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Editorial

The unrecognized physiological and clinical significance of the fetal aortic isthmus

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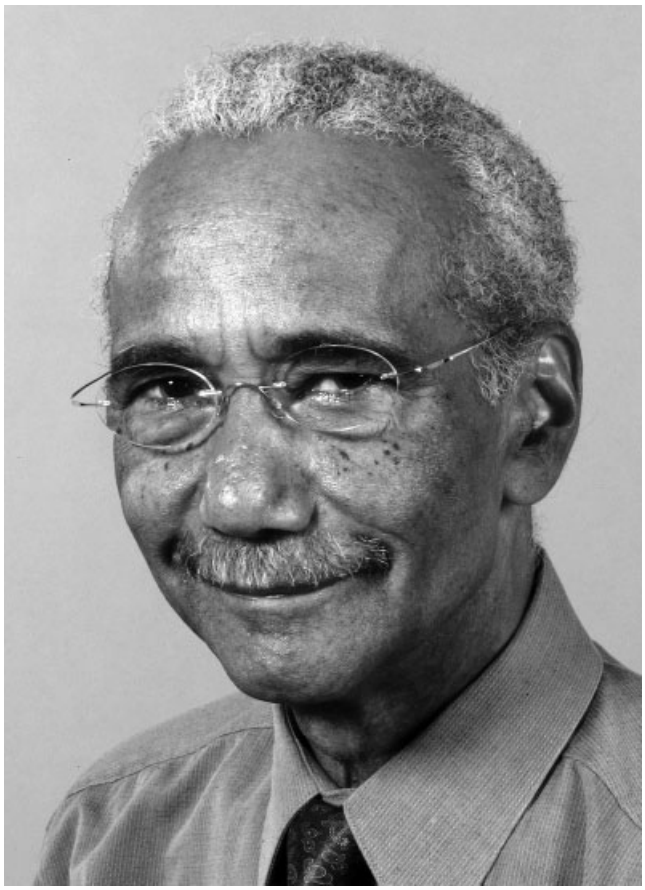

An undisputed feature of fetal circulatory dynamics is that the two ventricular pumps perfuse the same systemic circulation in a parallel fashion. Under normal conditions, the blood ejected by the right ventricle (RV) perfuses the subdiaphragmatic organs and carcass, with approximately 10–15% going into the pulmonary circulation, while the cephalic part of the fetus receives blood exclusively from the left ventricle (LV)[1,2]. Another generally accepted characteristic of the fetal circulation is the presence of intracardiac and extracardiac shunts; among the latter is the ductus arteriosus (DA). Although the fetal DA is actually part of the normal vascular outlet of the RV forming 'the pulmonary arch' with the main pulmonary artery (MPA) and descending thoracic aorta (DAo), its recognition as a vascular shunt has never been an issue for physiologists and perinatologists. Yet, a shunt, as defined in an electrical circuit, joins two points of the network and 'serves to *divert* part of the current'[3]. In postnatal life, where the ventricles are disposed in series, a patent DA does indeed *divert* blood from either the systemic or the pulmonary circulation, depending on the downstream impedances of the two circulatory systems. In fetal life, if blood flow going through the pulmonary arch down into the DAo had to be considered as a right-to-left shunt taking blood away from the lungs, then the two ventricles would have to be regarded as disposed in series as in postnatal life; the classical description of the parallel ventricular arrangement would then become irrational. The concept of a fetal circulation based on two circulatory systems arranged in parallel fashion (a concept which is fully justified) is incompatible with the identification of the DA as a shunt. *In utero*, the arterial vascular segment that conforms to the definition of, and behaves like, a shunt is the aortic isthmus. Indeed, the isthmus, located between the origin of the left subclavian artery and the aortic end of the DA, establishes communication between the two arterial outlets that perfuse in parallel the upper and lower body of the fetus (Figure 1a). This logical approach bears not only physiological significances but could have many clinical implications, especially with the advent of Doppler ultrasound in fetal monitoring.

PHYSIOLOGICAL CONSIDERATIONS

Normal isthmic flow patterns

Due to the disposition of the two arterial circuits on each side of the aortic isthmus, blood ejected by the fetal LV and RV has opposite effects on the direction of flow through the isthmus. Left ventricular stroke volume will cause forward flow while right ventricular ejection will have the opposite effect (Figure 1b). The final systolic pattern of isthmic flow will be determined by the relative contributions of left and right ventricular stroke volumes as well as the balance between vascular impedances of the upper and lower body.

In diastole (Figure 1c), when the two semilunar valves are closed, the direction of isthmic blood flow will be influenced only by the two downstream vascular impedances, especially in the brain for the upper body, and in the placenta for the subdiaphragmatic vascular system. Doppler flow velocity studies have confirmed that in the normal fetus, forward flow is present through the

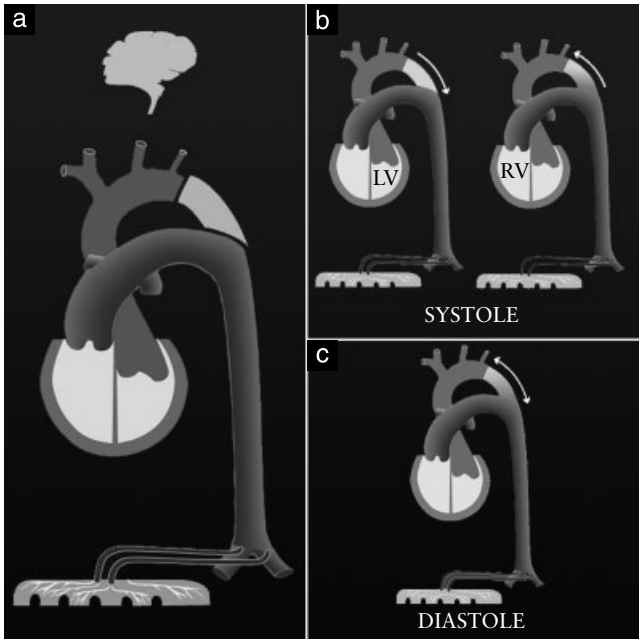

Figure 1 (a) Diagram of the fetal circulation, illustrating the unique position of the aortic isthmus, between the aortic and pulmonary arches. (b) During systole the left and right ventricular stroke volumes have opposite effects on the direction of flow through the isthmus. (c) During diastole the two downstream vascular impedances are the only determinants of the direction of the isthmic flow.

isthmus, both in systole and diastole, because of the low placental vascular impedance (Figure 2a). A number of elements should cause a progressive decrease of forward flow through the isthmus as gestation progresses; among them the right ventricular preponderance which increases during the second half of gestation[2] and placental vascular resistance which reaches a plateau in the last months of gestation, while cerebral vascular resistance follows a curvilinear pattern, peaking at mid-gestation and declining progressively at the end[4]. This reduction in flow could explain the relative narrowing of the isthmus observed in term fetuses. Systematic recordings of the isthmic flow velocity profile throughout gestation have shown that starting at approximately 25 weeks, a brief reversal of flow occurs toward the end of systole, and increases steadily with the progression of gestation[5] (Figure 2b). In term ovine fetuses this phenomenon has been found to be caused by a delayed onset and longer acceleration time of ductus flow velocity at the isthmus–ductus junction[6]. The same dynamic events can also be observed in the human fetus (Figure 2c).

To objectively monitor the flow pattern through the fetal aortic isthmus we developed an isthmic flow index (IFI), which reflects both the amount and direction of blood through this vascular segment. The proposed index was obtained by dividing the sum of the systolic (S) and diastole (D) Doppler flow velocity integrals by the systolic flow integrals: IFI = S + D/S. Positive and negative signs are assigned to antegrade and retrograde velocity values, respectively. The normal reference ranges of the IFI have been published recently[7]. For clinical purposes, five types

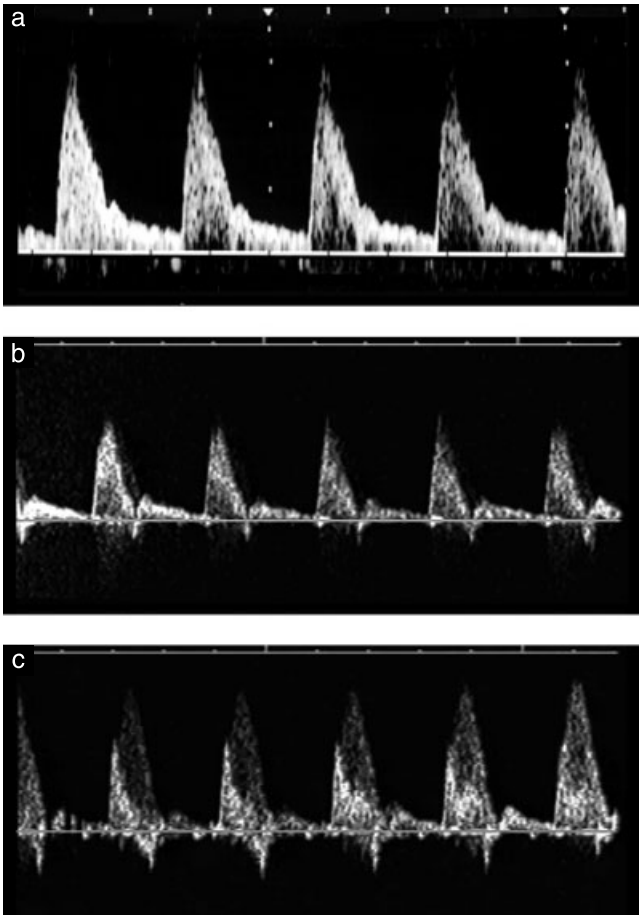

Figure 2 Doppler flow velocity patterns in the fetal aortic isthmus throughout gestation. (a) During the first half of pregnancy, forward flow is present both in systole and diastole. (b) During the second half of pregnancy, a brief reversal of flow appears at the end of systole as illustrated in this 32-week fetus. (c) In the same fetus a delayed onset and longer acceleration time of the ductal wave are observed at the isthmus–ductus junction, explaining the late systolic reversal of flow in the isthmus.

of IFI are possible (Figure 3). In Type I the index is higher than 1, meaning that antegrade flow is present both in systole and diastole. Normal fetuses have a Type I flow pattern in their aortic isthmus. However, because of the physiological hemodynamic changes mentioned above, a progressive decrease of the IFI is observed throughout the second half of pregnancy[7]. Type II corresponds to an absence of diastolic flow. The IFI is then equal to 1, below the normal range. In Type III, the IFI is between 1 and 0, expressing some diastolic flow reversal but with predominant antegrade flow. The closer the index is to 0, the greater is the retrograde flow. Type IV is observed when the retrograde and antegrade flows are equal and the IFI reaches 0. Finally, in Type V the index becomes negative, below 0, meaning that forward flow is decreased and retrograde flow increased to the point that net flow to the isthmus is retrograde.

CLINICAL CONSIDERATIONS

The normal direction of the isthmic shunt towards the subdiaphragmatic circulation can be altered by abnormal

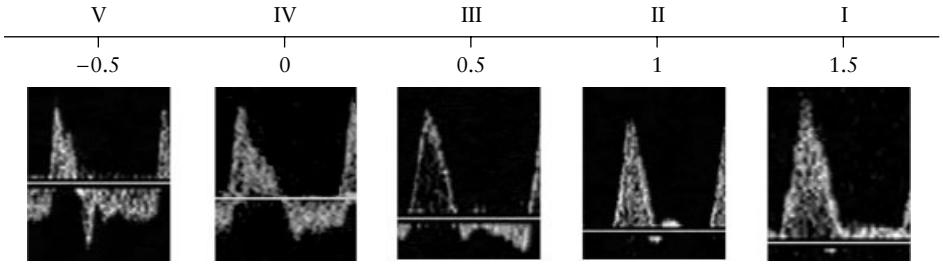

Figure 3 Illustrations of the five possible types (I–V) of the isthmic flow index. The Doppler flow waveforms at the bottom of the figure are taken from fetuses with placental circulatory insufficiency.

fetal conditions involving either the ventricles or the peripheral circulation.

The ventricles

A functional impairment or any stenotic lesion along one of the two parallel pathways of the fetal heart induces a redistribution of flow toward the unaffected side. For this reason, trans-stenotic gradients are unreliable for the assessment of fetal cardiac obstructive lesions[8]. By contrast, individual ventricular dysfunction will always influence fetal isthmic flow, and the changes observed will be different, depending on whether the left or the right side is affected.

Left ventricular dysfunction or stenosis is associated with a decrease of LV output and of normal forward flow through the isthmus. If the reduced isthmic flow remains antegrade (IFI > 1) this would mean that despite the stenosis, left ventricular stroke volume is still sufficient to maintain perfusion of both the upper body and part of the subdiaphragmatic circulation (Figure 4a). One can then safely predict that, after birth, the systemic circulation will not be dependent on a patent DA. Inversely, reverse isthmic flow (IFI < 1) associated with LV functional impairment indicates a significant fall in LV output, causing compensatory perfusion of at least part of the upper body circulation by blood coming from the RV (Figure 4b). In this instance, the LV will be unable to take charge of the postnatal systemic circulation, which will be dependent on the patency of the DA. In Figure 4b, since the hemodynamic problem concerns essentially the ejection phase of the cardiac cycle, retrograde flow occurs only in systole while normal forward diastolic flow towards the low resistance placental circulation is still recorded in the isthmus. The extreme of this condition is the hypoplastic left heart syndrome where the functioning RV perfuses not only the isthmus but also the entire aortic arch, including the coronary arteries. Serial recordings of flow patterns through the isthmus should, therefore, help the fetal sonographer in the important task of assessing the progression of a left-sided obstruction in prenatal life.

Right ventricular dysfunction or outlet stenosis increases forward flow through the isthmus since, in this condition, a greater portion of the combined cardiac output is made up of blood coming from the LV. The rise in volume flow through the isthmus explains the similarity in size between the isthmus and the adjacent aorta, as

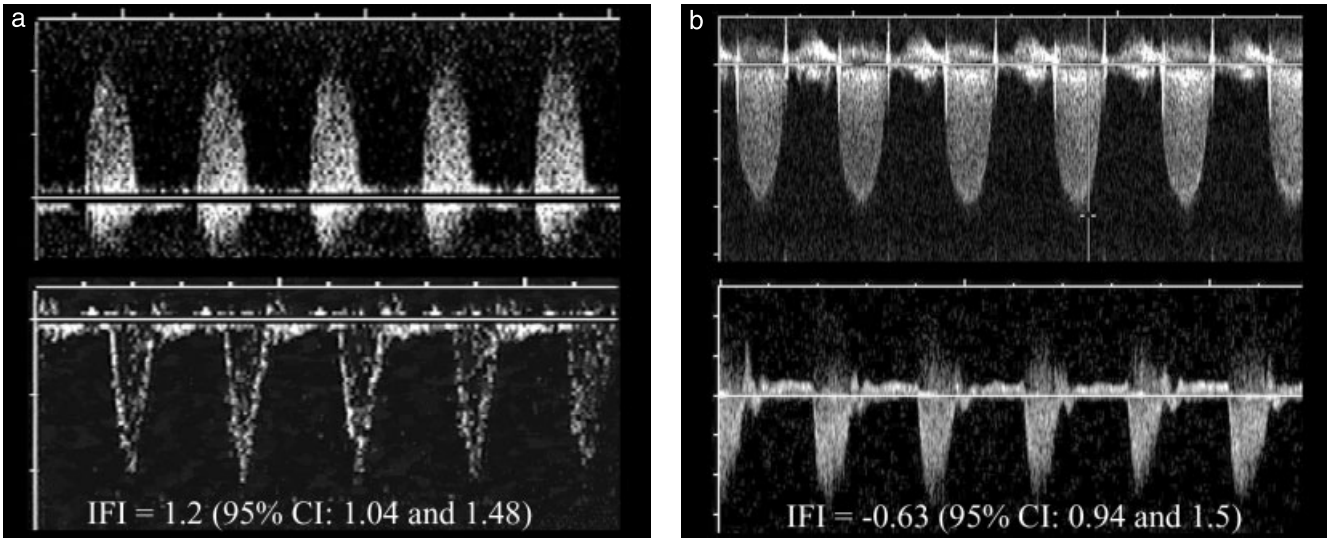

Figure 4 (a) Moderate aortic stenosis. The flow velocity patterns through the aortic valve (upper trace) and isthmus (lower trace) are illustrated. A peak systolic velocity of 2.2 m/s is recorded through the aortic valve. Flow through the isthmus is decreased but remains antegrade both in systole and diastole. (b) Severe aortic stenosis. The peak velocity of the transvalvular jet is 4 m/s (upper trace) and a reverse systolic flow is recorded through the isthmus (lower trace). IFI, isthmic flow index.

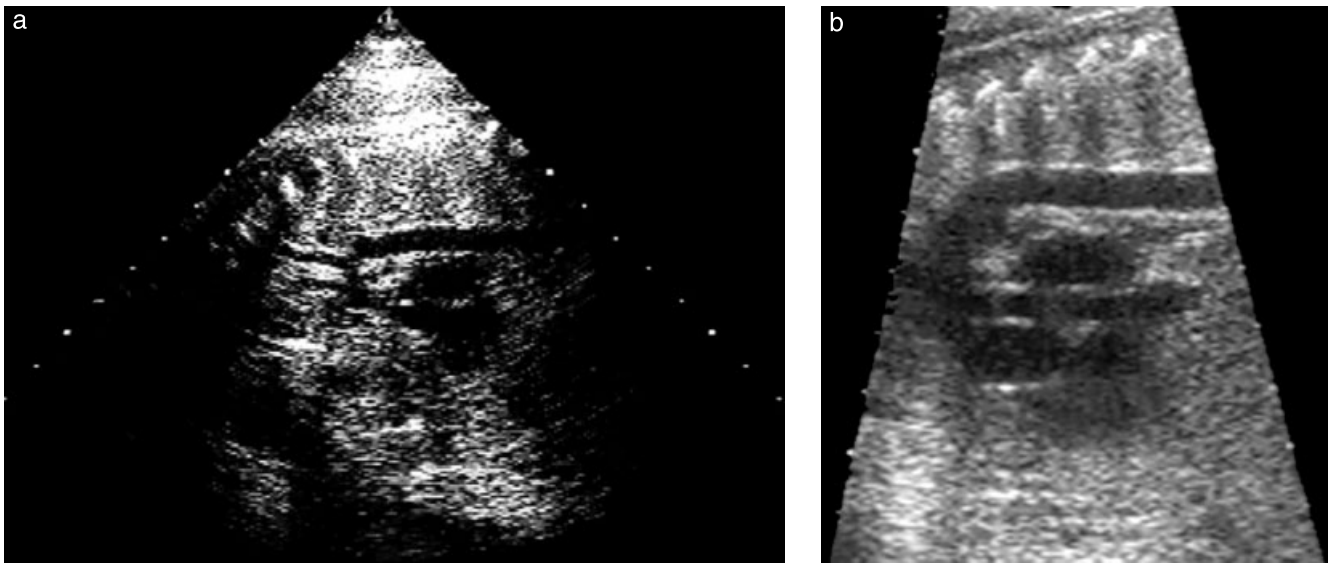

Figure 5 (a) Aortic arch of a normal 37-week fetus. Note the narrowing of the aortic isthmus. (b) Aortic arch of a 36-week fetus with tetralogy of Fallot. Note the absence of reduction of the isthmus diameter.

observed in term fetuses with prenatal pulmonary stenosis or tetralogy of Fallot (Figure 5). In our experience, the changes in IFI in these circumstances are variable. Further studies are needed to establish if this index can be used to predict the need for a shunt in the postnatal period to maintain perfusion of the lungs. For the time being the appearance of systolic flow reversal in the pulmonary arch during fetal life remains the most reliable predictive criterion of postnatal ductal dependency to maintain an adequate pulmonary circulation.

Peripheral vascular impedance

Since the fetal aortic isthmus is the sole link between the two arterial systems organized in parallel fashion, any change of flow or resistance affecting one of these arterial networks should influence flow patterns within the isthmus.

The cephalic circulation

In the upper body, *cerebral arteriovenous (AV) fistulae* represent typical examples of an abnormal decline in vascular impedance associated with a tremendous increase in flow. Doppler investigations of fetuses with cerebral AV fistula have demonstrated the presence of reverse diastolic flow in their aortic isthmus[9] (Figure 6). A unique circulatory dynamic is then established: the lower to upper body isthmic shunt joins LV output to perfuse the fistula while the markedly increased venous return comes back to the RV through the superior vena cava. This pattern explains the marked increase of flow through the pulmonary arch in prenatal life and the right ventricular hypertrophy classically observed in the postnatal electrocardiograms. It is worth mentioning that, as in critical left ventricular dysfunction, normal forward diastolic flow is still recorded in the aortic isthmus of fetuses with cerebral AV fistulae since their placental vascular impedance is normal. The same pattern of flow has been found in aorto-atrial fistulae (Sven-Erik Sonesson, pers. comm.). It can be speculated that the association of 'leaks' created by both the fistula and the normal diastolic isthmic shunt towards the placenta should cause a marked fall in systemic diastolic pressure. This low diastolic perfusion pressure could have, among other consequences, deleterious effects on placental blood flow and function.

The subdiaphragmatic circulation

In the lower body, *intrauterine growth restriction* (IUGR) due to placental circulatory insufficiency is one of the most frequent conditions where alteration of peripheral vascular impedance causes major changes in the isthmic shunt. In this condition, placental resistance, which is normally the lowest in the whole fetal circulation, increases. This alone could be responsible for at least a decrease in forward diastolic flow or in more severe cases a reversal of this flow through the isthmus. Another major element in the hemodynamic picture of IUGR fetuses is the reduction in O_2 delivery. Both experimental[10,11] and clinical[12–14] investigations have demonstrated that placental circulatory insufficiency causes fetal hypoxemia by reducing umbilical blood flow. The hypoxemia, by eliciting cerebral vasodilatation, potentiates the reversal effect of elevated placental resistance on the direction of the isthmic flow. The arterial hypoxemia is also responsible for vasoconstriction of the mesenteric, renal and musculoskeletal arteries, further increasing vascular impedance in the lower body. It is now well established that, depending on the degree of severity of the increase in placental vascular resistance, Doppler flow velocity waveforms of the umbilical artery will show decreased, absent or reverse diastolic velocities[15,16]. The same

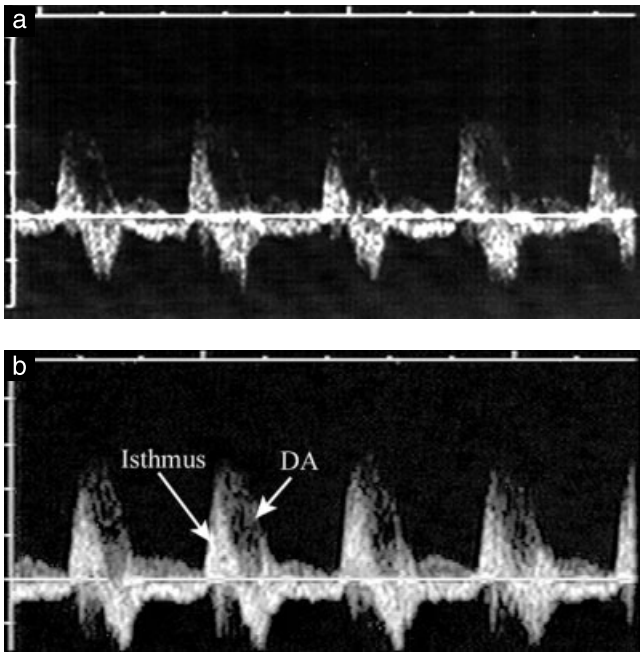

Figure 6 (a) Doppler flow pattern in the aortic isthmus of a 35-week fetus with cerebral arteriovenous fistulae. Note the retrograde flow after a brief systolic forward ejection wave. (b) A simultaneous recording of the velocity waveforms of both the ductus arteriosus and aortic isthmus of the same fetus demonstrates that, because of the marked increase in volume flow through the pulmonary arch, flow reversal through the isthmus occurs as early as mid-systole.

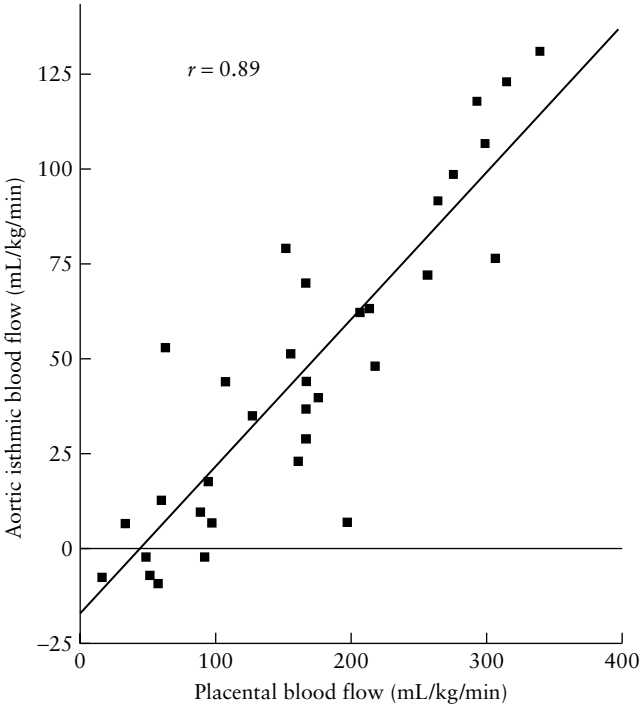

Figure 7 Linear regression analysis correlating aortic isthmic blood flow with placental blood flow[19]. Figure reproduced, with permission, from Bonnin P, Fouron JC, Teyssier G, Sonesson SE, Skoll A, Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow, *Circulation* 1993; **88:** 216–222. © American Heart Association.

changes in diastolic velocities described in the umbilical artery also occur in the isthmus[17,18] (Figure 3). More interestingly, quantitative assessment of isthmic flow during a stepwise increase in resistance to placental flow in fetal lambs demonstrated a strong positive correlation between actual umbilical blood flow and the amount of blood shunted through the isthmus[19] (Figure 7). In IUGR, therefore, the amount of flow going through the fetal aortic isthmus can be considered to be a good indicator of placental flow. Because O_2 delivery to the fetus is closely related to placental flow, one can extrapolate and consider that fetal O_2 delivery is also closely related to aortic isthmus blood flow.

Monitoring the flow pattern through the isthmus in IUGR fetuses could potentially play a major role in the prevention of postnatal sequelae of prenatal hypoxic brain injury. It is known that, despite the hypoxemia, the IUGR fetus can still maintain adequate cerebral oxygenation because of many adaptative mechanisms[20]. The defense system against cerebral hypoxia can, however, be overwhelmed. In clinical practice, IUGR fetuses suffering from placental circulatory insufficiency are being delivered on the basis of signs reflecting decompensation of their defense mechanisms[21]. The fetuses are then in metabolic acidemia and at significant risk of cerebral hypoxia[22,23]. Ideally, to prevent postnatal sequelae of cerebral hypoxia, the decision to deliver should be made just before decompensation. There are presently no signs that could help the attending physician to identify the fetus whose defense mechanisms against hypoxemia are about to fail. Experimentally, a stepwise increase in resistance to placental flow causes a fall in oxygen delivered to the brain only when predominant reverse diastolic flow is observed through the aortic isthmus[10]. IUGR fetuses with predominant reverse flow through their aortic isthmus also present signs of non-optimal postnatal neurodevelopmental outcome[24] as well as impairment of their venous Doppler[25], a late sign of fetal compromise. Finally, a good negative correlation has been found between the fetal IFI and postnatal neurodevelopmental outcome in the same group of IUGR fetuses (author's personal data). All these observations can be explained by the unique position of the isthmus. When reverse flows occurs in the aortic isthmus, blood coming from the MPA and DAo is being diverted from its normal destination, mainly the placenta. Because of the placental circulatory insufficiency, this preplacental blood has a lower O_2 content than normal. The brain is then partly perfused by blood deprived of substrates, placental and maternal, essential for fetal development and, at the same time, by red cells very poorly saturated in oxygen. Since the IFI is an indicator of the amount and direction of the shunt through the fetal isthmus, it could be used as a clinical marker for the identification of IUGR fetuses who need to be delivered before evidence of cerebral hypoxia. The greater the reverse isthmic flow, the lower is the IFI and the higher should be the risk of prenatal cerebral damage. Our ongoing clinical investigation aims presently

at establishing the IFI level corresponding to impending decompensation; at this level, delivery of an IUGR fetus would be rationally indicated before the appearance of signs of central nervous system impairment.

Absence of aortic isthmus vs. absence of ductus arteriosus

The difference between the significance of the DA and the aortic isthmus during prenatal life is well illustrated by the consequences of their obstruction or absence. The fetal aortic isthmus can be hypoplastic or absent. A hypoplastic aortic isthmus is usually associated with obstructive malformations of the LV and represents a secondary event related to decreased left ventricular output with a marked fall in the amount of blood shunting through the isthmus[26]. Complete absence of the aortic isthmus represents one of the types of interruption in the aortic arch. Both conditions are well tolerated during fetal life. A decrease or absence of shunt through the isthmus can be easily compensated for by a proportional increase in right ventricular flow through the pulmonary arch, maintaining the normally elevated turnover of blood in the umbilical circulation. This explains why marked right ventricular preponderance is classically observed in neonates with obstructions such as coarctation of the aorta. The aortic isthmus, therefore, is not an essential component of the fetal circulation, and its absence does not justify an aggressive approach during intrauterine life.

In contrast, the situation is quite different with the DA. Partial compression of the DA in fetal lambs has been reported to cause an immediate elevation of pulmonary pressure, associated with a transient rise in pulmonary flow[27]. The most intriguing finding was that pulmonary vascular resistance, which fell during the first 30 min of compression, steadily increased thereafter, suggesting the involvement of yet unidentified factors, such as injury to the pulmonary arterial endothelium, and augmented neural, humoral or local vasoconstricting stimuli that could be responsible for deterioration of the pulmonary arterial system. Complete surgical ligation of the DA in the sheep fetus produces structural remodeling of the peripheral pulmonary vascular bed, characterized by an increase in the proportion of muscularized pulmonary arteries at the level of the terminal bronchioles and within the acini[28]. In the same experimental model, marked changes have been demonstrated in the biochemical and mechanical properties of large capacitance pulmonary arteries as well as smaller resistance units[29]. In the human fetus, premature closure of the fetal ductus, which is a well-documented complication of maternal therapy with prostaglandin synthetase inhibitors, causes major alterations in right ventricular function leading to hydrops fetalis[30] and, in the pulmonary circulation, is responsible for the persistence of pulmonary hypertension after birth[31,32]. Primary absence of the DA is also commonly observed in tetralogy of Fallot with a dysplastic or absent pulmonary valve. Here again, this is a major malformation that results in lethal vascular and bronchial disorders[33,34]. All these observations support the contention that the DA is an integral element of the fetal circulation.

The situation is completely reversed when, after birth, the fall in pulmonary vascular resistance allows the entire cardiac output to go through the lungs. The two ventricles are then disposed in series. The aortic isthmus is no longer a shunt but becomes an integral part of the systemic arterial circuit; its absence creates major circulatory disturbances that require surgical correction. Conversely, the DA, if patent, conforms then with the definition of a shunt with all the well-known clinical consequences.

CONCLUSIONS

Based on the abovementioned experimental and clinical data, the following concepts regarding the fetal circulation are proposed:

Physiological

Concept I: The aortic isthmus, not the DA, is the only arterial shunt in the fetal circulation.
Concept II: A simple recording of the isthmic flow velocity pattern can provide information on global fetal cardiocirculatory dynamics.

Clinical

Concept III: Doppler flow recording in the aortic isthmus is a reliable indicator of fetal individual ventricular performance.
Concept IV: (a) In IUGR, flows through the placenta and the aortic isthmus are closely related. (b) In IUGR, monitoring of blood flow through the aortic isthmus allows indirect assessment of cerebral oxygenation.

REFERENCES

1. Rudolph AM, Heymann MA. Circulatory changes during growth in the fetal lamb. *Circ Res* 1970; **26**: 289–299.
2. Kenny JF, Plappert T, Doubilet P, Saltzman DH, Cartier M, Zollars L, Leatherman GF, St-John Sutton MG. Changes in intracardiac blood flow velocities and right and left ventricular stroke volume with gestational age in the normal human fetus: a prospective Doppler echocardiographic study. *Circulation* 1986; **74**: 1208–1216.
3. *Webster's Dictionary*. Ferguson Publishing Company: Chicago, IL, 1992; 895.
4. Mari G, Deter RL. Middle cerebral artery flow velocity waveforms in normal and small-for-gestational-age fetuses. *Am J Obstet Gynecol* 1992; **166**: 1262–1270.
5. Fouron JC, Zarelli M, Drblik SP, Lessard M. Normal flow velocity profile through the fetal aortic isthmus. *Am J Cardiol* 1994; **74**: 483–486.
6. Schmidt KG, Silverman NH, Rudolph AM. Phasic flow events at the aortic isthmus–ductus arteriosus junction and branch pulmonary artery evaluated by multimodal ultrasonography in fetal lambs. *Am J Obstet Gynecol* 1998; **179**: 1338–1347.

7. Ruskamp JM, Fouron JC, Raboisson MJ, Gosselin J, Infante-Rivard C, Proulx F. Reference values for an index of fetal aortic isthmus blood flow during the second half of pregnancy. *Ultrasound Obstet Gynecol* 2003; **21**: 441–444.
8. Castor S, Fouron JC, Teyssier G, Sonesson SE, Chartrand C, Skoll A, Drblik SP, Nyctelius H. Assessment of the severity of fetal pulmonic stenosis by ultrasonography. *J Am Soc Echocardiogr* 1996; **9**: 805–813.
9. Patton DJ, Fouron JC. Cerebral arteriovenous malformation: comparison of pre- and postnatal central blood flow dynamics. *Pediatr Cardiol* 1995; **16**: 141–144.
10. Fouron JC, Skoll A, Sonesson SE, Lessard M, Pfizenmaier M, Jaeggi E. Relationship between the flow through fetal aortic isthmus and cerebral oxygenation during placental circulatory insufficiency. *Am J Obstet Gynecol* 1999; **181**: 1102–1107.
11. Itskowitz J, LaGamma EF, Rudolph AM. Effects of cord compression on fetal blood flow distribution and O_2 delivery. *Am J Physiol* 1987; **252**: H100–H109.
12. Nicolaides KH, Economides DL, Soothill PW. Blood gases, pH, and lactate in appropriate- and small-for-gestational-age fetuses. *Am J Obstet Gynecol* 1989; **161**: 996–1001.
13. Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations: relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 115–120.
14. Weiner CP. The relationship between the umbilical artery systolic/diastolic ratio and umbilical blood gas measurements in specimens obtained by cordocentesis. *Am J Obstet Gynecol* 1990; **162**: 1198–1202.
15. Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* 1998; **92**: 31–38.
16. Marsal K. Ultrasound assessment of the fetal circulation as a diagnostic test: a review. In *Perinatal Development of the Heart and Lung*, Lipshitz J, Maloney J, Nimrod C, Carson G (eds). Perinatology Press: Ithaca, NY, 1987.
17. Fouron JC, Teyssier G, Maroto E, Lessard M, Marquette G. Diastolic circulatory dynamics in the presence of elevated placental resistance and retrograde diastolic flow in the umbilical artery. A Doppler echographic study in lambs. *Am J Obstet Gynecol* 1991; **164**: 195–203.
18. Fouron JC, Teyssier G, Bonnin P, Sonesson SE, Skoll A, Lessard M. Blood flow velocity profile in the fetal aortic isthmus: a sensitive indicator of changes in systemic peripheral resistances. II – Preliminary clinical observations. *J Matern Fetal Invest* 1993; **3**: 219–224.
19. Bonnin P, Fouron JC, Teyssier G, Sonesson SE, Skoll A. Quantitative assessment of circulatory changes in the fetal aortic isthmus during progressive increase of resistance to umbilical blood flow. *Circulation* 1993; **88**: 216–222.
20. Fouron JC, Skoll A. Fetal cardiovascular physiology and response to stress conditions. In *Medicine of Fetus and Mother*, Reece EA, Hobbins JC (eds). Lippincott-Raven: Philadelphia, PA, 1999; 115–130.
21. Romero R. Timing the delivery of the preterm severely growth-restricted fetus: venous Doppler, cardiotocography or the biophysical profile? *Ultrasound Obsett Gynecol* 2002; **19**: 118–121.
22. Hecher K, Snijders R, Campbell S, Nicolaides K. Fetal venous, intracardiac, and arterial blood flow measurements in intrauterine growth retardation; relationship with fetal blood gases. *Am J Obstet Gynecol* 1995; **173**: 10–15.
23. Rizzo G, Capponi A, Arduini D, Romanini C. The value of fetal arterial, cardiac and venous flows in predicting pH and blood gases measured in umbilical blood at cordocentesis in growth retarded fetuses. *Br J Obstet Gynaecol* 1995; **102**: 963–969.
24. Fouron JC, Gosselin J, Amiel-Tison C, Infante-Rivard C, Fouron C, Skoll A, Veilleux A. Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4 years. *Am J Obstet Gynecol* 2001; **184**: 630–636.
25. Mäkikallio K, Jouppila P, Räsänen J. Retrograde net blood flow in the aortic isthmus in relation to human fetal arterial and venous circulations. *Ultrasound Obstet Gynecol* 2002; **19**: 147–152.
26. Rudolph AM, Heymann MA, Spitznas U. Hemodynamic considerations in the development of narrowing of the aorta. *Am J Cardiol* 1972; **30**: 514–525.
27. Abman SH, Accurso FJ. Acute effects of partial compression of ductus arteriosus on fetal pulmonary circulation. *Am J Physiol* 1989; **26**: H626–H634.
28. Wild LM, Nickerson PA, Morin III FC. Ligating the ductus arteriosus before birth remodels the pulmonary vasculature of the lamb. *Pediatr Res* 1989; **25**: 251–257.
29. Belik J, Halayko AJ, Rao K, Stephens NL. Fetal ductus arteriosus ligation: pulmonary vascular smooth muscle biochemical and mechanical changes. *Circ Res* 1993; **72**: 588–596.
30. Murray HG, Stone PR, Strand L, Flower J. Fetal pleural effusion following maternal indomethacin therapy. *Br J Obstet Gynaecol* 1993; **100**: 277–282.
31. Levin DL, Mills LJ, Weinberg AG. Hemodynamic, pulmonary vascular and myocardial abnormalities secondary to pharmacologic constriction of the fetal ductus arteriosus: a possible mechanism for persistent pulmonary hypertension and transient tricuspid insufficiency in the newborn infant. *Circulation* 1979; **60**: 360–364.
32. Manchester D, Margolis HS, Sheldon RE. Possible association between maternal indomethacin therapy and primary pulmonary hypertension of the newborn. *Am J Obstet Gynecol* 1976; **126**: 467–469.
33. Rabinovitch M, Grady S, David J, van Praagh R, Sauer U, Buhlmeyer K, Castaneda AR, Reid L. Compression of intrapulmonary bronchi by abnormally branching pulmonary arteries associated with absent pulmonary valves. *Am J Cardiol* 1982; **50**: 804–813.
34. McCaughan BC, Danielson GK, Driscoll DJ, McGoon DC. Tetralogy of Fallot with absent pulmonary valve: early and late results of surgical treatment. *J Thorac Cardiovasc Surg* 1985; **89**: 280–287.

