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Retrograde net blood flow in the aortic isthmus in relation to human fetal arterial and venous circulations

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KEYWORDS: Doppler, Fetal heart, Hemodynamics, Physiology, Placental insufficiency

ABSTRACT

Objectives *To characterize changes in the human fetal arterial and venous circulations associated with retrograde aortic isthmus net blood flow.*

Methods *Study groups consisted of fetuses with placental insufficiency and/or fetal growth restriction and either antegrade (Group 1;* n = *18) or retrograde (Group 2;* n = *11) net blood flow in the aortic isthmus. The control group comprised 31 fetuses in uncomplicated pregnancies. Pulsatility indices of the umbilical, middle cerebral and proximal pulmonary arteries and the descending aorta, and pulsatility indices for veins of the ductus venosus and inferior vena cava were calculated. Right and left ventricular fractional shortenings were ascertained. The coronary artery blood flow was visualized and the presence of tricuspid regurgitation was noted.*

Results *In the study groups, the umbilical artery and descending aorta pulsatility indices were significantly higher (*$P < 0.05$*), and those of the middle cerebral artery lower (*$P < 0.001$*), than in the control group, with no difference between the two study groups. The proximal pulmonary artery pulsatility index was significantly higher in Group 2 (*$P < 0.001$*) than in Group 1 and the control group. In Group 2, the right ventricular fractional shortening was significantly lower (*$P < 0.01$*) than in Group 1. Coronary artery blood flow was visualized significantly more often (*$P < 0.03$*) and tricuspid regurgitation was present more frequently (*$P < 0.003$*) in Group 2 than in Group 1. In Group 2, the ductus venosus pulsatility index for veins was significantly higher than in Group 1 (*$P < 0.01$*) and the control group (*$P < 0.01$*), with no difference in the inferior vena cava pulsatility index for veins.*

Conclusions *Fetuses with retrograde aortic isthmus net blood flow demonstrate a rise in right ventricular afterload and increased pulsatility in ductus venosus blood velocity waveforms.*

INTRODUCTION

Results from animal studies have revealed that an increase in placental vascular resistance may change the fetal aortic isthmus blood flow profile before any significant change in umbilical artery (UA) Doppler velocimetry occurs[1]. In addition, studies on fetal lambs have shown that oxygen delivery to the brain is diminished in fetuses with retrograde net blood flow in the aortic isthmus[2]. Placental insufficiency, with a decreased number of villar arterioles, triggers compensatory mechanisms in the fetus, including redistribution of the arterial circulation, which helps to maintain an adequate oxygen supply to the most vital fetal organs: the brain and the heart. Redistribution of the arterial circulation includes an increased diastolic blood velocity component in the cerebral arteries and a decreased diastolic component in the descending aorta (DAo)[3]. Impaired placental function results in decreased right ventricular cardiac output of the fetus, while left ventricular cardiac output usually remains unchanged[4]. Further deterioration in the oxygen supply can decrease left ventricular cardiac output. Fetal cardiac dysfunction may lead to abnormal blood velocity waveforms in fetal systemic veins, including increased reverse flow during atrial contraction in the inferior vena cava (IVC), hepatic veins and ductus venosus (DV), and atrial pulsations in the portal and umbilical veins as a sign of increased fetal systemic venous pressure[5,6].

We aimed to characterize changes in the human fetal arterial and venous circulations which are associated with retrograde net blood flow in the aortic isthmus. Specifically, we aimed to investigate the relationship between: (1) placental function, (2) redistribution of arterial circulation, (3) afterload of the heart, and (4) the pulsatility of the blood velocity waveforms in the venous circulation, and the direction of aortic isthmus net blood flow in human fetuses with placental insufficiency and/or fetal growth restriction (FGR).

METHODS

This cross-sectional study was carried out between May 1998 and July 2000 at the University Hospital of Oulu, Finland. The research protocol was approved by the local ethics committee and all the subjects gave informed consent. Gestational age was confirmed by sonographic examination

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prior to 20 weeks of gestation in all cases. Cases with structural or chromosomal abnormalities were excluded.

Group 1 consisted of 18 fetuses which suffered from placental insufficiency (abnormal UA blood velocity waveform profile[6]) and/or FGR (fetal growth < 10th centile growth curve) and had antegrade net blood flow (Figure 1) in the aortic isthmus at 24–37 weeks of gestation. According to the guidelines of the American College of Obstetricians and Gynecologists[7], one mother had pregnancy-induced hypertension and 10 had severe pre-eclampsia. In seven cases placental insufficiency was diagnosed without a maternal hypertensive disorder. Umbilical artery Doppler tracings revealed a normal blood velocity waveform pattern (peak systolic/end diastolic velocity (S/D) ratio < 3.5) in one case, a decreased diastolic blood velocity component (S/D > 3.5) in 10 cases, and a retrograde diastolic blood flow component in seven cases. In 11 cases, neonatal birth weight was below the 10th centile growth curve. In every case of neonatal birth weight above the 10th centile growth curve, UA Doppler tracings demonstrated abnormal blood velocity waveforms indicating placental insufficiency. Cesarean delivery was performed because of signs of fetal distress in six cases as determined by abnormal non-stress test results and fetal biophysical profiles, and in eight cases the indication for Cesarean delivery was maternal hypertension and severe headache. The time interval between the last Doppler sonographic examination and delivery ranged from 0 to 4 days, with a median of 0 days.

Group 2 consisted of 11 fetuses with placental insufficiency and/or FGR and retrograde net blood flow in the aortic isthmus (Figure 1) at 24–37 weeks of gestation. In two cases pregnancy-induced hypertension was diagnosed, and two patients suffered from mild and two patients from severe pre-eclampsia. In five cases placental insufficiency was not associated with a maternal hypertensive disorder. Umbilical artery Doppler recordings showed normal blood velocity waveform patterns in three cases, a decreased diastolic blood velocity component in four cases and a retrograde diastolic blood flow pattern in four cases. With one exception, Cesarean delivery was performed because of signs of fetal distress in non-stress tests and abnormal biophysical profile scoring. Every neonate in this group had a birth weight under the 10th centile growth curve. The time interval between the last Doppler sonographic examination and delivery ranged from 0 to 2 days, with a median of 0 days.

The control group consisted of 31 cases with uncomplicated pregnancy and labor who were examined between 24 and 37 weeks of gestation. The birth weights of all the neonates were between the 10th and 90th centile growth curves. Perinatal data on the groups are given in Table 1.

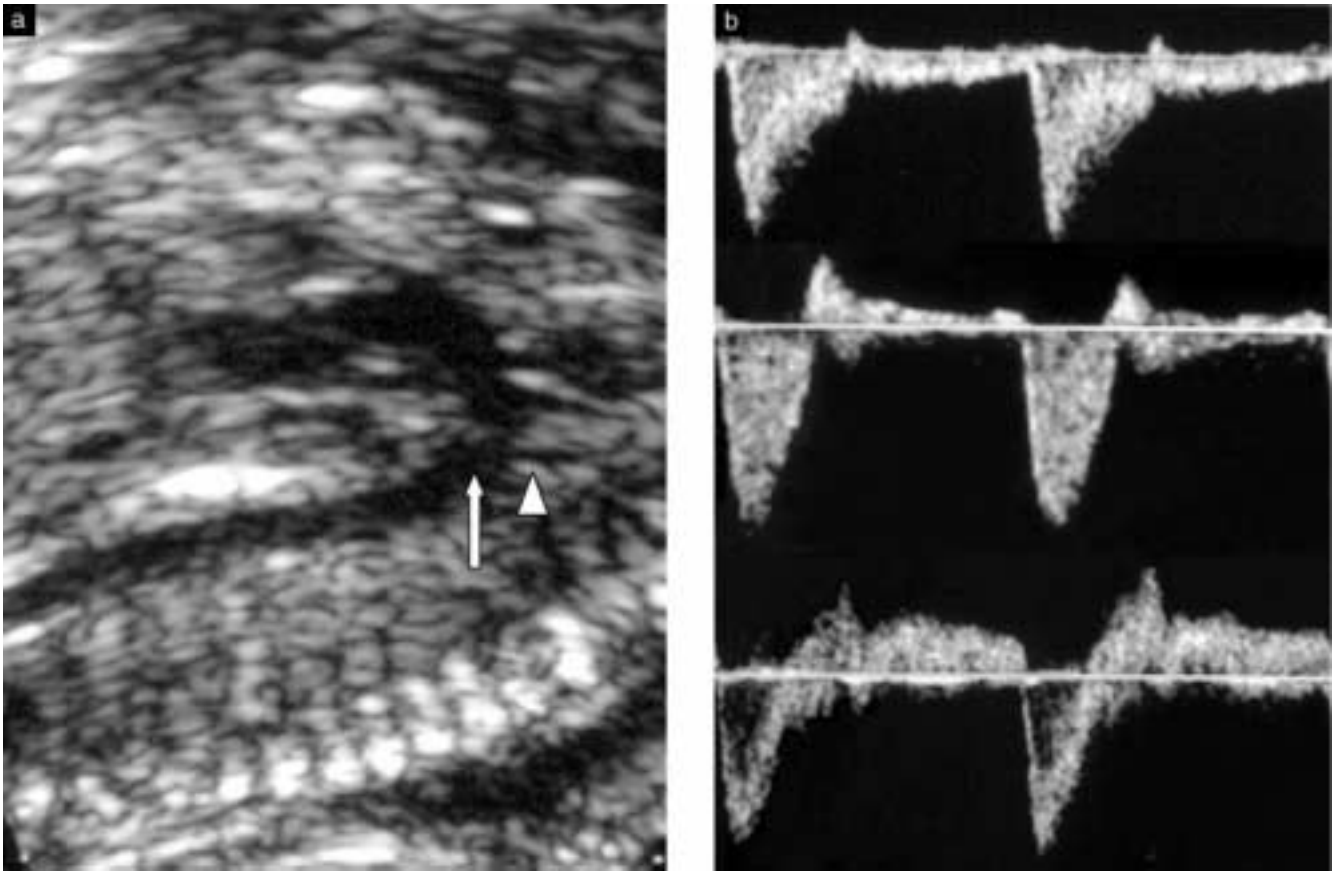

Figure 1 (a) Aortic arch in a sagittal view of the fetus. Aortic isthmus area (arrow) is close to the origin of the left subclavian artery (arrowhead). (b) Fetal aortic isthmus blood velocity waveform patterns in the three groups: with antegrade blood velocity component during the whole cardiac cycle in a fetus of the control group (top); with antegrade net blood flow (antegrade/retrograde ratio, 2.0) in a fetus of study Group 1 (middle); with retrograde net blood flow (ratio, 0.54) in a fetus of study Group 2 (bottom).

Image-directed pulsed and color Doppler ultrasound equipment (Acuson Sequoia 512, Mountain View, CA, USA) was used, with a 4–8-MHz convex or a 5-MHz sector probe. The high pass filter was set at minimum. The acoustic output of the system was displayed using mechanical and thermal indices which were controlled according to the guidelines published by EFSUMB[8]. An angle of < 15° between the vessel and the Doppler beam was accepted for analysis. Three consecutive cardiac cycles were analyzed from Doppler velocity waveforms and their mean values were used for further analysis. From the aortic isthmus blood velocity waveform profile, time-velocity integrals of antegrade and retrograde components were measured by planimetering the area underneath the Doppler spectrum, and their ratio was calculated. The net blood flow was considered antegrade if the ratio was ≥ 1, and retrograde when the ratio was < 1 (Figure 1).

Placental function was evaluated by calculating UA pulsatility index values (PI = (peak systolic velocity – end diastolic velocity)/time-averaged maximum velocity over the cardiac cycle). Redistribution of the arterial circulation was assessed by obtaining PI values of the DAo, proximal right or left pulmonary artery (PPA), middle cerebral artery (MCA) and UA, and by noting visualization of coronary arterial blood flow by pulsed and color Doppler. In addition, UA/MCA and DAo/MCA PI ratios were calculated to demonstrate the brain-sparing effect[3]. Blood flow profiles of the DAo were recorded at the level of the diaphragm. Blood velocity waveforms of the PPA were recorded immediately after the bifurcation of the main pulmonary artery before the first branch of the right or left pulmonary artery[9].

Fetal cardiac afterload was evaluated by calculating the PI values of the DAo, PPA and the ductus arteriosus (DA). From M-mode recordings, right and left ventricular inner diameters (RVD and LVD) were measured during diastole and systole, and right and left ventricular fractional shortenings (RVFS, LVFS) were calculated (ventricular fractional shortening (%) = ((inner diastolic diameter – inner systolic diameter)/inner diastolic diameter) × 100)[10]. The presence of tricuspid valve regurgitation was noted. Tricuspid regurgitation (TR) was classified as trivial (non-holosystolic ≥ 72 ms) or holosystolic[11].

Blood velocity waveforms of the IVC and DV were recorded and pulsatility indices of veins (PIV = (peak systolic velocity – velocity during atrial contraction)/time-averaged maximum velocity over the cardiac cycle) were calculated[12]. In addition, the presence of atrial pulsation in the left portal and umbilical veins was noted.

It has been demonstrated that intraobserver variability as regards PI measurements in the human fetal arterial circulation is < 4%, with correlation coefficients > 0.89[13]. In the present study, reproducibility and intraobserver variability of PIV calculations for the DV and IVC were analyzed in control-group fetuses (n = 31). Intraobserver variability of PIV values was < 9%, with correlation coefficients > 0.83.

Statistical analysis was performed by using analysis of variance when comparisons were made between the three groups and the data were normally distributed. If statistical significance was shown, the Scheffe F-test was used for further analysis. If the data was not normally distributed, the non-parametric Kruskal–Wallis test was used. Between two groups, comparisons were made by Student's t-test if the data were normally distributed; otherwise, the Mann–Whitney U-test was chosen. Categorial data were compared using the chi-square test. A P-value of 0.05 or less was selected as the level of statistical significance.

RESULTS

Maternal age, gestational ages at study entry and delivery, birth weights and Apgar scores of the neonates at 5 min in the different groups are given in Table 1. Umbilical artery pH and pO_2 values at birth did not differ between Groups 1 and 2 (Table 1). Cesarean delivery was performed more often in Group 2 than in Group 1 (10/11 vs. 6/18; $P < 0.01$) because of signs of fetal distress.

Umbilical artery PI values were significantly higher in Groups 1 and 2 than in the control group, with no difference between the study groups (Table 2). The DAo, PPA and DA PI values were significantly higher, and the PIs of the MCA were significantly lower in Groups 1 and 2 than in the control group (Table 2). In Group 2, the PI of the PPA was greater than in Group 1 ($P < 0.001$). The UA/MCA and DAo/MCA PI ratios were higher in Groups 1 and 2 than in the control group ($P < 0.01$ and $P < 0.0001$, respectively; Table 2), with no difference between Groups 1 and 2. Coronary artery blood velocity waveforms were visualized in seven of 11 cases (64%) in Group 2, and in four of 18 cases (22%) in Group 1 ($P < 0.03$). In Group 2, RVFS values were lower than in Group 1 ($P < 0.01$), while no difference in LVFS values was noticed. In addition, the right ventricular inner systolic

Table 1 Perinatal data of the study and control groups

	Control group (n = *31*) *(Mean (SD))*	*Study group 1* (n = *18*) *(Mean (SD))*	*Study group 2* (n = *11*) *(Mean (SD))*
Maternal age (years)	27.3 (5.7)	29.2 (3.3)	32.8 (6.7)
Gestational age at study entry (weeks)	29.9 (4.9)	29.9 (5.9)	32.1 (3.8)
Gestational age at delivery (weeks)	39.8 (1.4)	30.8 (4.0)‡	32.5 (3.9)‡
Apgar score at 5 min	9.0 (0.3)	7.8 (2.4)*	6.6 (3.2)†
Birth weight (g)	3487 (351)	1282 (674)‡	1252 (540)‡
Umbilical artery pH		7.24 (0.05)	7.26 (0.06)
Umbilical artery pO_2 (kPa)		2.13 (0.68)	2.31 (0.95)

*$P < 0.05$ vs. control group. †$P < 0.01$ vs. control group. ‡$P < 0.0001$ vs. control group.

Table 2 Pulsatility indices in fetal arteries and veins in control and study groups

	Control group	*Study group 1*	*Study group 2*
Fetal heart rate (bpm, mean (SD))	143 (8)	143 (6)	141 (10)
Umbilical artery (UA) PI (Mean (SD))	1.01 (0.18)	2.57 (1.44)†	2.80 (1.91)†
Ductus arteriosus PI (Mean (SD))	2.67 (0.29)	3.05 (0.42)†	3.15 (0.72)†
Descending aorta (DAo) PI (Mean (SD))	2.03 (0.22)	2.67 (0.60)*	3.13 (1.08)†
Proximal pulmonary artery PI (Mean (SD))	3.33 (0.26)	4.51 (1.44)*	7.55 (3.87)‡¶
Middle cerebral artery (MCA) PI (Mean (SD))	1.96 (0.29)	1.44 (0.43)†	1.33 (0.25)‡
DAo/MCA PI (Mean (SD))	1.05 (0.17)	2.06 (0.90)‡	2.36 (0.63)‡
UA/MCA PI (Mean (SD))	0.53 (0.11)	2.04 (1.40)†	2.03 (1.21)†
Inferior vena cava PIV (Median (range))	2.15 (1.13–2.89)	2.46 (1.02–6.19)	3.30 (1.76–11.94)
Ductus venosus PIV (Median (range))	0.56 (0.30–0.71)	0.60 (0.26–1.24)	1.10 (0.33–3.81)†§

*$P < 0.05$ vs. control group. †$P < 0.01$ vs. control group. ‡$P < 0.0001$ vs. control group. §$P < 0.01$ vs. Group 1. ¶$P < 0.001$ vs. Group 1. PI, pulsatility index; PIV, pulsatility index for veins.

Table 3 Right and left ventricular inner dimensions during systole and diastole, and ventricular fractional shortenings in the two study groups

	Study group 1 (Mean (SD))	*Study group 2 (Mean (SD))*
Right ventricle		
Diastolic dimensions (cm)	1.20 (0.28)	1.35 (0.21)
Systolic dimensions (cm)	0.84 (0.25)	1.11 (0.16)*
Fractional shortening (%)	30.1 (7.0)	17.7 (8.0)†
Left ventricle		
Diastolic dimensions (cm)	1.20 (0.29)	1.27 (0.16)
Systolic dimensions (cm)	0.83 (0.17)	0.91 (0.16)
Fractional shortening (%)	30.4 (5.1)	28.2 (5.2)

*$P < 0.05$ vs. Group 1. †$P < 0.01$ vs. Group 1.

diameter was greater in Group 2 than in Group 1 ($P < 0.05$) (Table 3). Tricuspid regurgitation was present in seven of 11 cases (64%) in Group 2, and in two of 18 (11%) cases in Group 1 ($P < 0.003$).

At the level of the IVC, PIV values did not differ between the groups (Table 2, Figure 2). However, the PIV of the DV was significantly higher in Group 2 than in the control group and Group 1. Atrial pulsation in the intra-abdominal umbilical vein was noted in seven of 11 cases (64%) in Group 2, and in seven of 18 cases (39%) in Group 1, with no significant difference between the groups ($P = 0.20$).

DISCUSSION

The aortic isthmus has a dynamic role in connecting the right and left ventricular circulatory systems of the fetus. According to the results of acute experiments on fetal lambs, it appears that retrograde net blood flow in the fetal aortic isthmus leads to diminished oxygen delivery to the brain[2]. On this basis, the present study was designed to investigate the association between placental function, redistribution of arterial circulation, afterload of the heart and the pulsatility of the blood velocity waveforms in the venous circulation, and the direction of aortic isthmus net blood flow in human fetuses with placental insufficiency and/or FGR.

Placental function, as assessed by calculating placental vascular impedance, was similarly impaired in fetuses with

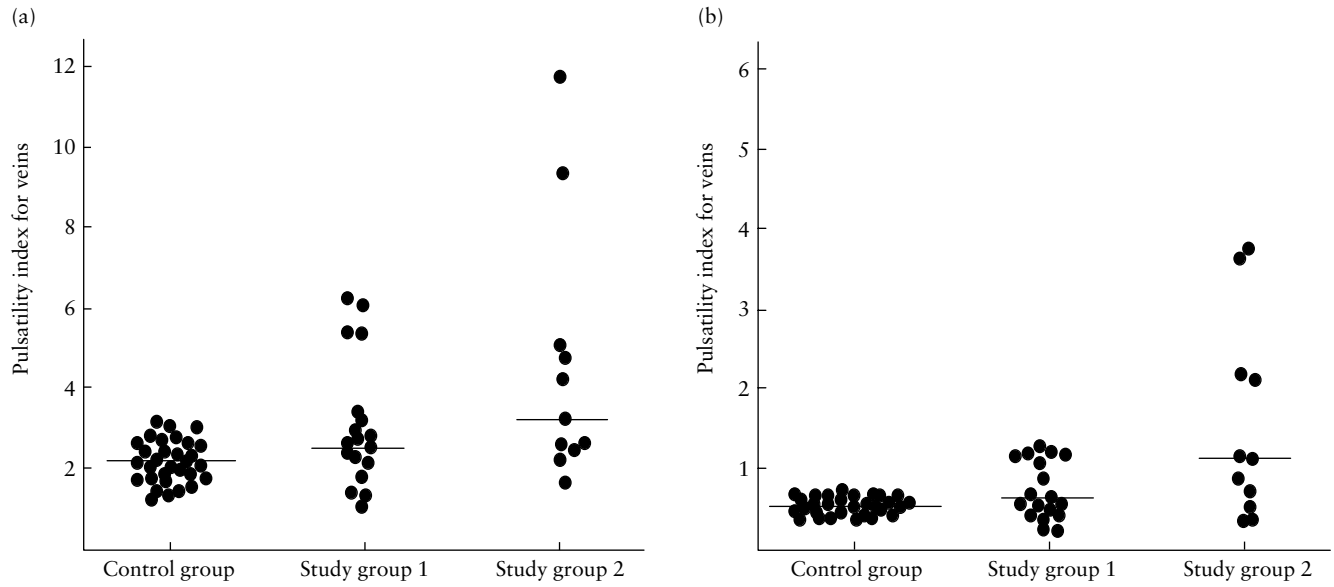

Figure 2 Inferior vena cava (a) and ductus venosus (b) pulsatility indices for veins in the control and study groups. In study Group 2, the ductus venosus pulsatility index for veins was greater ($P < 0.01$) than in the control group and study Group 1.

either antegrade or retrograde net blood flow in the aortic isthmus, compared with the control group. In addition, UA pH and pO_2 values at birth did not differ between the study groups. It is important to note that retrograde aortic isthmus net blood flow could be detected in the presence of a UA blood velocity waveform which was normal in appearance. This is in agreement with the results of studies on fetal lambs, which have shown that the aortic isthmus blood flow profile can change prior to deterioration of the UA blood velocity waveform pattern[1].

Redistribution of fetal arterial circulation, as indicated by the PI ratios between the UA and MCA, and the DAo and MCA, did not differ between the fetuses with antegrade or retrograde net blood flow in the aortic isthmus. However, in fetuses with retrograde net blood flow in the aortic isthmus, PPA PI values were higher than in fetuses with antegrade net blood flow. Circulation in the fetal pulmonary arterial bed is regulated by fetal oxygen tension, at least beyond 31 weeks of gestation[13]. Hypoxemia causes vasoconstriction and increases pulmonary arterial vascular resistance, and the effects of hyperoxemia are the reverse[14]. In addition, an increase in pulmonary arterial pressure is capable of inducing vasoconstriction of the pulmonary arterial bed after 26 weeks of gestation[15]. In placental insufficiency, oxygen delivery from the placenta to the fetus can be diminished, thus lowering the oxygen content of the fetal blood, which, in turn, could lead to vasoconstriction of the pulmonary arterial circulation. In addition, these fetuses tend to be hypertensive[16] and pulmonary arterial pressure is increased, which may lead to vasoconstriction of the pulmonary arterial bed.

In fetuses with retrograde net blood flow in the aortic isthmus, the afterload faced by the right ventricle is higher than in fetuses with antegrade net blood flow. Fetal right ventricular afterload is mainly a result of vascular resistance in the fetal lower body, placenta and pulmonary arterial bed. Umbilicoplacental vascular impedance did not differ between the fetuses with either antegrade or retrograde net blood flow in the aortic isthmus. In the DAo vascular impedance demonstrated no difference between the two study groups, and the DA blood velocity waveform profiles showed no signs of ductal constriction. However, RVFS was decreased in fetuses with retrograde net blood flow in the aortic isthmus. It appears that the pulmonary arterial circulation has an important role in the regulation of right ventricular afterload. In addition, the incidence of TR was higher in fetuses with retrograde net blood flow in the aortic isthmus, indicating altered loading conditions of the right ventricle in these fetuses.

In the present study, fetuses with retrograde net blood flow in the aortic isthmus demonstrated increased pulsatility in their DV blood velocity waveform profiles compared with fetuses with antegrade net blood flow. Pulsatility of the IVC blood velocity waveforms did not differ between the groups. It is known that in the human fetus, highly oxygenated blood entering from the placenta flows through the DV and left hepatic vein and streams across the foramen ovale to the left atrium and ventricle[17], while blood from the fetal lower body flows through the IVC and other hepatic veins, and enters the right atrium and ventricle. This parallel circulatory system of the fetal heart ensures a well-oxygenated blood supply to the coronary and cerebral circulations. Our preliminary findings have shown that in fetuses with retrograde net blood flow in the aortic isthmus the proportion of foramen ovale volume blood flow of left ventricular cardiac output is significantly less than in fetuses with antegrade net blood flow. In addition, fetuses with retrograde net blood flow have signs of elevated left atrial pressure. These results suggest that in fetuses with retrograde net blood flow in the aortic isthmus, the oxygen content of the blood entering the left ventricle is diminished compared with fetuses with antegrade net blood flow, even in the presence of similar umbilical vein pO_2 values. This is also supported by the fact that visualization of coronary arterial blood flow, described earlier as a heart-sparing effect[18], was significantly more common in fetuses with retrograde net blood flow in the aortic isthmus, suggesting vasodilatation of the coronary arteries and increased coronary arterial blood flow in these cases. In addition, oxygen consumption of the fetal heart could be increased in pregnancies complicated by placental insufficiency. It seems that fetuses with retrograde net blood flow in the aortic isthmus are unable to increase foramen ovale volume blood flow, which could explain the increased pulsatility in the DV blood velocity waveforms. On the other hand, diminished placental volume blood flow could make the DV blood flow profile more sensitive to changes in atrial pressure. Altogether, these findings suggest that the oxygen content of the blood directed to the coronary and cerebral circulations is diminished in fetuses with retrograde aortic isthmus net blood flow. This could explain the more frequent Cesarean delivery rate because of signs of fetal distress in these pregnancies.

The methodological problems concerning human fetal PI measurements have been discussed intensively. In the present study, the angle between the Doppler beam and the vessel was kept at $< 15°$ to minimize methodological errors. Intraobserver variability as regards PI calculations in the human fetal arterial circulation has been shown to be $< 4\%$[13] and in the present study the corresponding value for PIV calculation in the venous circulation was $< 9\%$.

In conclusion, placental function seems to be equally impaired in fetuses with either antegrade or retrograde net blood flow in the aortic isthmus. Fetal arterial redistribution, as determined by PI ratios between the UA and MCA, and the DAo and MCA, was similar regardless of the direction of aortic isthmus net blood flow. However, a heart-sparing effect was more often documented in fetuses with retrograde aortic isthmus net blood flow. Right ventricular afterload was higher in fetuses with retrograde net blood flow than in fetuses with antegrade net blood flow in the aortic isthmus, and fetal pulmonary arterial circulation had an important role in the regulation of right ventricular afterload. Increased pulsatility in the DV blood velocity waveforms in fetuses with retrograde net blood flow in the aortic isthmus was demonstrated.

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