# Relationship between flow through the fetal aortic isthmus and cerebral oxygenation during acute placental circulatory insufficiency in ovine fetuses

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**OBJECTIVE:** We sought to investigate whether the reversal of blood flow through the aortic isthmus, as observed during an increase in placental vascular resistance, could be responsible for a significant fall in oxygen delivered to the fetal brain.

**STUDY DESIGN:** With the appearance of reverse flow in the aortic isthmus, preplacental blood with low oxygen saturation could contaminate the ascending aorta blood destined for the brain. Stepwise compression of the umbilical veins of 8 exteriorized fetal lambs was realized at approximately 140 days of gestation. Four other animals were used as controls. Flows through the aortic isthmus and both carotid and umbilical arteries were measured by Doppler echocardiography in the basal state (hemodynamic class 1) and during moderate (class 2), severe (class 3), and extreme (class 4) increases in resistance to placental flow. Oxygen delivered to the brain was calculated from carotid blood flow and oxygen content.

**RESULTS:** In the control group no change was noted in umbilical and carotid arteries or in the aortic isthmus blood flow. Oxygen delivered to the brain remained stable. In the study group the increase in resistance to placental flow caused a significant fall in umbilical flow and carotid oxygen content, while blood flow in the carotid arteries increased slightly. The values for aortic isthmus flow and oxygen delivered to the brain during the 4 hemodynamic classes were, on average, as follows: class 1, 98.2 and 2.9 mL/(min · kg); class 2, 52.8 and 3.1 mL/(min · kg); class 3, 3.7 and 2.6 mL/(min · kg); and class 4, –29.8 and 0.7 mL/(min · kg), respectively.

**CONCLUSION:** During an acute increase in placental vascular resistance, delivery of oxygen to the brain is preserved despite a significant drop in arterial oxygen content as long as net flow through the isthmus is anterograde. (Am J Obstet Gynecol 1999;181:1102-7.)

**Key words:** Placental insufficiency, cerebral hypoxia, aortic isthmus, Doppler echocardiography

An increase in placental vascular resistance is a well-recognized cause of intrauterine growth restriction in association with a fall in umbilical blood flow and impairment of the maternofetal gas exchange. A concomitant decrease in the amount of oxygen available to the fetus is also observed. This hypoxemia can be efficiently compensated by many defense mechanisms, among them the blood flow centralization in favor of organs such as the heart, adrenals, and brain.[1, 2] In severe placental circulatory insufficiency, these mechanisms can be overwhelmed. There is presently no clinical means that allows identification of growth-restricted fetuses who have reached the point at which these defense mechanisms are about to fail, yet identification of this turning point is crucial for prenatal prevention of hypoxic brain injuries. Doppler echocardiographic investigations have recently demonstrated that, in the presence of an increase in placental vascular resistance, changes in flow patterns through the aortic isthmus precede those classically described in the umbilical artery.[3, 4] For instance, a retrograde diastolic flow is observed in the aortic isthmus, whereas the diastolic velocities are decreased or absent in the umbilical artery. With the appearance of a reverse flow in the aortic isthmus, preplacental blood with low oxygen saturation coming from the pulmonary artery or descending aorta contaminates the ascending aortic blood destined for the brain. In these circumstances there is an obvious risk of cerebral hypoxia despite the local vasodilatation and preservation of cerebral blood flow. The present experimental study was therefore planned to investigate the relationship between oxygen

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delivered to the brain and the flow patterns within the aortic isthmus during stepwise increases in resistance to placental flow.

## Material and methods

**Surgical protocol.** Twelve pregnant ewes with gestational ages that ranged from 130 to 140 days were included in this study. After a 48-hour fasting period during which only water was allowed, the animals were anesthetized with a combination of intravenous ketamine (3 mg/kg) alternating with intravenous pentobarbital sodium (2 mg/kg). After a midline laparotomy, the uterus was incised and marsupialized to keep it inside the maternal abdominal cavity. Through a small hysterotomy, the hind limbs were first exteriorized, and a polyvinyl catheter was introduced into one of the femoral arteries and advanced a few centimeters into the iliac arteries for continuous arterial pressure measurements. The fetus was then completely exteriorized and kept close to the uterine incision in such a manner that only a few centimeters of umbilical cord was outside the uterine cavity. The animal was covered to prevent evaporation, and the rectal temperature was kept constant with a heating lamp at 38.5°C ± 0.5°C. A surgical glove filled with warmed sodium chloride solution was placed over the nose and mouth. A polyvinyl catheter was introduced into the tibial artery of one of the forelimbs and advanced to its origin to permit assessment of blood gases perfusing the brain. The base of the neck, as well as both sides of the thorax and the upper abdomen, were shaved for better echocardiographic imaging. After careful dissection, a clamp was placed loosely around each of the umbilical veins. All these manipulations could be completed in approximately 15 to 20 minutes. This protocol has been found acceptable by the animal care committee of our institution.

**Experimental protocol.** The study was designed to obtain 4 different hemodynamic conditions identified in the text as classes 1 to 4, with class 1 corresponding to the baseline data. For each hemodynamic class, the following data were collected: heart rate, arterial blood pressure (with a Gould [Gould Electronics Inc, Eastlake, Ohio] physiologic apparatus), and Doppler flow velocity waveforms through the intra-abdominal umbilical arteries, the carotid arteries, and the aortic isthmus obtained by using an Acuson 128XP/10c (Acuson Corporation, Mountain View, Calif) ultrasound system with 5- and 7.5-MHz transducers. To be sure of the level of resistance to placental flow, the umbilical arteries were always the first and last site to be insonated at each of the 4 hemodynamic classes. Then all the other sites were insonated at random. The technical aspects concerning umbilical artery Doppler flow velocity waveform recordings suitable for quantitative measurements have been described previously.[3] For the aortic isthmus, the transducer was placed in the second right intercostal space and oriented toward the base of the heart; the complete aortic arch was thus well visualized. In the ovine fetus the aortic isthmus is a relatively long vascular segment because there is only one artery (the cephalic trunk) that comes off the arch. The diameter measurements, as well as the Doppler samplings, were always obtained midway between the cephalic trunk and the point of implantation of the ductus arteriosus. The flow velocities were always recorded on videotapes with an angle of <30° in relation to the direction of flow. The maximal internal diameters of all vessels were measured on the screen after maximum image amplification by using the equipment's calipers; this diameter was used to obtain the cross-sectional area of the vessel (Area = $\pi$[Diameter/2]$^2$). The mean value from 5 diameter and velocity waveform measurements was taken at each step of the experiments. Quantitative assessment of blood flow through the aortic isthmus and the umbilical and carotid arteries was carried out by using the usual Doppler formula: Blood flow = Flow velocity integral · Flow area · Heart rate. The sum of the values obtained in the 2 carotid and the 2 umbilical arteries provided blood flow values to the head and to the placenta, respectively. In the aortic isthmus the reverse, when present, was subtracted from the forward flows, and the results are given as net flows.

Each experimental step lasted approximately 20 minutes, and the whole experiment was always completed within 3 hours after exteriorization of the fetus. Hemodynamic classes were defined as follows: Baseline corresponded to data obtained while the clamps were placed around the umbilical artery but not tightened, with the umbilical circulation therefore being normal. In 4 animals used as controls, all the data collection was done without further manipulation of the umbilical veins; the control experiments were stopped 3 hours after fetal exteriorization. For the other 8 animals, the clamps around the umbilical veins were tightened, and the different classes were based on the flow pattern monitored in the umbilical artery. Class 2 was characterized by a decrease of approximately 50% of the diastolic component of the Doppler flow velocity waveforms in the umbilical artery assessed on the video screen of the apparatus. Class 3 was characterized by complete absence of a diastolic component in the umbilical artery Doppler flow velocity waveforms or appearance of late diastolic reverse flow. Finally, class 4 was characterized by a retrograde flow occurring during the entire diastole. At each step, the pulsatility index in the umbilical artery was also calculated.[5]

Blood samples (0.5 mL) were also drawn from the tibial artery and designated in the text as *carotid artery blood gases*. On this arterial blood sampling, pH, $P_{O_2}$, $P_{CO_2}$, oxygen saturation, and hemoglobin levels were measured by using a blood gas analyzer (Radiometer,

**Table I.** Data on pulsatility indexes in umbilical artery and corresponding carotid artery blood oximetry and arterial pressure obtained in controls and during 4 levels of resistance to placental flow in study group

| | | *Oximetry* | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Umbilical artery pulsatility index* | $P_{O_2}$ *(mm Hg)* | $P_{CO_2}$ *(mm Hg)* | *pH* | *Base excess (mmol/L)* | *Oxygen saturation (%)* | *Hemoglobin (g/100 mL)* | *Mean pressure (mm Hg)* |
| Control group | | | | | | | | |
| 1 h | 0.9 ± 0.1 | 16.8 ± 1.4 | 43.2 ± 5.6 | 7.34 ± 0.04 | –2.5 ± 4.5 | 58.2 ± 8.1 | 13.3 ± 1.4 | 68.2 ± 4.9 |
| 2 h | 0.8 ± 0.1 | 19.8 ± 1.4 | 40.7 ± 5.7 | 7.37 ± 0.02 | –1.3 ± 3.7 | 67.9 ± 7.3 | 12.4 ± 1.4 | 68.9 ± 8.6 |
| 3 h | 0.9 ± 0.2 | 16.7 ± 1.6 | 37.8 ± 8.2 | 7.39 ± 0.05 | –2.1 ± 5.6 | 57.5 ± 13.0 | 12.6 ± 0.7 | 68.1 ± 7.3 |
| Study group | | | | | | | | |
| Class 1 (basal) | 0.8 ± 0.3 | 22.9 ± 4.9 | 48 ± 4.3 | 7.31 ± 0.06 | –2.8 ± 3.1 | 65.6 ± 6.5 | 11.9 ± 1.1 | 71.3 ± 9.7 |
| Class 2 | 1.1 ± 0.4* | 18.9 ± 4.6* | 53.8 ± 9.8 | 7.26 ± 0.08 | –2.7 ± 3.1 | 52.7 ± 11.3* | 12.7 ± 1.4* | 67.2 ± 9.9 |
| Class 3 | 2.0 ± 0.9† | 17.6 ± 3.1‡ | 58.1 ± 6.1* | 7.20 ± 0.14 | –5.2 ± 6.4* | 42.8 ± 15.2* | 13.6 ± 1.3* | 67.8 ± 11.4 |
| Class 4 | 12.7 ± 12.6† | 7.6 ± 4.0‡ | 109.9 ± 10.1† | 6.91 ± 0.12‡ | –11.0 ± 6.5* | 11.8 ± 1.9† | 13.6 ± 1.1* | 51.3 ± 18.4 |

Values represent average ± 1 SD.
*$P < .05$, blood flow class versus basal level.
†$P < .001$, blood flow class versus basal level.
‡$P < .005$, blood flow class versus basal level.

Copenhagen) and oximeter equipment (IL Saturometer; Radiometer). Carotid artery oxygen content was calculated by using the following formula: Carotid oxygen content = (Hemoglobin · Oxygen saturation · 1.36) + (Partial pressure of oxygen · 0.00003), where 1.36 is the oxygen-carrying capacity of hemoglobin (in milliliters per gram) and 0.00003 is the solubility coefficient for oxygen. The amount of dissolved oxygen was judged insignificant and ignored. The following simplified formula was therefore applied: Carotid oxygen content = Hemoglobin · Oxygen saturation · 1.36. Finally, the following gave the amount of oxygen delivered (in milliliters per kilogram · minute) to the head and the brain: Carotid artery oxygen content · Carotid blood flow. At the end of the experiments, all the animals were weighed, and the flow data were corrected accordingly.

**Statistical analysis.** Statistical compilation was performed by using multivariate analysis of variance with the $R_{ao}R$ and V tests and univariate analysis of variance with contrast analysis and the F test (Statistica 5.0; Statsoft Inc, Tulsa, Okla). Two sets of multivariate analyses of variance were first applied to assess the effect of time on the control group and the effect of blood flow class on the 8 studied animals. When multivariate analyses of variance showed a significant effect of time or blood flow class, a univariate analysis of variance was then applied to compare each step with basal state values. An unpaired Student *t* test was used to compare data from the control group with corresponding baseline values observed before umbilical vein compression. All data were expressed as mean ± SD. $P < .05$ was considered statistically significant.

## Results

The pulsatility indexes, carotid artery blood gases, and arterial pressure collected in the control and study groups are presented in Table I. No changes were noted in the control group in any of the variables studied during the 3 hours of observation. No difference was found between the baseline variables (class 1) of the study group and the same variables for the control group. At the first level of increase in resistance to placental flow (hemodynamic class 2), a rise in umbilical artery pulsatility index and a significant decrease in $P_{O_2}$ and oxygen saturation of the carotid artery blood was observed. The $P_{CO_2}$ rose moderately, but the values did not reach statistical significance. At the next level of compression (class 3), the increases in pulsatility index, hypoxemia, and hemoglobin desaturation were more severe. A mild acidosis was observed, related both to a further rise in $P_{CO_2}$ and to a fall in base excess. The results for classes 1 to 3 are based on 8 observations for all variables. In 3 fetuses attempts to create the fourth and final hemodynamic class were quickly followed by marked deterioration of myocardial function and circulatory collapse, preventing complete data recording. In the 5 remaining fetuses, complete reversal of diastolic flow was recorded in the umbilical artery (class 4), and all the other parameters were profoundly modified; marked metabolic and respiratory acidosis was present in association with extreme hypoxemia. A moderate but statistically significant increase in hemoglobin value was also observed during the stepwise increase of resistance to placental flow. Arterial blood pressure did not change until hemodynamic class 4 was reached; at this point a mild fall in mean arterial pressure was recorded.

The simultaneous modifications in flow patterns occurring in the aortic isthmus and the umbilical and carotid arteries of one of the lamb fetuses during the increase in resistance to placental flow are illustrated in Fig 1. This example demonstrates the earlier changes occurring in the aortic isthmus flow pattern in comparison

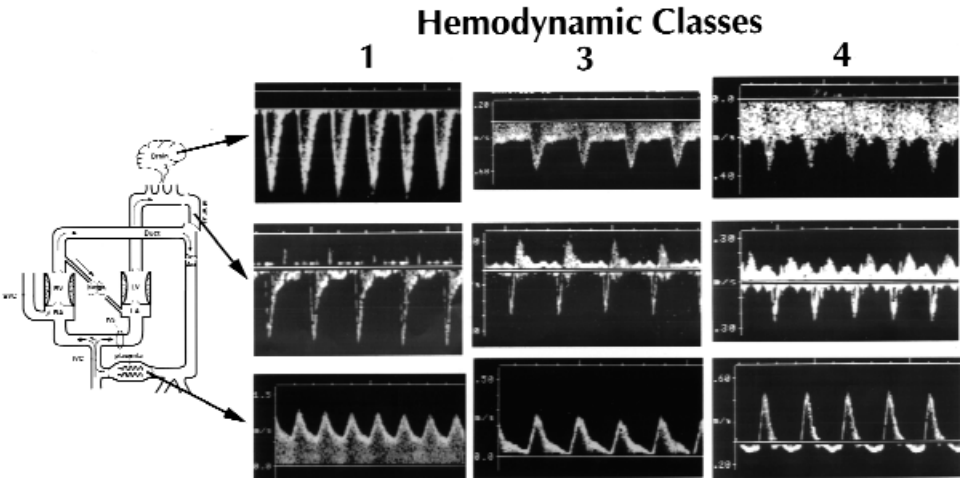


**Fig 1.** Example of flow velocity patterns in carotid artery *(top)*, aortic isthmus *(middle)*, and umbilical artery *(bottom)* recorded in same fetus at basal state (hemodynamic class 1) and during stepwise increases in resistance to placental flow (class 3 and 4). In *class 1* normal flow velocity patterns are observed in all 3 arteries. Note forward systolic and diastolic velocities in aortic isthmus and scant diastolic signals in carotid artery. *Class 2* is not shown in interest of space. In *class 3* increase in diastolic velocities in carotid artery is striking, whereas almost no velocity is recorded at end of diastole in umbilical artery. Reverse diastolic flow is already present in aortic isthmus; ratio of forward / reverse velocity integrals in isthmus is ~1. In *class 4* diastolic component in carotid artery has increased even more. Reverse diastolic velocities are recorded in umbilical artery. In aortic isthmus retrograde blood flow velocity integral is now greater than forward systolic component.

with the umbilical artery. The concomitant vasodilatation and fall in cerebral vascular resistance are also well illustrated by the appearance of a marked diastolic component in the carotid artery flow velocity waveforms while umbilical veins were being compressed. The effects of duration of the experiment and of the stepwise increases in umbilical vein compression on blood flow in umbilical and carotid arteries are shown in Fig 2. In the control group values in both arteries remained stable at approximately 185 and 28 mL / (min · kg), respectively. In the study group, with the umbilical vein compression, the umbilical flow started to decrease early, and the difference was already significant between baseline and class 2 values. The umbilical flow kept decreasing with the changes in levels of resistance, and at hemodynamic class 4 the average umbilical flow was 24 mL / (min · kg), which was close to ⅒ of the baseline data. An inverse effect was observed at the level of the carotid arteries where, concomitantly, blood flow increased slightly after the 2 first levels of umbilical vein compression (classes 2 and 3) and reached a plateau between classes 3 and 4.

The amount of oxygen delivered to the brain during these hemodynamic adjustments is illustrated in Fig 3. No significant change was noted in the supply of oxygen in the control group and during the first 3 hemodynamic classes created by umbilical vein compression, which was approximately 3 mL / (min · kg). In contrast, all fetuses in class 4 showed an abrupt fall in oxygen delivered to the brain with a mean of 0.7 mL / (min · kg). The concomitant flow through the aortic isthmus is also illustrated in Fig 3. Although the aortic isthmus flow did not vary in the control group, remaining at approximately 96 mL / (min · kg), major changes were observed in the isthmus flow velocity waveforms during the progressive increase in resistance to placental flow. First, a fall in the forward diastolic flow was observed, and end-diastolic reverse flow quickly started to appear (class 2). At hemodynamic class 3, the forward systolic and reverse diastolic waves were close to equality (Fig 1), and the net isthmus flow was almost nil. All fetuses in class 4 showed a net isthmus flow that was retrograde. Fig 3 shows that the passage of the net isthmus flow from forward to reverse was concomitant with the significant drop in oxygen delivered to the brain.

## Comment

To reproduce various degrees of increase in resistance to placental flow and simultaneously record Doppler flow velocity waveforms in the umbilical artery, aortic isthmus, and carotid arteries suitable for quantitative flow assessment, it was necessary to exteriorize the fetuses. With the precautionary measures taken, especially the maintenance of the uterus within the abdominal cavity with very little umbilical cord outside, the results of the control group demonstrated that it was possible to maintain stable hemodynamic conditions at least during 3 hours after fetal exteriorization. It is interesting that the value for the actual blood flows in the umbilical artery of the control group and at basal state of the study group were quite comparable with data previously published for ovine fetuses kept within the uterine cavity.[6]

The first consequence of an increase in placental resistance is a decrease in umbilical blood flow. This point has

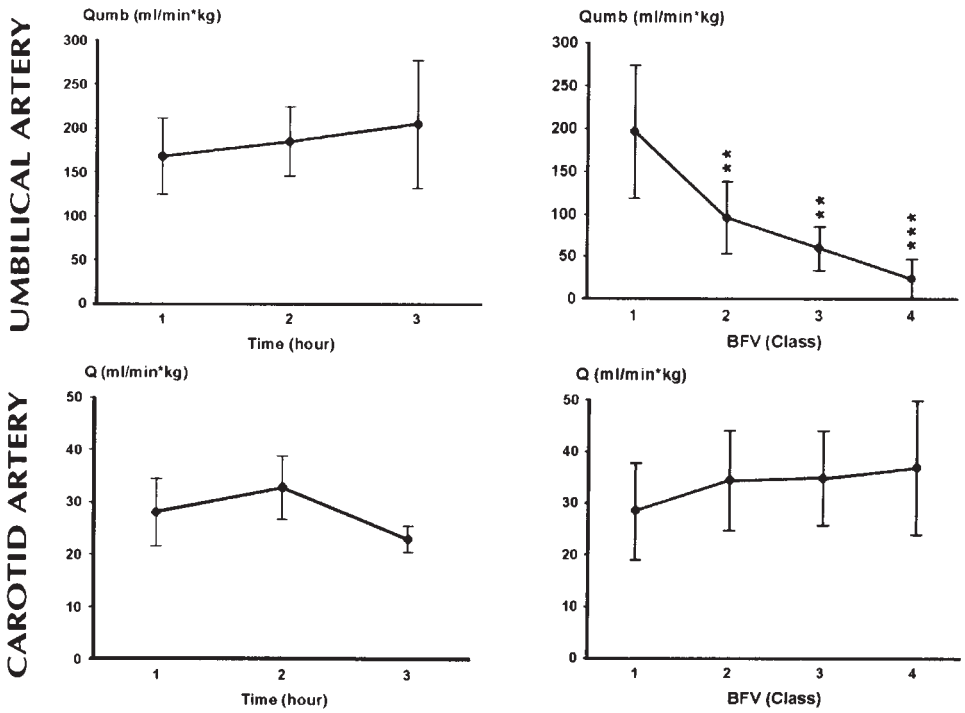


**Fig 2.** Mean and SD for blood flows *(Q)* in umbilical *(top)* and carotid *(bottom)* arteries expressed in milliliters per minute · kilogram. In control group *(left)* no significant change was observed. In study group *(right)* umbilical flow started to decrease early; concomitantly, in carotid arteries blood flow increased slightly. *BFV,* Blood flow velocity class. Comparison with baseline data: *2 asterisks, P* < .01; *3 asterisks, P* < .001.

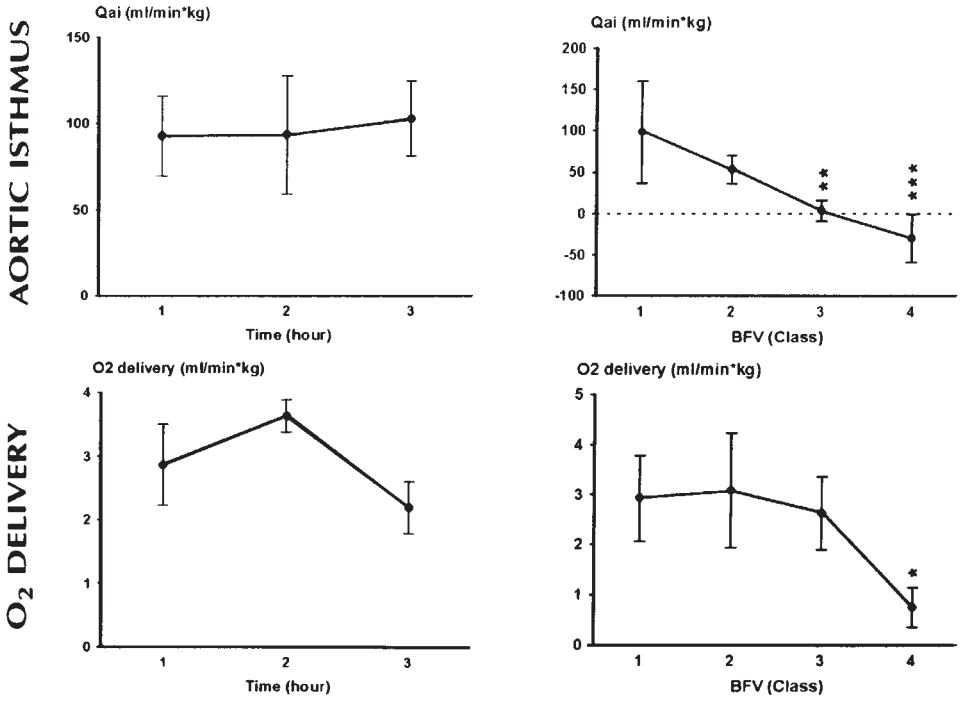


**Fig 3.** *Top,* Flows in aortic isthmus (mean and SD). No change is observed in control group *(left),* whereas in study group *(right)* increase in placental resistance causes a marked drop in isthmus anterograde flow. When hemodynamic class 4 is reached, net flow through isthmus is retrograde. *Bottom,* Oxygen delivered to brain. No difference was found between values obtained in control group and those of 3 first classes of study group. Only fetuses in class 4 demonstrated a significant fall in oxygen delivered to brain. Comparison with baseline data: *1 asterisk, P* < .05; *2 asterisks, P* < .01; *3 asterisks, P* < .001.

been previously observed in both ovine[3] and human[7] fetuses. As a consequence the amount of well-oxygenated blood coming back from the placenta and reaching the central venous circulation decreases, and the final mixture made of venous blood coming from the inferior and superior venae cavae has a lower $Po_2$ and oxygen saturation. This has been well illustrated in our group of fetuses, which demonstrated, as early as during hemodynamic class 2, a fall in carotid artery $Po_2$ concomitant with the decrease in umbilical blood flow. This state of hypoxemia does not necessarily result in tissue hypoxia, particularly at the level of the brain. The fetus has various defense mechanisms against cerebral hypoxia. One of them is the cerebral vasodilatation aimed at increasing the amount of blood getting to the brain and maintaining normal oxygen supply.[8] The present study confirms that this redistribution of blood toward the brain can be quite efficient to maintain normal delivery of oxygen to this organ. In the presence of hypoxemia, cerebral vasodilatation aims at increasing or maintaining blood flow to the brain despite the fall in cardiac output because of the reduced umbilical flow. The changes in the carotid flow velocity waveforms are an expression of the fall in downstream impedance, which is a consequence of the vasodilatation. Cerebral vasodilatation therefore is a sign of hypoxemia but, taken as an isolated finding, does not help to define at which point the cerebral tissue is becoming hypoxic. Monitoring the changes in umbilical Doppler flow velocity waveforms does not help either. Clinical reports have shown that fetuses with abnormal flow velocity patterns in the umbilical arteries can indeed have normal neurologic development.[9, 10]

The concepts of a fetal circulatory dynamic with 2 circulatory systems working in parallel and connected to each other by the aortic isthmus[11] could lead to new criteria helping to identify impending cerebral hypoxia in growth-restricted fetuses with placental circulatory insufficiency. The unique position of the aortic isthmus is well illustrated in the representation of the fetal circulation shown in Fig 1. Our experiments showed that oxygen delivered to the brain does not decrease until net flow through the aortic isthmus becomes retrograde. The reasons for these concomitant events are not directly provided by our experimental protocol. It could well be that the appearance of a net retrograde flow through the isthmus causes enough contamination of arterial blood going to the brain by red blood cells with very low oxygen content coming from the pulmonary artery or the descending aorta to cause a breakdown in the defense mechanisms against cerebral hypoxia.

This study could have major clinical implications. The isthmus can indeed be clearly identified during human fetal echocardiography, and the normal flow pattern through this vascular segment has been described.[12] In clinical conditions such as severe intrauterine growth restriction requiring close monitoring, semiquantitative assessment of isthmus flow could be achieved by simply measuring forward and reverse flow velocity integrals in this vascular segment. This simple measurement could theoretically keep the concerned obstetrician informed about the state of efficiency of the defense mechanisms against fetal cerebral hypoxia. As long as the ratio of forward/reverse velocity integrals is >1, the risk of cerebral damage should be minimal. The sign of an impending failure of these defense mechanisms could be the finding of an isthmus velocity ratio ~1. This study, however, concerns exteriorized fetuses in which an acute increase in resistance to placental flow was created. In human fetuses with growth restriction caused by placental circulatory insufficiency, the hypoxemia is usually of longer duration, and other mechanisms, such as an increase in the amount of oxygen extracted from the red blood cells, could also play a significant protective role against cerebral hypoxia. Only a prospective clinical study using the flow patterns through the fetal aortic isthmus as an indirect marker of cerebral oxygenation and assessing the postnatal neurologic and psychosocial development of these children before and during school age will help to clarify this important aspect of fetal medicine.

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