# Quantitative Assessment of Circulatory Changes in the Fetal Aortic Isthmus During Progressive Increase of Resistance to Umbilical Blood Flow

Philippe Bonnin, MD; Jean-Claude Fouron, MD; Georges Teyssier, MD; Sven-Erik Sonesson, MD, PhD; and Amanda Skoll, MD

*Background.* **This study investigated the effects of impairment to placental flow on flow patterns through the aortic isthmus because in the fetus, this vascular segment is the link between the parallel vascular systems perfused by the left and right ventricles.**

*Methods and Results.* **A progressive increase in resistance to blood flow through the placenta was created in seven exteriorized fetal lambs by mechanical umbilical vein compression. Blood flows were measured in the ascending aorta, pulmonary artery, aortic isthmus, and umbilical artery at baseline and at each compression level. The severity of the levels of compression was determined by changes in the flow profile through the umbilical artery. An increase in placental resistance causing a fall in umbilical blood flow of approximately 50% was associated with a retrograde diastolic flow through the aortic isthmus even though the diastolic flow through the umbilical artery remained forward. Because of the systolic predominance, however, the net flow in the isthmus was forward. With a more severe increase in placental resistance corresponding to a decrease of 75% in umbilical blood flow, the net flow through the isthmus approached zero. A strong positive correlation was found between the umbilical blood flow and the net flow through the aortic isthmus ($r=.89$).**

*Conclusions.* **Variations in Doppler blood flow velocity waveforms and integrals of the aortic isthmus can be used as a sensitive indicator of the state of the umbilical circulation. (*Circulation* 1993;88:216-222)**

KEY WORDS • **umbilical blood flow** • **placental resistance** • **aortic isthmus** • **fetus**

During fetal life, the aortic isthmus occupies a unique position between the two parallel vascular systems: the cephalic and upper body arteries perfused by the left ventricle and the descending aorta and the umbilical circulation perfused almost exclusively by the right ventricle. Under normal conditions, when the placental resistance is very low, a forward systolic and diastolic flow is recorded through the aortic isthmus. With a severe increase in placental resistance causing reverse flow in the umbilical artery, qualitative changes in the isthmic flow profile have been observed that also are characterized by a reverse diastolic flow.[1] These changes have been shown to appear before any significant modifications in the umbilical artery Doppler flow velocity profile.[2] However, the quantitative aspects of this unique hemodynamic situation have never been investigated. It could be speculated that a mild to moderate increase in placental resistance would result in a progressive fall in the net forward flow through the fetal aortic isthmus before the appearance of the reverse flow described in the severe cases. This information could be of importance in the search of Doppler indices reflective of the severity of fetal distress caused by changes in placental vascular resistance. Therefore, the aim of the present study was to determine quantitatively the amount of blood actually flowing through the aortic isthmus during stepwise increases in resistance to umbilical flow.

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From the Fetal Cardiology Unit, Service of Pediatric Cardiology, Department of Pediatrics, and the Department of Obstetrics and Gynecology, Saint-Justine Hospital, University of Montreal, Canada.

Address for reprints: Jean-Claude Fouron, MD, Saint-Justine Hospital, Fetal Cardiology Unit, Division of Cardiology, 3175, Côte Ste-Catherine, Montreal, Quebec, Canada H3T 1C5.

## Methods

### *Surgical Protocol*

Seven fetal lambs between 135 and 140 days of gestation weighing 3.8±0.8 kg (mean±SD) were prepared according to a surgical protocol described previously.[1] In brief, the ewes were fasted for 24 hours before surgery and anesthetized with alternating intravenous injections of ketamine HCl (3 mg/kg) and pentobarbital (2 mg/kg) every 20 to 40 minutes. The uterus was exposed through a midline laparotomy and marsupialized. The fetus was exteriorized, and the head was placed in a rubber bag containing warm saline solution to prevent spontaneous breathing. The fetus was kept near the laparotomy, leaving only a few centimeters of umbilical cord outside the uterine cavity for direct Doppler measurements. A radiant heater was used to maintain central fetal temperature between 38.5° and

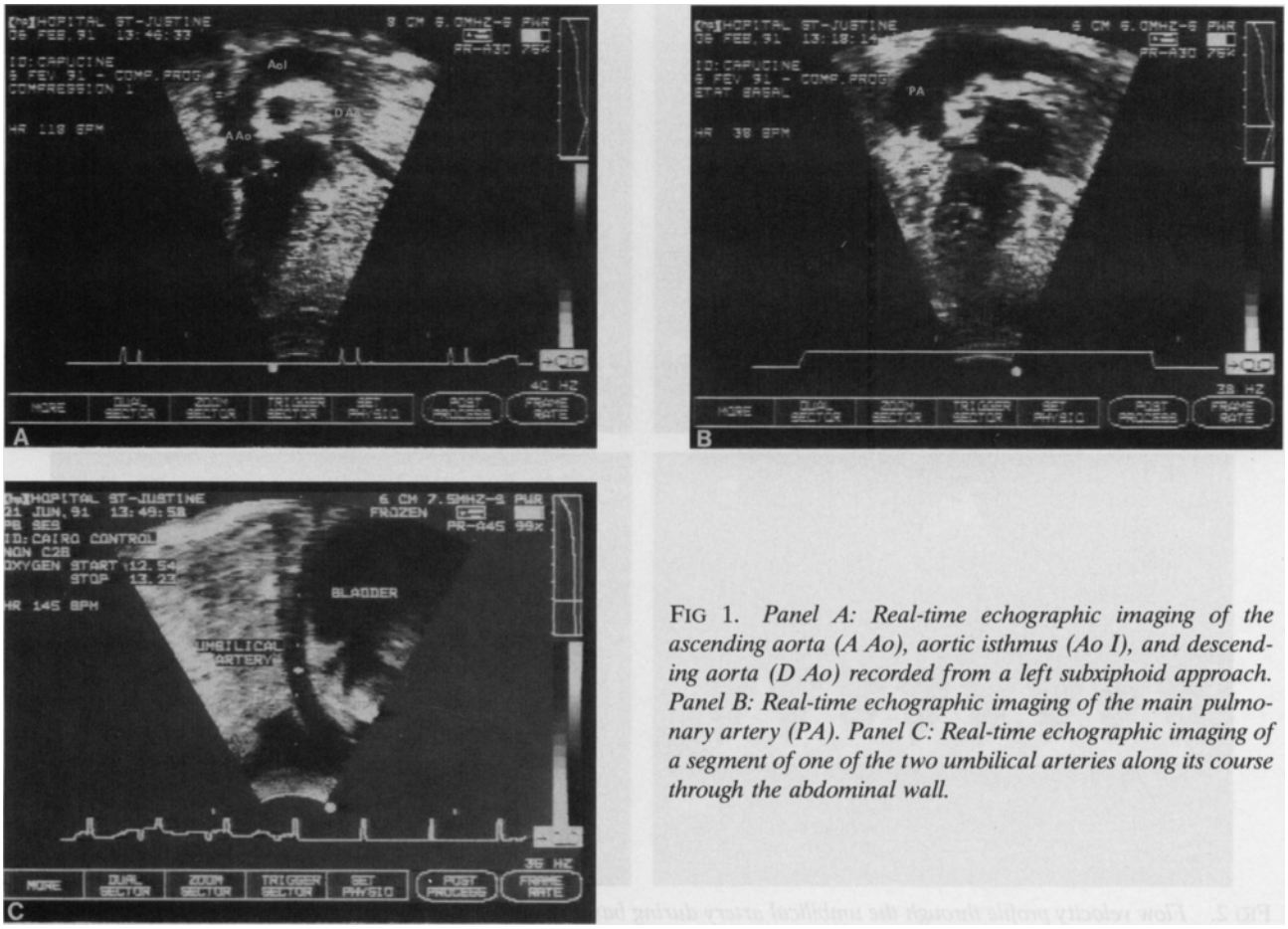


FIG 1. *Panel A: Real-time echographic imaging of the ascending aorta (A Ao), aortic isthmus (Ao I), and descending aorta (D Ao) recorded from a left subxiphoid approach. Panel B: Real-time echographic imaging of the main pulmonary artery (PA). Panel C: Real-time echographic imaging of a segment of one of the two umbilical arteries along its course through the abdominal wall.*

39.5°C. A polyvinyl catheter was introduced into the right femoral artery and advanced into the abdominal aorta for blood gas analysis and arterial blood pressure measurements. The arterial blood pressure was recorded continuously with a Cambridge recorder. Arterial pH, $Po_2$, and $Pco_2$ were measured on samples of 0.8 mL of blood using a blood gas analyzer from Instrument Laboratory Equipments.

*Doppler Ultrasound Study*

A real-time echocardiograph (Hewlett-Packard Sonos 100) was used in this study. Pulsed Doppler emission with a 100-Hz low pass filter allowed measurements of blood flow velocities. From the left subcostal approach, simultaneous real-time imaging of the ascending aorta, aortic arch, common brachiocephalic trunk, and descending aorta was obtained using a 5-MHz transducer (Fig 1A). In the fetal lamb, the aortic arch only gives rise to a common brachiocephalic trunk; the segment between the origin of this trunk and the implantation of the ductus arteriosus is equivalent to the aortic isthmus in the human. With a slight tilting of the transducer, the main pulmonary artery could be visualized (Fig 1B). A 7.5-MHz transducer was also placed over the fetal abdominal wall close to the umbilical cord insertion. The ultrasound beam was oriented in such a way that a few centimeters of one of the umbilical arteries could be viewed in its path within the abdominal wall (Fig 1C). Clear visualization of all studied arteries allowed orientation of the Doppler beam in a parallel direction to the long axis of these arteries. The Doppler spectral display of blood flow velocities was recorded on videotape for later analysis. Great care was taken to maintain the same angle for every scanning session.

*Experimental Protocol*

After surgery, the experimental protocol started when two successive measurements of arterial blood pressure, blood gas, and heart rate were within normal physiological limits; this time period never exceeded 15 minutes. Doppler blood flow velocity waveforms were recorded in the following successive order: umbilical artery, pulmonary artery, ascending aorta, aortic arch, and once again the umbilical artery. For the pulmonary artery and aorta, the Doppler sample volume was placed just above the valves at the point where maximal deflection of the Doppler signal could be obtained.

A Goldblatt clamp was carefully placed around the two umbilical veins. A stepwise compression was achieved to obtain four levels of venous resistance in addition to the baseline level. The severity of the venous compression was assessed by observing on the video screen of the echocardiograph the secondary changes created on the diastolic flow pattern of the umbilical artery (Fig 2). At each level of venous resistance, a decrease of approximately 50% of the previous umbilical artery diastolic flow velocity was achieved. At the last level of compression (Fig 2d), absent or reverse diastolic flow was observed in the umbilical artery.

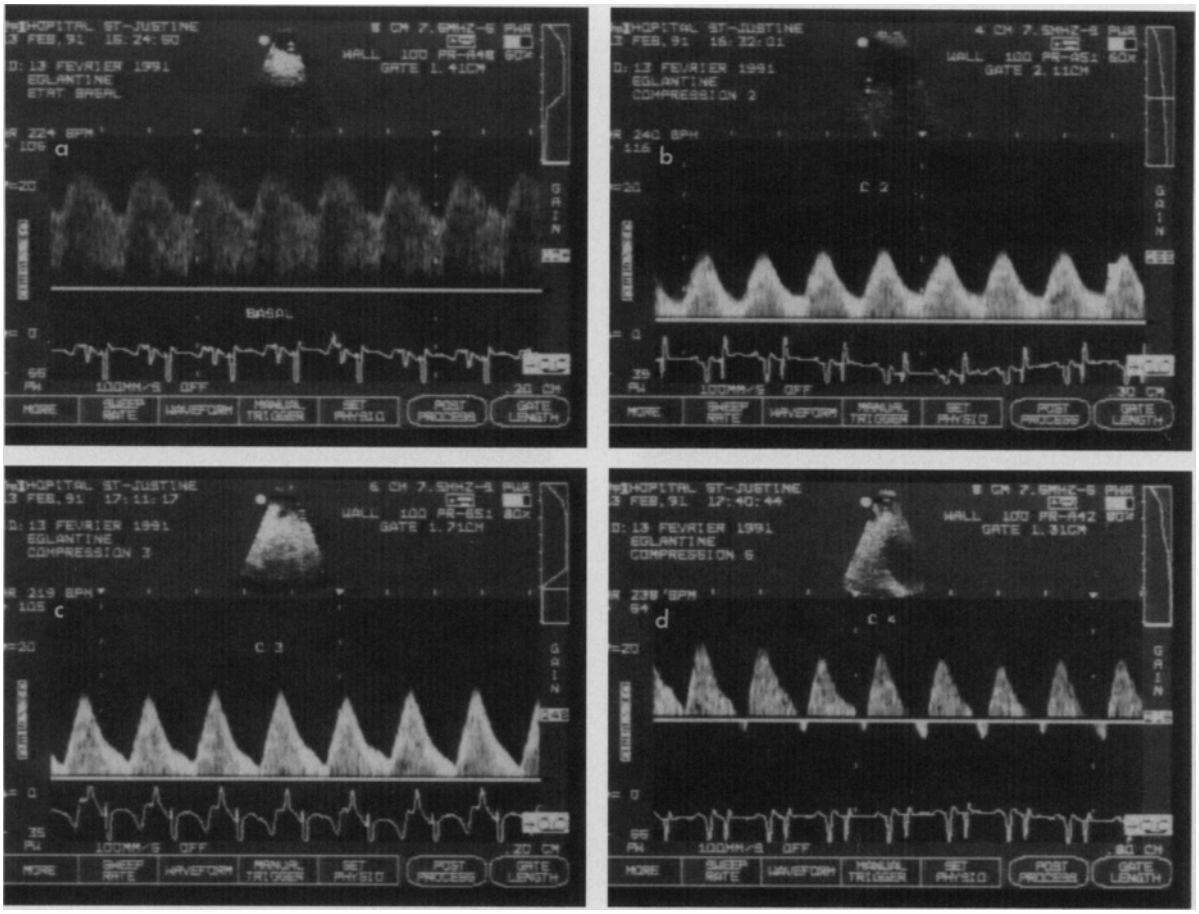

FIG 2. *Flow velocity profile through the umbilical artery during basal (panel a) and the last three progressively increasing stages of compression (panels b, c, and d). As shown, a progressive decrease in forward diastolic flow was noted (panels b and c) that ultimately resulted in a brief retrograde diastolic flow during the final level of compression (panel d).*

After each level of compression, a 5- to 10-minute period was allowed for stabilization. Doppler recordings were then obtained as quickly as possible. Arterial blood gas analysis and blood pressure were measured toward the end of the Doppler scanning. The complete collection of data lasted 20 minutes for each level of umbilical vein compression.

For each level of venous resistance, the largest diameter of the ascending aorta, pulmonary artery, aortic arch, and umbilical artery was measured at the site of Doppler interrogation from the two-dimensional echocardiogram. Five consecutive measurements of these variables were obtained, and the results were reported as an average of these readings. From the spectral display of the Doppler signal, velocity time integral (VTI) was also measured and averaged on five consecutive cardiac cycles in the pulmonary artery, ascending aorta, aortic arch, and umbilical artery.

### *Data Analysis*

Blood flows were calculated using the following formula.

$$Q = \pi(D/2)^2 \cdot VTI \cdot HR$$

where Q is the blood flow in milliliters per minute, D represents the vessel diameter, VTI is the averaged velocity time integral during one cardiac cycle, and HR represents the heart rate.

Placental blood flow was calculated as twice the amount of blood flow measured in one of the two umbilical arteries. Total resistance ($mm\ Hg \cdot mL^{-1} \cdot min^{-1} \cdot kg^{-1}$) in the umbilical-placental circulation was calculated by dividing mean arterial pressure (mm Hg) by umbilical blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$). In the aortic arch, if retrograde diastolic flow was observed, the corresponding VTI was systematically subtracted from the forward VTI. The resultant VTI was used for flow calculations to determine the net flow (forward or reverse) through the aortic isthmus.

Three additional fetuses formed the control group. They were submitted to the same protocol but did not undergo umbilical vein compression. For the controls, data collection was performed at baseline and at the middle and end of the observation period.

### *Statistics*

An ANOVA for repeated measurements was applied to compare data recorded at each level of placental resistance. The relation between parameters was assessed by simple and polynomial regressions (STATVIEW, Macintosh SE). The level of significance was set at $P < .05$. All values represent mean ± SD unless otherwise specified.

## Results

For the three control animals, no significant changes were found between the three separate data collection

**TABLE 1. Heart Rate, Mean Arterial Blood Pressure, and Femoral Blood Gases at Baseline and the Four Increasing Levels of Umbilical Vein Compression**

| Level of umbilical vein compression | Heart rate (bpm) | Mean arterial blood pressure (mm Hg) | $Pa_{O_2}$ (mm Hg) | $Pa_{CO_2}$ (mm Hg) | pH |
|---|---|---|---|---|---|
| Baseline | 222±37 | 59±9 | 17±7 | 38±2 | 7.34±0.04 |
| 1 | 195±43 | 56±8 | 17±6 | 42±5* | 7.33±0.04 |
| 2 | 195±45 | 58±5 | 16±5 | 44±6* | 7.32±0.03 |
| 3 | 180±36 | 63±10 | 14±2 | 49±6* | 7.28±0.04* |
| 4 | 190±49 | 61±6 | 13±2 | 62±22* | 7.17±0.12* |

bpm, Beats per minute.
*Significant difference with baseline values at $P<.05$.

periods. Their respective results for baseline, middle, and end of the observation period are as follows: mean blood pressure (mm Hg): 50, 54, 53; heart rate (beats per minute): 231, 218, 205; femoral artery $Po_2$ (mm Hg): 18, 17, 17; $Pco_2$ (mm Hg): 44, 41, 42; pH: 7.30, 7.33, 7.35; left ventricle output ($mL \cdot kg^{-1} \cdot min^{-1}$): 180, 195, 199; right ventricle output ($mL \cdot kg^{-1} \cdot min^{-1}$): 285, 260, 258; placental blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$): 206, 206, 286; and aortic isthmus blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$): 77, 95, 86. Further comparisons between these data from the control group and baseline values from the experimental group were not found to be statistically significant.

As shown in Table 1, mean arterial blood pressure and heart rate for the experimental group did not change significantly from baseline values for any stage of umbilical vein compression. Although $Pa_{O_2}$ decreased during compression, these changes were not statistically significant from the baseline value. On the other hand, the increase observed in the $Pa_{CO_2}$ values during compression were significantly different for the results between baseline and all levels of compression. Finally, a significant decrease in pH was only observed between the last two levels of compression and the baseline value.

Fig 3 illustrates changes in resistance achieved in the umbilical circulation during progressive compression. As seen in this figure, a progressive increase in resistance was found after the second level (C2) of compression. The size of the vessel internal diameters for the seven animals ranged from 0.76 to 0.98 cm in the ascending aorta, 0.88 to 1.19 cm in the common pulmonary artery, 0.59 to 0.62 cm in the aortic arch, and 0.40 to 0.45 cm in the umbilical artery. No significant changes were observed between basal and umbilical vein compression states for any vessel internal diameter.

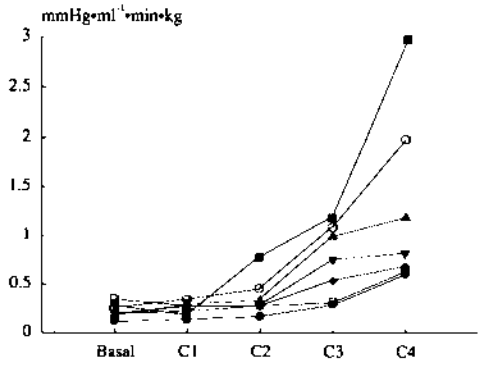


FIG 3. *Graph illustrates changes in resistance achieved in the umbilical circulation during the four levels of compression (C).*

The results for all blood flows revealed a progressive decrease from the baseline values starting with the first compression (Table 2). The decreases observed in the placental and aortic arch blood flow as well as the right and left ventricle outputs were found to be statistically significant from baseline values at all levels of compression. The left ventricular output decreased less than the right ventricular output, as demonstrated by the significant increase in the percentage of the combined cardiac output coming from the left ventricle (43±6% at basal state to 48±6% at the fourth level of compression; $P<.05$).

The aortic isthmus blood flow showed the most dramatic changes. An example of these changes is shown in Fig 4. At basal state (Fig 4a), a forward systolic and diastolic flow was observed through the isthmus that resulted in a net blood flow of 91±26 $mL \cdot kg^{-1} \cdot min^{-1}$. In the presence of a moderate increase in placental resistance causing a fall in placental blood flow of approximately 45% (Fig 4c), forward diastolic flow was still present in the umbilical artery while an inversion of the diastolic velocity in the aortic isthmus was being observed. The forward systolic flow was still predominant, however, and the net flow through the isthmus remained anterograde. During a severe increase in placental resistance resulting in a decrease of about 75% in the placental blood flow, the diastolic retrograde component was almost equal to the forward systolic component (Fig 4d); consequently, the net flow through the isthmus was negligible.

Left and right ventricular outputs as well as aortic isthmus blood flow showed a strong positive correlation with umbilical blood flow (Fig 5, panels A, B, and C, respectively).

## Discussion

Cardiac output determination by the Doppler echocardiographic technique has been described in fetal animals as well as in human fetuses.[3-7] Previous studies have also demonstrated the possibility of using the same method for the assessment of blood flow in the peripheral arteries.[8] The measurement of vessel diameter is the main source of error in Doppler flow calculation. In the present study, five consecutive measurements were averaged to minimize the possible systolic and diastolic variations in vessel size. This last precautionary measure is less crucial in the aortic and pulmonary arteries whose diameters, measured just above the valves,

**TABLE 2. Umbilical Artery Blood Flow, Left and Right Ventricular Outputs, and Aortic Isthmus Blood Flow at Baseline and the Four Increasing Levels of Umbilical Vein Compression**

| Level of umbilical vein compression | Placental blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$) | Right ventricular output ($mL \cdot kg^{-1} \cdot min^{-1}$) | Left ventricular output ($mL \cdot kg^{-1} \cdot min^{-1}$) | Aortic arch blood flow ($mL \cdot kg^{-1} \cdot min^{-1}$) |
|---|---|---|---|---|
| Baseline | 253±76 | 261±33 | 198±53 | 91±26 |
| 1 | 197±82* | 196±49* | 159±49* | 62±36* |
| 2 | 178±76* | 156±44* | 122±38* | 47±31* |
| 3 | 115±57* | 129±49* | 112±31* | 16±20* |
| 4 | 63±34* | 101±51* | 92±47* | 4±9* |

*Significant difference with baseline values at $P<.05$.

change very little with cardiac cycles. In the umbilical artery, however, multiple measurements taken during both cardiac cycles are mandatory because forward blood flow is normally recorded in this vessel both in systole and diastole. The baseline values presented in this study for umbilical blood flow and left and right ventricular outputs are in accordance with previous studies on fetal lambs.[9]

By increasing resistance to umbilical blood flow, secondary circulatory events were elicited, which, by themselves, could alter flow patterns through the aortic isthmus. This is especially true for the fall in the observed cardiac output and the probable cerebral vasodilation caused by the hypoxemia and hypercarbia. Indeed, because close to 50% of the combined cardiac output normally goes through the umbilical circulation, any reduction in flow in this area should significantly decrease the venous return through the inferior vena cava and consequently reduce the ventricular output. Obviously, a decrease in cardiac output will cause a reduction in blood flow through the aortic isthmus. Indeed, a good correlation has been found in this study between the output from both right and left ventricles and net aortic isthmic flow (Fig 5). However, reverse flow in the aortic isthmus related exclusively to a fall in output could have only occured if blood ejected by the left ventricle was markedly reduced compared with that of the right ventricle. The extreme of this situation is

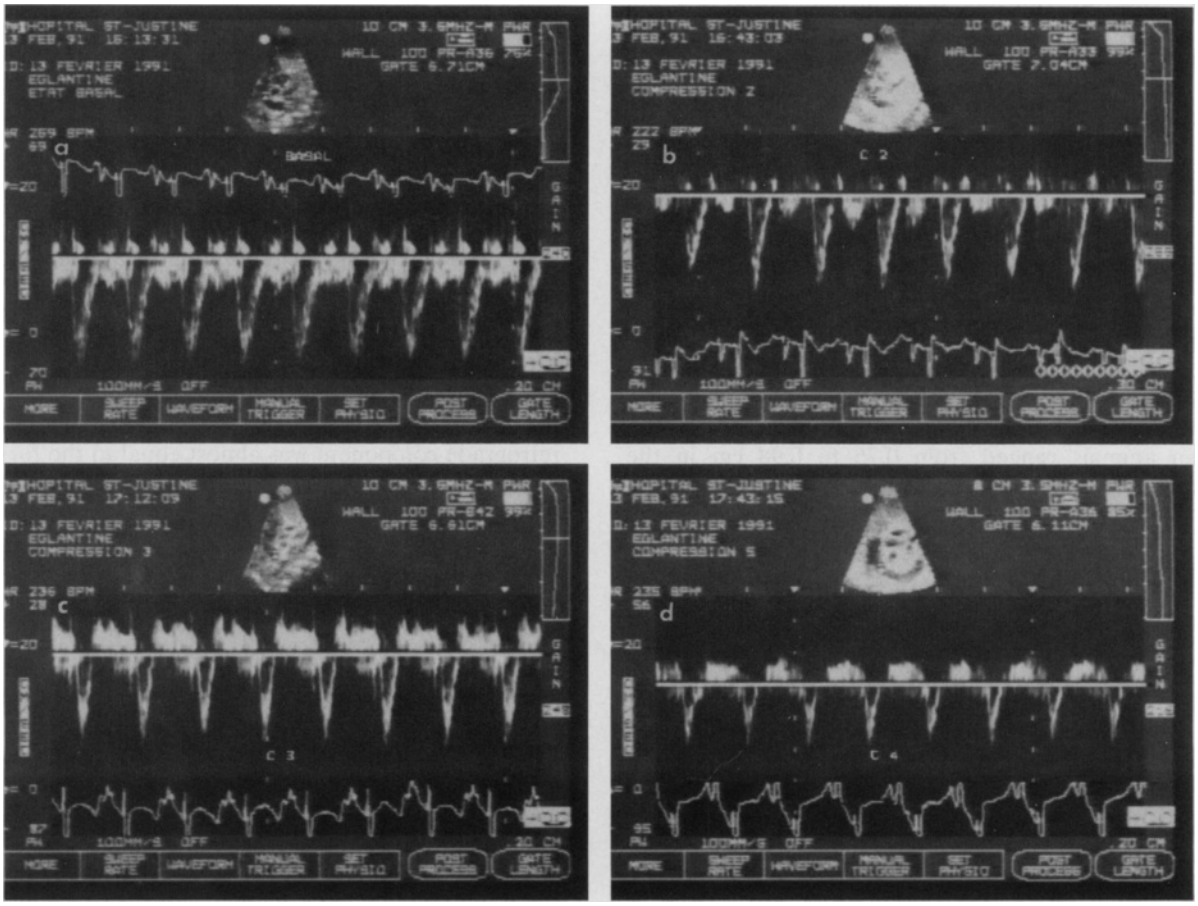


FIG 4. *Aortic isthmic flow velocity profiles at basal state (panel a) and in response to changes in resistance to placental blood flow (panels b, c, and d). Note the progressive decrease in systolic forward flow velocity integrals (panels b, c, and d). In diastole, forward velocity signals also decreased up to the second level of compression (panel b); a retrograde flow, however, is observed during the last two levels of compression (panels c and d).*

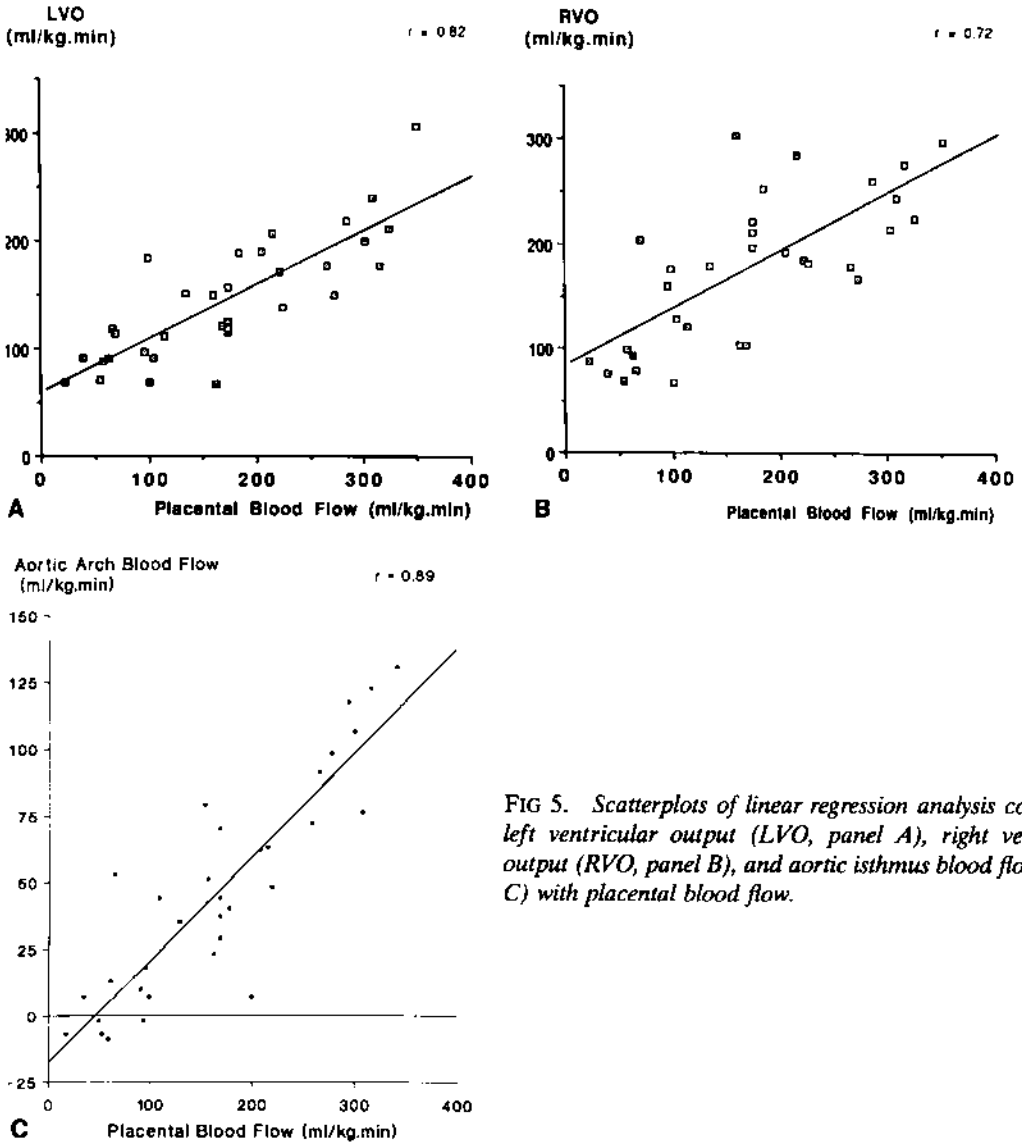


FIG 5. *Scatterplots of linear regression analysis correlating left ventricular output (LVO, panel A), right ventricular output (RVO, panel B), and aortic isthmus blood flow (panel C) with placental blood flow.*

found in the hypoplastic left heart syndrome where reverse systolic and diastolic flows are recorded in the aortic arch. Actually, our data showed the opposite: There was a proportionally greater reduction in the right ventricular output than in the left, an observation that has also been described previously.[10,11] The fall in cardiac output alone, therefore, cannot totally explain the flow patterns observed in our animals. It is nevertheless responsible for the absence of increase in blood pressure observed despite the rise in afterload.

Changes in cerebral vascular resistance is another variable that could have influenced the flow patterns in the isthmus during our experiments. Cerebral vasodilation is known to occur in the presence of hypoxemia and even more so in the presence of hypercarbia. It is conceivable that vasodilation of the cerebral arteries, by modifying the balance between the upper and lower body vascular resistance, could alter the flow velocity profile through the isthmus. However, an increase in resistance in the umbilical circulation, by creating a higher vascular resistance in the lower body, would further exacerbate this imbalance, resulting in the reverse diastolic flow observed in the aortic isthmus. It can be safely assumed, therefore, that the combination of both an increase in resistance in the umbilical circulation and a fall in cerebral vascular resistance is responsible for the diastolic flow patterns observed in the aortic isthmus.

To our knowledge, quantitative variations of flow through the aortic isthmus during increasing resistance to placental flow have never been investigated. The present study shows that the net flow through the isthmus can become negligible with an increase in placental resistance. A unique hemodynamic situation is then reached where the two parallel arterial vascular systems are completely independent: The left ventricle exclusively perfuses the ascending aorta and the upper body; the descending aorta, no longer receiving any significant contribution of higher oxygenated blood from the left ventricle, is only perfused by the right ventricle. In three of the lambs, a retrograde net flow was found through the isthmus during the last level of compression. In these cases, blood coming from the proximal descending aorta was then diverted toward the common brachiocephalic trunk. This would also mean that the lowest vascular resistance in the entire vascular system was no longer at the placental level but somewhere

in the upper body, in all likelihood at the cerebral level.[1] The consequences of these various hemodynamic adjustments on tissular oxygenation, especially on oxygen availability to the brain, deserve further investigation.

The observations made during moderate increase of resistance (compression level 3) are of special interest. At that point, while forward diastolic flow was being recorded in the umbilical artery, blood was flowing through the aortic isthmus in retrograde fashion. This phenomenon is well illustrated in Fig 2c and Fig 4c, which show the flow velocity profiles in the umbilical artery and aortic isthmus recorded on the same animal at 1-minute intervals during compression level 3. This confirms previous reports on the high sensitivity of fetal isthmic flow profile to changes in peripheral vascular resistances.[2]

Because these experiments were carried out on exteriorized and anesthetized fetuses, any attempt to apply these findings to clinical situations associated with impairment of placental circulation, such as intrauterine growth retardation, must be made with caution. Preliminary clinical observations on human fetuses, however, demonstrate that in cases of intrauterine growth retardation with impairment of the placental circulation, the alterations in diastolic flow velocity patterns occur sooner and are more dramatic at the level of the isthmus compared with the umbilical artery.[2] These observations made in utero are in keeping with our experimental findings. The fetal aortic isthmus, because of its particular position in the circulatory system, is therefore a vascular segment where measurement of blood flow allows assessment of the equilibrium between the downstream resistances of the two vascular systems perfused in parallel fashion by the two ventricles. The study further demonstrates a striking correlation between the actual umbilical blood flow and the net flow through the isthmus; the observed strong positive correlation of .89 suggests that in the absence of cardiac malformation (left heart hypoplasia) or vascular anomalies such as cerebral arteriovenous fistula, Doppler flow velocity studies in the aortic isthmus could be used as an indicator of the state of the umbilical circulation. Indeed, because no change in vessel diameter was noted during the four levels of umbilical vein compression, a simple comparison between forward and reverse flow velocity integrals through the isthmus would be sufficient to quickly and reliably evaluate the severity of impairment of umbilical blood flow. In clinical conditions where an increase in placental resistance is suspected, this feature could become extremely useful. Further clinical investigations are needed to validate these experimental observations.

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