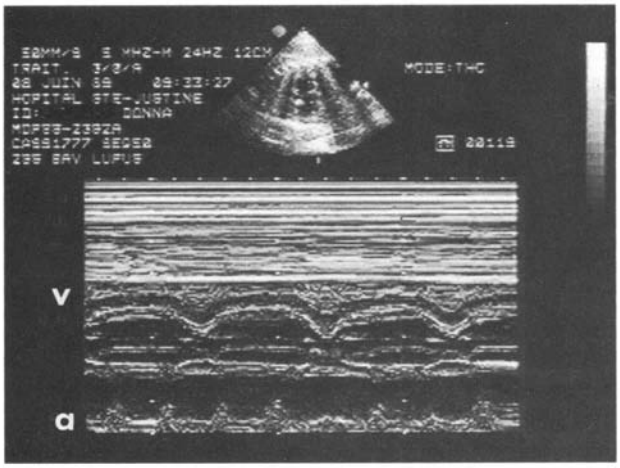

Figure 4. *Example of an intrauterine atrioventricular block. a: atrial rate of 150 beats/min (v: ventricular rate of 65 beats/min). Strong ventricular contractions are observed without any sign of cardiac failure.*

to alloimmunization. A recent report concerning the survival of a twin fetus in whom the other twin was acardiac is another illustration of the ability of the fetal myocardium to adapt to chronic diastolic overload.[34] In this example, the heart of the normal fetus was dilated (cardiothoracic ratio of 0.62) because of the increase in volume secondary to the perfusion of the acardiac monster. Besides confirming that the fetal myocardium can respond to the Frank-Starling mechanism, all these cases lead to speculations on possible biochemical maturational adaptation occurring in these fetal hearts with chronic volume overload. Advance maturation of the diastolic function is indeed a possibility. This is another area which deserves investigation.

Circulatory dynamics

The main hemodynamic features of the fetal circulation are presented in Table 3. The effect of elevated pulmonary vascular resistance on the pulmonary circulation has already been discussed. As for the low placental vascular resistance, this specific feature is now widely used as a Doppler index of fetal monitoring. Because of the low placental resistance, forward flow in this artery is normally recorded both in systole and diastole.[35] In cases of intrauterine growth retardation with an increased resistance to placental flow, the diastolic component of the flow velocity waveform disappears, or can even be reversed. Methods of measuring the volume of flow through the placenta based on Doppler recordings of blood velocities through the abdominal portion of the umbilical vein have also been described.[36,37]

The third characteristic of fetal circulatory dynamics is the parallel disposition of the two ventricles. In extrauterine life, it is well known that the left and right ventricles are disposed in series. Their outputs, therefore, are necessarily equal. In the fetus, both pumps are perfusing the same systemic circulation, the left via the ascending aorta, the right via the pulmonary trunk and the arterial duct. This arrangement has at least four hemodynamic consequences. First, the individual ventricular outputs do not need to be equal, and fetal cardiac output is logically expressed as a combined ventricular output. Another consequence is that both ventricles share the same systolic ejection pressure, which is about 70 to 80 mm Hg. Close to term, a slight increase in pressure has been reported in the pulmonary trunk compared to the systemic pressure. This could be due either to the greater flow through the right ventricle, or more likely to an active constriction of the duct. This last point would support the observation that Doppler flow recordings in the ducts of term fetuses show the highest peak velocity when compared to other arteries in the human central fetal circulation. As a third consequence, there is a reciprocal influence of the diastolic function of the two ventricles through a widely patent oval foramen. Fourthly, the parallel arrangement of the two ventricles is the key element in the intrauterine survival of fetuses with complex malformations. This could be called the "deviation road" concept. For example, in the case of hypoplasia of the left heart, the blood can be diverted toward the right ventricle without significant impairment in peripheral perfusion as long as right ventricular function is preserved.

Another widely accepted characteristic of the fetal circulation is the presence of intra- and extracardiac shunts, namely the oval foramen and the venous and arterial ducts. The physiologic and ultrasonographic aspects of the oval foramen have already been described. The venous duct is a vascular structure that can be readily identified using sonographic technique. Normally, Doppler flow recordings through the venous duct show an acceleration of velocity suggesting a gradient between the umbilical vein and the inferior caval vein. This gradient has been estimated to reach a peak of 3 mmHg during atrial filling.[38] This flow profile has been found altered in hydrops fetalis.[39] placental compromise[40] or in various conditions affecting central venous pressures.[40] Doppler velocimetry through the arterial duct has also been well investigated. The intrauterine constriction of the ovine duct by inhibition of prostaglandin synthetase has also been demonstrated in

Table 3. Hemodynamic features of the fetal circulation.

- An elevated pulmonary vascular resistance and reduced pulmonary flow
- A low placental vascular resistance and high umbilical flow
- Two ventricles working in parallel
- The presence of shunts

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the human.[42-43] Doppler criteria for a restrictive duct have been proposed by Huhta and collaborators and include a peak velocity over 2.0 m/sec in systole and 0.4 m/sec in diastole as well as a pulsatility index lower than two. The concept of the duct being an extracardiac shunt, while correct in extrauterine life where the two ventricles are in series, is questionable if not irrational during fetal life, where the two arterial outlets form two arches, the aortic and pulmonary arches, disposed in parallel. The arterial duct is but one segment of the pulmonary arch. This aspect will be discussed in the following section on the Doppler flow velocity profiles through the aortic isthmus.

The aortic isthmus

The aortic isthmus, located between the origin of the left subclavian artery and the aortic end of the arterial duct, establishes a communication between the two parallel systems of the fetal circulation permitting blood to be shunted from one system to another.

During systole, blood ejected by the fetal left ventricle should cause a forward flow through the isthmus, while the influence of right ventricular ejection could result in a retrograde flow. The final systolic pattern of the profile of isthmic flow will be determined by the relative contribution of the left and right ventricular ejections as well as the peripheral vascular impedance. Doppler investigation of the flow through the fetal aortic isthmus shows that a forward systolic flow is normally recorded. With the progression of gestation, however, a distinct and brief retrograde flow is noted at the end of systole. This short reversal of flow could be a reflection of right ventricular preponderance during this period of gestation.[44] In severe dysfunction of the left ventricle, as in aortic atresia with hypoplastia of the left heart, the isthmic flow is essentially a branch from the right ventricle, and the systolic flow is retrograde.

In diastole, when the two arterial valves are closed, the direction of flow in the isthmus will be influenced only by the relative impedance of the vascular beds of the upper and lower bodies. Doppler studies have confirmed that, in normal fetuses, forward flow is also present through the fetal isthmus in diastole because of the low resistance of the placental vascular system. This observation is in agreement with a correlative echocardiographic and morphometric study demonstrating that in mid-gestation the isthmus of the human fetus is not as small as that reported in animal models. The distribution of the fetal circulation is, however, chang-

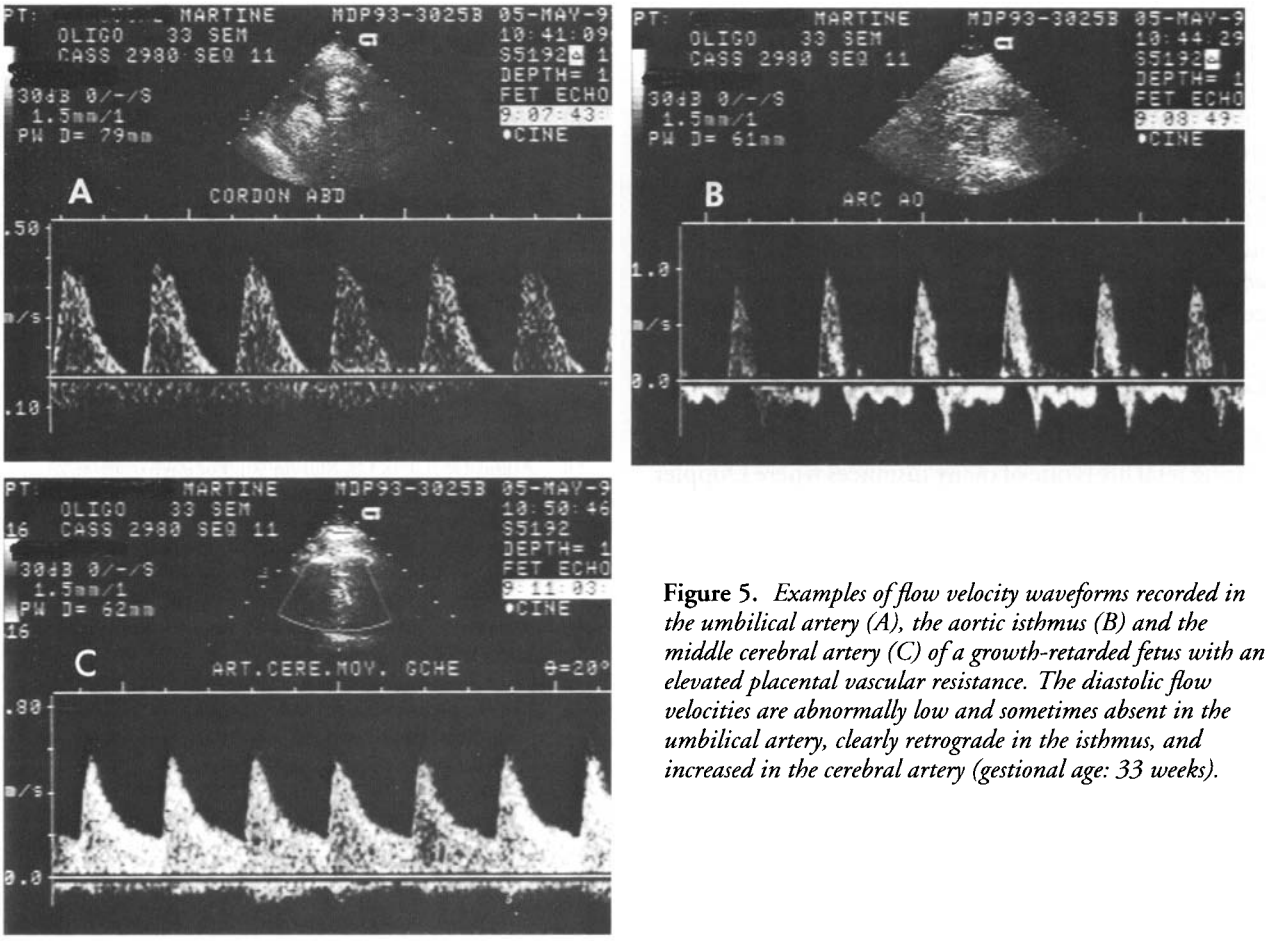

Figure 5. *Examples of flow velocity waveforms recorded in the umbilical artery (A), the aortic isthmus (B) and the middle cerebral artery (C) of a growth-retarded fetus with an elevated placental vascular resistance. The diastolic flow velocities are abnormally low and sometimes absent in the umbilical artery, clearly retrograde in the isthmus, and increased in the cerebral artery (gestional age: 33 weeks).*

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ing with advancing gestation; among other variations, Doppler investigation has shown a progressive fall in the resistance index of the cerebral circulation during the third trimester.[45] while placental vascular impedance does not change during the same period.[10] This could decrease the amount of forward flow through the isthmus and create a growth discrepancy between this vascular segment and the adjacent arteries.

The normal orientation of the isthmic flow towards the subdiaphragmatic circulation can be altered by abnormal circulatory conditions involving not only the ventricles, as previously discussed, but also the peripheral circulation. Any decrease in resistance in the upper body should decrease the forward flow in the isthmus, mainly during diastole. Such a condition is present in fetuses with cerebral arteriovenous fistulas with aneurysm of the vein of Galen, in whom reversed diastolic flow is documented in the aortic isthmus while forward flow is simultaneously recorded in the descending thoracic aorta.[46] An increase in resistance to flow through the lower body will have the same effect.[47] Cases of intrauterine growth retardation due to placental insufficiency and an increase in placental vascular resistance are frequent examples of such a condition. In severe cases where reverse diastolic flow is observed in the umbilical artery, the same pattern has been described in the aortic isthmus.[48] It has also been demonstrated that changes in Doppler diastolic flow velocities in the isthmus precede, and are always more severe than those of the umbilical artery[49] (Figure 5). In accordance with the accepted concept of two fetal ventricles working in parallel and perfusing two separate vascular systems, one must rationally conclude that the fetal aortic isthmus, not the arterial duct, is the only arterial segment where blood is shunting from one circulatory system, the cephalic, to the other system, the subdiaphragmatic.

Conclusion

The concept of the aortic isthmus being a vascular shunt during fetal life is one of many instances where Doppler echocardiography has not only confirmed previous fundamental experimental observations, but has broadened our understanding of fetal circulatory dynamics. With the help of ultrasound technology, the fetus has become a patient. The door is now open to major developments such as safe surgical approaches to fetal cardiac malformations, specific therapeutic protocols for the treatment of fetal arrhythmia, reliable criteria of functional myocardial assessment and, above all, development of new cardiovascular indices for monitoring fetal well-being that would allow rapid identification of fetal distress and hypoxemia before occurrence of even minor cerebral damage. Training programs for future pediatric cardiologists should take into account these realistic perspectives. I hope that this review will have succeeded in stressing at least one very important point: we should show discretion in directly applying to the fetal circulation accepted concepts derived from extrauterine observations.

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