Relationships among Doppler-derived umbilical artery absolute velocities, cardiac function, and placental volume blood flow and resistance in fetal sheep

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Acharya, Ganesh, Tiina Erkinaro, Kaarin Mäkikallio, Tomi Lappalainen, and Juha Rasanen. Relationships among Doppler-derived umbilical artery absolute velocities, cardiac function, and placental volume blood flow and resistance in fetal sheep. Am J Physiol Heart Circ Physiol 286: H1266–H1272, 2004.—We hypothesized that umbilical artery (UA) absolute blood flow velocities measured by Doppler ultrasonography reflect placental volume blood flow (QUA) and placental vascular resistance (RUA) in a late gestation fetal sheep model. In addition, we examined the relationships between umbilical artery absolute blood flow velocities and parameters of fetal cardiac function. Twenty-six sheep fetuses were instrumented at 112–132 days of gestation. After a 5-day recovery period, experiments were performed under general anesthesia in 16 normal fetuses, in 5 fetuses after maternal administration of phenylephrine, and in 5 fetuses after placental embolization. The QUA and arterial blood pressures were measured using a transit-time ultrasonic flow probe and a catheter placed into the descending aorta, respectively. UA peak systolic velocity (PSV), end-diastolic velocity (EDV), time-averaged maximum velocity (TAMXV), pulsatility index (PI), mean velocity (Vmean), fetal cardiac output, ventricular ejection forces, and the proportion of isovolumetric relaxation time (IRT%) in the cardiac cycle were measured with the use of Doppler ultrasonography. Significant positive linear correlations were found between UA EDV, TAMXV, and Vmean versus QUA, whereas UA PI had a significant negative correlation with QUA. Significant negative correlations were shown between UA EDV, TAMXV, and Vmean versus RUA. A significant positive correlation was present between UA PI and RUA. Doppler-derived UA parameters did not correlate with fetal arterial blood pressures, cardiac output, ventricular ejection forces or IRT%. In fetal sheep, Doppler-derived UA PI and absolute velocities, except PSV, are closely related to directly measured QUA and RUA, validating the use of noninvasive Doppler velocimetry in the assessment of placental circulation.

Fetal hemodynamics: placental circulation

Fetal central and peripheral hemodynamics and placental circulation are frequently studied noninvasively by Doppler ultrasonography. Umbilical artery (UA) Doppler blood flow velocity waveforms can be used to identify fetuses that might benefit from increased surveillance or planned delivery. Owing to difficulties encountered with volumetric blood flow assessment in small, pulsatile, convoluted UAs, qualitative analysis of blood flow velocity waveforms (15), or semiquantitative indexes, such as pulsatility index (PI), resistance index, and the systolic-to-diastolic ratio are often used. Mathematical (32) and hemodynamic (13) models have recently provided insights into the associations between Doppler indexes and anatomic and physiological characteristics of the placental circulation. It has been estimated that an exponential increase in UA PI is obtained only after >60% of the placental terminal vascular branches are obliterated (32). In fetal growth restriction, weight-indexed placental volume blood flow has been shown to be diminished (5, 23). A reduction in placental volume blood flow (QUA) can occur before changes in Doppler-derived UA blood flow velocity waveform indexes. UA absolute blood flow velocities may reflect QUA and provide physiologically relevant information regarding flow conditions. The significance of absolute blood flow velocity measurements can only be addressed by means of studies that allow simultaneous measurements of pressure, resistance, and volume flow (22).

Doppler-derived UA blood flow velocity waveforms represent temporal changes in the velocity of blood cells during the cardiac cycle and are under the influence of upstream (heart), downstream (resistance), and local factors. Changes in placental vascular resistance (RUA) may alter UA blood flow velocity waveforms. On the other hand, the local factors are thought to be relatively unimportant because UAs do not branch in the umbilical cord, and usually there is no degenerative vascular disease. The fetal cardiac performance may influence UA blood flow velocity waveforms, and the acceleration slope of the waveform has been suggested as a measure of cardiac contractility (16). However, it is not known whether UA absolute blood flow velocities are related to parameters of cardiac function.

The purpose of this study was to validate the use of UA Doppler velocimetry in the assessment of placental circulation under varying flow conditions.

We tested the hypothesis that UA absolute blood flow velocities measured noninvasively by Doppler ultrasonography reflect QUA and RUA in a fetal sheep model. In addition, we examined the relationship between UA absolute blood flow velocities and parameters reflecting fetal cardiac function.

MATERIALS AND METHODS

The research protocol was approved by the Animal Care and Use Committee of the University of Oulu. All experiments were performed in accordance with the guidelines of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (1986) and in compliance with the European Union Directive ETS 123 (1997).

Animal model. Twenty-six pregnant sheep with an average body weight of 71 kg (range 50–84 kg) were operated on at 112–132 days of gestation (term 145 days). Before surgery, food was withdrawn for

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18 h. After premedication with intramuscular ketamine (2 mg/kg) and midazolam (0.2 mg/kg), general anesthesia was induced with intravenous propofol (4–7 mg/kg) and maintained with isoflurane (1–2.5%) in an oxygen-air mixture delivered via an endotracheal tube, combined with intravenous boluses of fentanyl as required. Mechanical ventilation was maintained throughout the surgical procedure.

After a midline laparotomy was performed, the fetal lower body was exposed with a hysterotomy, and 18-gauge polyurethane catheters were placed into the fetal inferior vena cava and descending aorta via the femoral vein and artery. A small incision was made around the fetal abdomen just below the umbilical cord insertion and the UAs were exposed. A 4-mm transit-time ultrasonic flow probe (Transonic Systems; Ithaca, NY) was placed around both UAs and secured to the fetal abdomen. Thereafter, the fetus was returned to the uterine cavity, the lost amniotic fluid was replaced with saline, 1,000,000 units of benzyl penicillin were instilled into the amniotic cavity, and the hysterotomy and laparotomy incisions were closed. All catheters and probes were tunneled subcutaneously and exteriorized through a small incision in the ewe’s flank. Postoperative analgesia was provided with buprenorphine (0.01 mg/kg). The catheters were flushed daily with heparinized saline. The ewes were given 1 g of ampicillin, and the fetuses received 1,000,000 units of benzyl penicillin daily.

Data acquisition. Data acquisition was carried out on anesthetized and instrumented ewes (10, 30). Ventricular ejection forces were weight indexed. General anesthesia was induced with propofol (4–7 mg/kg) and maintained throughout the experiments with isoflurane (1–1.5%). Muscle relaxation was induced with 20 mg rocuronium to facilitate mechanical ventilation. Tidal volume, respiratory rate, and gas concentrations were adjusted to maintain normoventilation. The animals were allowed to stabilize for 30 min before the measurements. The measurements were performed under normal conditions in 16 fetuses, after maternal administration of phenylephrine (2.32 ± 0.52 mg) intravenously in five fetuses, and after placental embolization in five fetuses. Placental embolization was performed 24 h before the experiments with the use of 45- to 150-μm microspheres (Contour Emboli, Target Therapeutics; Fremont, CA). A dry volume of 0.25 ml microspheres was suspended in 0.5 ml of 20% albumin and diluted with 10 ml of sterile saline solution. Bolus doses of 1 ml were injected via the femoral artery catheter into the descending aorta every 15 min until fetal arterial oxygen saturation decreased by 30% of the preembolization value.

A fetal arterial blood sample was drawn during the measurement period for analysis of acid-base values (39). Fetal arterial and systemic venous pressures were measured using appropriate pressure transducers (Biopac Systems; Santa Barbara, CA). The QA, i.e., the total volume of blood conveyed by two umbilical arteries to the placenta, was measured with a peripheral transit-time ultrasonic flow probe (model T206, Transonic Systems). The RA was computed by dividing fetal mean arterial pressure (MAP) by QA. All of these variables were recorded continuously at a 100-Hz sampling rate using a polygraph (UIM100A, Biopac Systems) and computerized data-acquisition software (AcqKnowledge version 3.5.7 for Windows, Biopac Systems). The recordings were later unpacked in 1-min periods as medians of the values measured for each variable, and the means of the last 5 min of the ultrasonographic examination period were used for analysis.

Doppler ultrasonography was performed with the use of a sonogram (Sequoia 512, Acuson; Mountain View, CA) with a 4- to 8-MHz convex probe. The high-pass filter was set at minimum. Doppler-derived blood flow velocity waveforms of the UA were obtained from the free loop of umbilical cord using color and pulsed Doppler ultrasonography. The angle of insonation was kept <15°. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and time-averaged maximum velocity (TAMXV), i.e., the average value of maximum frequency shift over cardiac cycle, were measured from the blood flow velocity waveforms, and PI values were calculated [PI = (PSV – EDV)/TAMXV]. In addition, the time-velocity integral (TVI) of the UA blood flow velocity waveform was obtained by planimetry of the area underneath the Doppler spectrum and UA mean velocity (Vmean) was calculated as TVI × FHR, in which FHR is fetal heart rate. Three consecutive cardiac cycles were assessed, and mean values were used for further analysis.

The diameters of the aortic valves (AoV) and pulmonary valves (PV) were measured in frozen real-time images during systole by using the leading-edge method (21). Three separate measurements of valve diameter were obtained, and the mean value was used for calculation of the cross-sectional area (CSA) of the valve. From the blood flow velocity waveforms of the AoV and PV, TVIs were measured and volumetric blood flows (Q) across the PV and AoV were calculated (Q = CSA × TVI × FHR). Right ventricular (RV) cardiac output (RVCO) equals QPV and left ventricular (LV) CO equals QAV, and their sum is combined CO (CCO). Ventricular outputs were weight indexed.

Fetal cardiac systolic function was assessed by calculating the RV and LV ejection forces by using the formula (1.055 × CSA × TVI)/CSA, in which TVI is the TVI during the acceleration period of systole and CSA is the time to peak velocity interval (10, 30). Ventricular ejection forces were weight indexed.

LV inflow and outflow blood flow velocity waveforms were simultaneously recorded, and the proportion (%) of isovolumetric relaxation time (IRT) in the cardiac cycle was calculated to assess fetal cardiac diastolic function (36). The IRT was measured as the time period between the end of ejection and the onset of filling.

Q.ua was measured in 15 fetuses before and after general anesthesia. Intraobserver variabilities of UA absolute blood flow velocity measurements were determined. In addition, the corresponding variabilities of UA TVI and PI values were assessed.

Data were analyzed using SPSS for Windows version 11.0 (SPSS; Chicago, IL). Values are presented as means ± SD. Differences between groups were assessed by ANOVA. If statistical significance was shown, Scheffe’s F-test was used for post hoc analysis. Linear regression analysis was used to show the relationships between measured parameters. A two-tailed value of P < 0.05 was used as the level of statistical significance.

RESULTS

Fetal hemodynamic parameters, which were measured invasively and by Doppler ultrasonography, are presented in Tables 1 and 2. The QUA was lower and the RA was higher in the fetuses after maternal administration of phenylephrine and placental embolization compared with the normal group (Table 1).

The QUA (407 ± 125 vs. 401 ± 136 ml/min; P = 0.813) measured in 15 sheep before and after general anesthesia was not significantly different. Intraobserver variabilities of UA absolute blood flow velocity measurements varied from 1.7% to 3.2% (95% confidence interval, 0.8–5.1%), and the corresponding variability in UA TVI and PI calculations was from 1.1% to 5.1% (95% confidence interval, 0.2–6.8%).

Doppler-derived UA EDV (R = 0.68, P < 0.001) and TAMXV (R = 0.52, P = 0.006) values showed positive correlations with QUA (Fig. 1). However, UA PSV did not correlate (R = 0.32, P = 0.107) with QUA. The UA PI values demonstrated a negative correlation (R = 0.55, P = 0.003) with QUA (Fig. 1). There were significant negative correlations between UA EDV (R = 0.49, P = 0.012) and TAMXV (R = 0.39, P = 0.05) with RA, whereas PSV (R = 0.20, P = 0.325) did not correlate with RA. The UA PI values showed a positive correlation (R = 0.58, P = 0.019) with RA (Fig. 2).

Fetal systolic, diastolic, and mean arterial blood pressures did not correlate (R = 0.03–0.38, P = 0.058–0.77) with UA PSV, EDV or TAMXV or with UA PI values.
UMBILICAL ARTERY VELOCITIES AND PLACENTAL PHYSIOLOGY

Table 1. Values of the physiological variables obtained by direct invasive measurements on anesthetized pregnant sheep and fetuses at 117–137 days of gestation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 16)</th>
<th>Group II (n = 5)</th>
<th>Group III (n = 5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal respiratory, rate/min</td>
<td>17±0.77</td>
<td>18±0.55</td>
<td>18±0.71</td>
<td>0.141</td>
</tr>
<tr>
<td>Maternal tidal volume, liter</td>
<td>0.61±0.08</td>
<td>0.58±0.08</td>
<td>0.64±0.03</td>
<td>0.420</td>
</tr>
<tr>
<td>Inhaled O₂ concentration, %</td>
<td>43.8±7.8</td>
<td>51.8±9.8</td>
<td>46.0±8.7</td>
<td>0.428</td>
</tr>
<tr>
<td>Gestational age, days</td>
<td>125±46</td>
<td>125±39</td>
<td>131±52</td>
<td>0.075</td>
</tr>
<tr>
<td>Fetal weight, kg</td>
<td>2.5±0.07</td>
<td>2.6±0.2</td>
<td>2.0±0.7</td>
<td>0.260</td>
</tr>
<tr>
<td>QUA, ml/min</td>
<td>398±121</td>
<td>262±148</td>
<td>206±117*</td>
<td>0.012</td>
</tr>
<tr>
<td>RUA, mmHg·ml⁻¹·min</td>
<td>0.15±0.05</td>
<td>0.23±0.11</td>
<td>0.31±0.16*</td>
<td>0.008</td>
</tr>
<tr>
<td>Arterial Po₂, kPa</td>
<td>3.17±0.5</td>
<td>2.71±0.4</td>
<td>1.96±0.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td>31.4±8.5</td>
<td>21.3±6.5</td>
<td>13.2±5.4*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial Pco₂, kPa</td>
<td>6.02±0.7</td>
<td>7.20±1.0*</td>
<td>7.50±0.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.32±0.04</td>
<td>7.25±0.08*</td>
<td>7.30±0.05</td>
<td>0.045</td>
</tr>
<tr>
<td>Arterial base excess, mmol/l</td>
<td>−0.2±2.6</td>
<td>−2.0±3.6</td>
<td>1.4±2.6</td>
<td>0.179</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>65±7.3</td>
<td>64±9.2</td>
<td>66±6.6</td>
<td>0.925</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>44±6.2</td>
<td>40±8.0</td>
<td>43±6.2</td>
<td>0.636</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>51±6.3</td>
<td>48±8.4</td>
<td>51±6.4</td>
<td>0.709</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 26 sheep. QUA, placental volume blood flow to the umbilical artery; RUA, placental vascular resistance; BP, blood pressure; MAP, mean arterial pressure. Group I, normal; group II, after maternal injection of phenylephrine; group III, after embolization of placenta. *Compared with group I.

The UA Vmean demonstrated a positive correlation (R = 0.64, P < 0.001) with QUA and a negative correlation (R = 0.47, P = 0.014) with RUA (Fig. 3). However, UA Vmean did not correlate with fetal MAP (R = 0.05, P = 0.825) or weight-indexed CCO (R = 0.06, P = 0.771).

The UA PSV, EDV, TAMXV, and PI values did not correlate with weight-indexed LVOO, RVCO, LV ejection forces, RV ejection forces, or LV IRT% (Table 3). Similarly, the QUA (R = 0.01–0.14, P = 0.518–0.966) and the RUA (R = 0.11–0.23, P = 0.301–0.591) did not correlate with ventricular COs, ejection forces, or IRT%.

DISCUSSION

Mean UA flow over the cardiac cycle is determined by the mean driving pressure across the circulation (i.e., aorta to inferior vena cava) and the total placental vascular resistance (1). In placental insufficiency, diminished weight-indexed placental volume blood flow has been demonstrated in human fetuses (5, 23). A drop in QUA may even occur before the development of an abnormal UA blood flow velocity waveform pattern, and thus volume flow may be a physiologically more important parameter than impedance. This study was designed to investigate the relationships between Doppler-derived UA absolute blood flow velocities and PI values, and QUA and RUA in a fetal sheep model under varying flow conditions. In addition, noninvasive parameters of fetal cardiac function were correlated with Doppler-derived UA absolute blood flow velocities and PI values. We investigated these relationships not only during normal conditions but also after manipulating placental circulation pharmacologically and by placental embolization to obtain more insight into mechanisms of blood flow in physiology and disease. We used phenylephrine, a α₁-adrenoreceptor agonist, which is known to induce concentration-dependent constriction of the UA (3), to alter QUA and RUA. However, we injected the drug to the mother rather than to the fetus to avoid its direct effect on the fetal heart. We used placental embolization to obliterate peripheral vasculature in the placenta. This is shown to reduce QUA and increase RUA in animal models (34). Progressive emboliza-

Table 2. Doppler-derived parameters of cardiac function and umbilical artery blood flow velocities in fetal sheep at 117–137 days of gestation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 16)</th>
<th>Group II (n = 5)</th>
<th>Group III (n = 5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVCO, ml·min⁻¹·kg⁻¹</td>
<td>289±82.2</td>
<td>230±51.4</td>
<td>225±27.8</td>
<td>0.119</td>
</tr>
<tr>
<td>RVCO, ml·min⁻¹·kg⁻¹</td>
<td>484±170</td>
<td>478±115</td>
<td>487±88.1</td>
<td>0.995</td>
</tr>
<tr>
<td>LVEFO, ml/kg</td>
<td>6.0±1.4</td>
<td>5.4±2.7</td>
<td>4.2±0.4</td>
<td>0.154</td>
</tr>
<tr>
<td>RVeFO, ml/kg</td>
<td>7.2±2.9</td>
<td>8.7±3.0</td>
<td>6.7±1.2</td>
<td>0.448</td>
</tr>
<tr>
<td>IRT %</td>
<td>9.7±1.6</td>
<td>10.6±0.8</td>
<td>11.3±2.3</td>
<td>0.208</td>
</tr>
<tr>
<td>FHR, beats/min</td>
<td>175±23</td>
<td>174±36</td>
<td>182±21</td>
<td>0.834</td>
</tr>
<tr>
<td>Umbilical artery velocimetry parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vmean, cm/s</td>
<td>41.1±10.1</td>
<td>36.8±5.2</td>
<td>36.7±9.2</td>
<td>0.524</td>
</tr>
<tr>
<td>PSV, cm/s</td>
<td>59.1±13.0</td>
<td>58.0±10.6</td>
<td>53.5±10.0</td>
<td>0.675</td>
</tr>
<tr>
<td>EDV, cm/s</td>
<td>26.6±10.1</td>
<td>18.8±3.7</td>
<td>22.7±9.3</td>
<td>0.256</td>
</tr>
<tr>
<td>TAMXV, cm/s</td>
<td>40.3±10.1</td>
<td>36.4±7.3</td>
<td>36.5±8.7</td>
<td>0.601</td>
</tr>
<tr>
<td>PI</td>
<td>0.85±0.30</td>
<td>1.07±0.17</td>
<td>0.89±0.39</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 26 fetal sheep. LVCO, left ventricular (LV) cardiac output; RVCO, right ventricular (RV) cardiac output; LVEFO, LV ejection force; RVeFO, RV ejection force; IRT%, proportion of isovolumetric relaxation time in the cardiac cycle; Vmean, mean velocity; PSV, peak systolic velocity; EDV, end-diastolic velocity; TAMXV, time-averaged maximum velocity; PI, pulsatility index.
Fig. 1. Linear regression slopes demonstrating relationships between Doppler-derived umbilical artery peak systolic velocity (PSV; A), end-diastolic velocity (EDV; B), time-averaged maximum velocity (TAMXV; C), and pulsatility index (PI; D) values and placental volume blood flow ($Q_{UA}$) measured directly using a perivascular ultrasonic transit-time flow probe. ●, Measurements in normal fetuses; △, measurements in fetuses after maternal phenylephrine injection; □, measurements in fetuses after placental embolization.

Fig. 2. Linear regression slopes demonstrating relationships between Doppler-derived umbilical artery PSV (A), EDV (B), TAMXV (C), and PI (D) values and invasively measured placental vascular resistance ($R_{UA}$). The symbols and definitions are the same as in Fig. 1.
tion of the placental vasculature finally leads to abnormal UA blood flow velocity waveform patterns (19).

UA EDV and TAMXV correlated significantly with $Q_{UA}$, whereas PSV did not correlate with it. In early pregnancy, an absent diastolic blood flow component is a normal finding in UA blood flow velocity waveform patterns (4). With advancing gestation, the diastolic blood flow velocity waveform component increases proportionately more than the corresponding systolic component. Thus the diastolic part of the cardiac cycle seems to be more important in reflecting $Q_{UA}$ than the systolic portion. In addition, we found a significant negative correlation between UA EDV and $R_{UA}$. It has been demonstrated in anesthetized pigs that in the abdominal aorta Doppler-derived minimum diastolic velocity correlates negatively and PI values positively with total peripheral resistance (8). Furthermore, UA diastolic blood flow velocities have been shown to decrease with progressive placental embolization without any significant change in systolic velocities (19).

The UA PI is believed to reflect hemodynamic and morphological events taking place at the level of placental villi (7, 19, 33). Abnormal blood flow velocity waveforms, especially the reduced diastolic blood flow component and increased PI, are assumed to reflect increased resistance at the level of placental microcirculation. In the present study, UA PI values correlated negatively with $Q_{UA}$ and positively with $R_{UA}$. These findings demonstrate that changes in $R_{UA}$ are reflected in UA PI values. The changes in $R_{UA}$ and PI values are more related to changes in $Q_{UA}$ than fetal blood pressure because fetal arterial blood pressures did not correlate with UA absolute blood flow velocities or PI values.

We found a positive linear correlation between UA $V_{\text{mean}}$ and $Q_{UA}$ and a negative correlation between $V_{\text{mean}}$ and $R_{UA}$. The mean flow velocity is in direct proportion to volume blood flow, and our finding of a significant linear correlation between Doppler-derived UA $V_{\text{mean}}$ and $Q_{UA}$ demonstrates that in
fetuses it is possible to calculate volume blood flows when the cross-sectional area of the vessel can be accurately measured. Blood pressure is almost directly proportional to regional volume blood flow and vascular resistance. In this study, MAP did not correlate with QUA or UA Vmean, and in fetuses with embolized placenta leading to a significant reduction in QUA, the arterial blood pressures did not differ from those measured in normal conditions. This suggests that the variations in QUA are caused mainly by changes in RUA.

It has been estimated that in near-term fetal sheep ~40% of total CO is directed to the placenta (25). In human fetuses, the corresponding proportion is ~30% (29). In the present study, weight-indexed fetal COs did not correlate with Doppler-derived UA absolute blood flow velocities or PI values. In addition, there was no relationship between weight-indexed CCO and UA Vmean. Our findings demonstrate that in near-term fetal sheep, QUA is not related to changes in fetal CO, which may vary as a result of changes in fetal activity and behavioral status (24). The fact that no significant change in the CO was observed despite a significant reduction in QUA after placental embolization suggests that fetuses maintain their CO during moderate compromise as seen in human fetuses with severe placental insufficiency (17).

Ventricular ejection forces reflect the energy transferred from ventricular myocardial shortening to work done by accelerating blood into the circulation and can be used for the assessment of ventricular systolic function (30). Ventricular ejection force assessment does not require estimation of ventricular volumes and is independent of ventricular configuration (30). It is calculated by multiplying the mass of blood ejected over a certain time period by its acceleration. Animal studies have shown that early systolic flow is less affected by changes in afterload and preload than flow during late systole (20). The present study also demonstrates that an increase in afterload does not alter fetal cardiac ejection force development as no significant relationship was observed between RUA and ventricular ejection forces. In addition, UA absolute blood flow velocities and PI values were not related to ventricular systolic function.

The IRT represents the time interval between closure of the semi-lunar valve and opening of the atroventricular valve. This time interval is needed for the ventricle to drop its pressure from a systemic to an atrial level. Relaxation of the myocardium is an active process dependent on the ability of myocytes to reduce the concentration of cytosolic Ca2+ that requires Ca2+ transport out of the cytosol by four pathways involving sarcoplasmic reticulum Ca2+-ATPase, sarcolemmal Na+/Ca2+ exchange, sarcolemmal Ca2+-ATPase, or mitochondrial Ca2+ uniport (2). The IRT% can be used to describe early diastolic function of the heart. Previous studies (35) in human fetuses with placental insufficiency showed that IRT% is increased compared with control fetuses. However, in pregnancies complicated by placental insufficiency, IRT% was not further increased in fetuses with biochemical evidence of cardiac failure and myocardial cell damage compared with fetuses with no biochemical evidence of cardiac compromise (17). In the present study, a significant reduction in QUA and an increase in RUA caused by placental embolization did not appear to cause any significant change in IRT% suggesting that fetuses maintain their cardiac performance, despite moderately increased afterload.

Regarding the validity of our study, the experimental observations were made after a recovery period of 5 days, and the values of the measured parameters indicate stable fetal sheep preparations. The QUA was directly measured using a transit-time ultrasonic flow probe, a technique that has been well established and validated in animal experiments (18, 28). The Doppler technique has been increasingly applied in animal research in the field of fetal physiology (6, 12, 14, 26, 27, 31). The sheep is a suitable model for investigations of UA waveforms (9), and imaging quality in the sheep is excellent owing to a relatively thin abdominal wall and the presence of multiple small placentomes rather than one thick placenta (11). In the present study, intraobserver variability calculations demonstrated that UA absolute blood flow velocities could be measured reliably. However, there are some important limitations of this study. All of the measurements were performed while the sheep were under general anesthesia, which may constitute a confounding factor. However, it would be difficult to obtain all these measurements in alert sheep. In addition, the values of QUA measured before and after general anesthesia were found to be similar in this study. We believe that our results obtained during stable general anesthesia are close to physiological variations. Similarly, the observations made within a narrow gestational age range (117–137 days) in this study may limit their validity and significance for the remainder of gestation. Although one should be cautious about extrapolating the results derived from the animal experiments to the human fetus, the sheep model has been extensively used for research in fetal hemodynamics and the UA blood flow velocity waveforms are similar in normal ovine and human pregnancy.

We conclude that in fetal sheep Doppler-derived UA absolute blood flow velocities, except PSV, and PI values are closely related to QUA and RUA, validating their use in noninvasive assessment of placental circulation. The variations in QUA are mainly determined by changes in RUA. Doppler-derived parameters of fetal cardiac function did not correlate with QUA and RUA, and UA absolute blood flow velocities. This suggests that the fetal heart has the capability and reserve to maintain its function in conditions with increased afterload and the UA absolute blood flow velocities cannot be used in the assessment of fetal cardiac function.

GRANTS

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