Pulsatile Pressure–Flow Relations and Pulse-Wave Propagation in the Umbilical Circulation of Fetal Sheep

S. Lee Adamson, K.J. Whiteley, and B. Lowell Langille

The relations between pulsatile pressures and flows in the umbilical-placental circulation have been investigated using chronically instrumented fetal sheep. Under resting conditions, mean arterial pressure fell by 30±6%, from 44±2 to 31±2 mm Hg between the aortic termination and the arteries feeding the cotyledons, and pressure waves were substantially damped during propagation between the two recording sites. This high flow resistance and wave attenuation are attributed to the thick walls and extreme length of the umbilical arteries. Unique relations between pulsatile components of pressure and flow, characterized as vascular impedance spectra, were also observed. At rest, impedance to pulsatile flow was only slightly below resistance to steady flow, and impedance phase was positive at low frequencies. Pulse-wave reflections had more modest effects in this bed than others. Thus, oscillations in impedance spectra and percent wave transmission with increasing frequency, which are widely accepted manifestations of wave reflections, were relatively small. Positive impedance phases at low frequencies indicated that novel mechanisms influence phase relations between pressure and flow. A significant vascular compliance residing in the peripheral vascular beds could account for this finding. The vasodilator nitroprusside enhanced wave-reflection effects, whereas the vasoconstrictor angiotensin II reduced these effects. These changes were opposite to the effects of vasoactive substances in other systems, probably because these drugs act predominantly on the supply (umbilical) arteries rather than on the peripheral placental vasculature. When peripheral vascular resistance was selectively elevated by infusing 50-μm microspheres, reflection effects were enhanced: the pressure pulse in the umbilical artery was transmitted without attenuation, or was amplified, and impedance spectra more closely resembled patterns typical of other vascular beds. Specifically, impedance modulus fell sharply with increasing frequency, and impedance phase was negative at low frequency. In addition, we observed coordinated oscillations in impedance modulus and phase that are characteristic of beds that exhibit wave-reflection effects. These findings indicate that the specialized anatomy and control mechanisms observed in the umbilical circulation result in unique hemodynamic function, in which wave-propagation effects exert influences not readily predictable from studies on other systems. (Circulation Research 1992;70:761–772)

KEY WORDS • impedance • wave propagation • wave reflections • hemodynamics

The relations between pulsatile arterial pressures and flows have been studied extensively for the last 3 decades. This work has yielded a sophisticated understanding of the mechanical function of complete mammalian vascular systems and specific vascular beds. In particular, Fourier transform techniques and impedance analysis have demonstrated that arterial hemodynamics is greatly influenced by propagation of the pulse wave and its reflection back toward the heart, primarily from peripheral arterial beds. In lower vertebrates, this approach has shown that different models are needed to simulate systems that operate under very different constraints, e.g., poikilothermy versus homeothermy. More recently, Zahka et al provided important new information on the changing hemodynamic load that the developing vascular system imposes on the embryonic heart.

We were intrigued by the possibility that the fetal circulation may exhibit unique hemodynamic function. Fetal mean arterial pressures are less than half those of adults, and the outflow to the systemic circulation is derived from both ventricles, because of the presence of central vascular shunts. However, it is the presence of the large umbilical-placental vascular bed that probably has the greatest impact on pulsatile pressure–flow relations in the fetal arterial system. This circulation receives ~40% of the combined output of both ventricles; thus, it has a preeminent effect on central cardiovascular function. In addition, the peripheral placental beds reside at the terminations of two rela-

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Supported by a grant-in-aid from the Heart and Stroke Foundation of Ontario. S.L.A. is a Research Scholar and B.L.L. is a Career Investigator of the Heart and Stroke Foundation of Ontario.

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Received July 15, 1991; accepted December 5, 1991.
tively unbranched umbilical arteries whose length is typically more than double that of the aorta. Consequently, the pulse wave must traverse substantial distances before it reaches a discrete reflecting site (the terminal placental vasculature). In contrast, peripheral reflection sites in other vascular systems are distributed at various distances from the inflow to the system. Low spatial dispersion of reflecting sites should produce more obvious reflection effects in the umbilicalplacental circulation. Finally, the long umbilical arteries contribute a significant resistance to this circulation that can be selectively modulated by vasoactive substances. Thus, we previously reported that angiotensin constricted umbilical arteries, norepinephrine constricted umbilical veins, and neither significantly affected the microvascular beds of the cotyledons of anesthetized fetal sheep. Vasomotion of these supply arteries may substantially affect pulse-wave propagation.

We have assessed pulsatile pressure–flow relations in the umbilical circulation of the unanesthetized fetal sheep. These studies revealed that this vascular bed exhibits unique and unexpected properties. Consequently, novel models are required to adequately characterize this critically important component of the fetal circulation.

**Materials and Methods**

**Surgical Methods**

Pregnant ewes were anesthetized with thiopental sodium (Pentothal, 1 g i.v.) and were intubated and artificially ventilated. Anesthesia was maintained with 1% halothane in oxygen. The uterus was exposed through a midline abdominal incision and incised, and the fetal hind limbs were withdrawn. The common umbilical artery and the left internal iliac artery were exposed using retroperitoneal dissection through the left flank of the fetus. A 2F catheter-tip pressure transducer (model SPR-407, Millar Instruments, Houston, Tex.) was introduced via the left internal iliac artery and was advanced until the tip lay at the entrance to the common umbilical artery. During surgery, the position of the catheter tip was established by palpating the aorta. Catheter position was confirmed at necropsy. A cuff-type electromagnetic flow probe (C&C Instruments, Culver City, Calif.) was placed around the common umbilical artery in six fetuses. Probes were available in 0.5-mm-diameter increments, and a probe slightly larger than the external diameter of the vessel was selected for these chronic recordings. In practice, a 5-mm-diameter probe was used in six of the seven experiments that were analyzed. In the seventh, a 4-mm-i.d. probe was placed around the left umbilical artery because the common umbilical artery of this fetus was too short to allow placement of the probe. Measured flows were doubled to estimate total umbilical blood flow in this animal. The common umbilical artery and the proximal portions of the two daughter branches are much less vasoactive than the more distal umbilical arteries. Consequently, we consistently obtained reliable flow recordings during infusions of vasoactive agents, with no evidence of the instabilities that occur when contact between vessel and probe is lost. A cuff occluder (In Vivo Metric, Healdsburg, Calif.) implanted around the distal abdominal aorta was inflated briefly to establish zero flow of the electromagnetic flowmeter several minutes before each intervention used in the experiment. The femoral artery and vein were exposed on the right side through a skin incision in the upper leg of the fetus. Two vinyl catheters (1.2 mm o.d., model V4, Bolab, Lake Havasu City, Ariz.) were inserted into the vein and advanced 8 and 10 cm so that they entered the inferior vena cava. A vinyl catheter was advanced 8 cm into the femoral artery so that its tip lay downstream from the renal arteries. The arterial catheter was used to monitor mean arterial blood pressure, to obtain arterial blood samples for determination of blood gas tensions and pH, and to administer bolus injections of microspheres to embolize the placenta. One venous catheter was used to monitor venous blood pressure, and the other was used to infuse vasoactive agents during experiments. The positions of all catheters were confirmed at necropsy. The fetus was then returned to the uterus, and a cotyledon near the incision site was gently manipulated into view. The cotyledon vein was catheterized with vinyl tubing (1.2 mm diameter, model V4, Bolab), which was advanced —5 cm toward the heart. The cotyledon artery was catheterized in a similar manner, except that a catheter that would optimally record phasic pressures was used (see below). The uterine and abdominal incisions were closed with all catheters exteriorized through a small flank incision in the ewe.

**Postoperative Care**

Ewes received an analgesic (2 mg s.c. levorphanol tartrate, Hoffman-LaRoche, Mississauga, Canada) immediately after surgery and prophylactic antibiotics on the day of surgery and on the first 2 postoperative days. The cotyledon vessels were perfused continuously with a slow drip of heparinized, boiled 0.9% NaCl between surgery and experimentation to prevent clotting. Other vascular catheters were flushed daily with heparinized 0.9% NaCl. Experiments were performed on the third postoperative day on seven of the 10 fetuses we instrumented. Three fetuses were lost to the study. One ewe went into preterm labor, one fetus died in utero of unknown causes, and one fetus developed severe acidosis during the experiment, which was then discontinued. Data requiring pressure recordings from a cotyledon artery are missing from an additional animal because continuous infusion of heparinized saline through the pressure catheter was inadvertently stopped and a clot obstructed its tip. Animal surgery and experimentation was conducted according to guidelines approved by the Canadian Council of Animal Care.

**Experiments**

Experiments were performed between 127 and 133 days of gestation (mean, 128.4±0.8 days), i.e., 2–3 weeks before full term. Blood pressures in the aorta, inferior vena cava, amniotic cavity, and cotyledon vein were monitored using fluid-filled pressure transducers (model P23, Spectramed, Oxnard, Calif.). Fetal heart rate was determined with a tachometer (model 7P4, Grass Instrument Co., Quincy, Mass.) using a pulsatile arterial signal. These signals as well as phasic and mean umbilical blood flow, phasic aortic pressure measured with a Millar transducer, and cotyledon artery pressure
were continuously recorded on a strip-chart recorder (model 78D, Grass Instrument).

The following drugs were diluted from commercial preparations immediately before use and were infused via the fetal inferior vena cava using a continuous infusion pump (0.5 ml/min, Harvard Apparatus, South Natick, Mass.): norepinephrine bitartrate (10 μg/ml, Levophed, Winthrop, Aurora, Canada), angiotensin II (2 μg/ml, Sigma Chemical Co., St. Louis, Mo.), and 5% dextrose in 0.9% NaCl (vehicle control). Sodium nitroprusside (300 μg/ml, Nipride, Hoffman-LaRoche, Etobicoke, Canada) was infused at a rate sufficient to achieve a 30% decrease in mean arterial blood pressure rather than a set rate because of the highly variable blood pressure response to this agent.13 The average infusion rate of nitroprusside was 0.08 ml/min (range, 0.02–0.1 ml/min). The order of drug administration was selected sequentially from a 4×4 Latin square. The duration of infusion was 5 minutes, and it was followed by a 60-minute recovery period before the next drug was administered. Arterial blood samples (1 ml) were collected from the catheter in the abdominal aorta at −1, +5, and +20 minutes relative to the start of infusion. Samples were analyzed immediately for blood gas tensions and pH at 37°C using a blood gas analyzer (model 178, Corning Medical, Medfield, Mass.).

One hour after completion of the drug infusion experiment, further baseline measurements were obtained. Plastic, 50-μm-diameter microspheres (3M, St. Paul, Minn.) were then introduced into the distal abdominal aorta in bolus injections of 500,000 each. One bolus was given every 15 minutes until common umbilical blood flow during diastole decreased to zero or less. Physiological variables, including blood gas tensions and pH, were measured 10–15 minutes after each bolus of microspheres.

Data Analysis

Measurements of systolic and diastolic aortic blood pressures from Millar transducers, cotyledon arterial blood pressures, and umbilical blood flow were obtained from the chart recording 1 minute before and at the end of each 5-minute infusion and 10 minutes after each embolus of microspheres. Fetal heart rate, inferior vena cava blood pressure, cotyledon vein blood pressure, amniotic pressure, mean umbilical blood flow, and mean abdominal aortic blood pressure (measured using a fluid-filled catheter filtered with a 0.5-Hz low-pass filter) were also recorded at these points. Pressures were expressed relative to intrauterine (amniotic) pressure. If a filtered signal was not available, mean pressure was calculated as diastolic pressure plus one third of the pulse pressure. Total vascular resistance in the placental circulation was calculated by dividing the pressure difference between the aorta and vena cava by the blood flow in the common umbilical artery. The resistances in the three segments of the placental circulation were determined by dividing the pressure drop across the umbilical artery, the cotyledons, and the umbilical vein by umbilical blood flow. Phasic arterial blood pressures and flow, mean aortic blood pressure, and amniotic pressure were recorded on a digital tape recorder (model 4000, A.R. Vetter Co., Rebersburg, Pa.) for subsequent computer analysis. On tape playback, five consecutive cardiac cycles that were free of obvious artifacts were selected during the last minute of each drug infusion, during the minute immediately before the first bolus of microspheres, and 10 minutes after the embolus that caused an approximate threefold increase in total placental vascular resistance. These data were digitized at a sampling rate of 250 Hz using a data acquisition program (CADA, Hartronix, Concord, Canada), and the data were stored on magnetic disk. Aliasing errors were avoided by filtering pressure and flow signals with low-pass filters with cutoff frequencies below half the sampling rate. The pressure signal and flow signal were passed through a 60-Hz and a 100-Hz low-pass filter, respectively, during the experiment. For each infusion of each of five consecutive cardiac cycles, and the average modulus and phase were then calculated for the five waveforms. Vascular impedance modulus and phase were determined from the discrete Fourier transforms of the phasic aortic blood pressure signal (recorded with the Millar transducer at the inlet to the common umbilical artery) and the flow signal recorded in the umbilical artery. Impedances were averaged over all animals for each intervention. For averaging, data were grouped in bins that were centered on multiples of the mean heart rate. Careful comparisons of averaged and individual impedances revealed that the averaging procedures did not mask details of impedance curves.

Percent transmission versus frequency for the pressure wave propagated along the umbilical artery was calculated as the ratio of the amplitudes of cotyledon artery pressure and aortic pressure for each harmonic. Pressure-wave transmission was corrected for the frequency response of the cotyledon arterial catheter/ manometer system (see “Frequency Response and Calibration of Instrumentation”). Pulse-wave velocities were determined from the foot-to-foot time delay between aortic and cotyledon artery pressure signals.14

Frequency Response and Calibration of Instrumentation

Flow probes were calibrated by the timed collection method with a steady flow of 0.9% NaCl in vitro before and after each experiment. Discrepancy in flow probe recalibrations was ≤7%. The frequency response of the electromagnetic flowmeter (Gould model SP200, Spectramed) was measured using an electronic simulation of the flow probe.15 At the 100-Hz maximum frequency filter setting used in our experiments, the 3-dB point for the flowmeter was 65 Hz; therefore, <5% distortion resulted at the maximum frequency examined in this study (15 Hz). No correction was made. The flowmeter also introduced a constant delay of 4 msec. The resulting phase shift was corrected when computing impedance phase.

The catheter-tip pressure transducer used to record aortic blood pressure is extremely accurate in recording phasic pressure signals (frequency response flat to 10 kHz), but zero drift occurred between the time of implantation and experimentation (3 days). Zero drift was corrected by adjusting the baseline to ensure that mean blood pressure obtained with this device was equal to that obtained using the fluid-filled catheter in the abdominal aorta.
Ideally, pressure and flow signals should be measured at exactly the same location for impedance calculations. In our studies, the catheter-tip pressure transducer was located between 2 and 16 mm upstream of the flow probe. This separation introduced an error in impedance phase that increases linearly with frequency. This error was small, −1°/Hz, so no phase correction was made during our data analysis. The maximum error occurred at the highest frequencies reported in this study (−15 Hz), and this was <1°, which is too small to affect any of the conclusions we have drawn from our data.

To determine percent transmission of the pressure wave along the umbilical artery, it was necessary to accurately assess the frequency response of the manometer used to record cotyledon artery pressure. A catheter-tip pressure transducer could not be used because of the narrow lumen of these vessels. Instead, we inserted ~5 cm of a 24-cm length of polyethylene tubing (1.2 mm i.d., 1.7 mm o.d., PE 190, Clay Adams) into a cotyledon artery. This catheter was attached to a polyvinyl chloride pressure monitoring line (122 cm long, Cobe, Lakewood, Colo.) that had a relatively large bore and rigid wall (1.9 mm i.d., 3.2 mm o.d.). This catheter assembly was attached to a pressure transducer (model CDIXIII, Cobe). The tubing and transducer were filled from a 1-l reservoir of 0.9% NaCl that had been boiled to minimize air content and hence reduce bubble formation. Heparin was added to the saline reservoir after boiling (10 units/ml). A "pop test" (see page 147 of Nichols and O'Rourke) was performed to determine the undamped natural frequency of the catheter/manometer system immediately before inserting the catheter into the cotyledon artery and again, in four animals, at necropsy. Damped natural frequencies of 19.2±0.7 Hz (range, 16.6–21.7 Hz) were achieved, and these varied by <16% over the duration of the experiments. At necropsy, natural frequencies were 17.4±0.8 Hz (range, 15.6–19.2 Hz). Pop test data (natural frequency and damping) were used to correct pressure signals for manometer distortion when computing pressure-wave transmission.

Statistics

Results are presented as mean±SEM. The overall effects of drugs were assessed using a repeated-measures analysis of variance model (SAS PROC GLM). When the overall test was significant at the 5% level, paired-sample t tests were used to test the differences between the changes caused by each of the three drugs and the change caused by vehicle infusion. The Bonferroni procedure was used to correct for multiple comparisons. A paired-sample t test was also used to test the difference between a control measurement obtained immediately before beginning embolization and that obtained after embol had caused a threefold increase in total placental vascular resistance. Vascular resistances were analyzed for statistical significance after a log transformation to normalize their distributions. A difference was considered significant at p<0.05.

Results

Fetal Cardiorespiratory Parameters

Fetal body weight was 3.0±0.2 kg. At the start of the experiment, average fetal arterial oxygen tension was 17±1 mm Hg, carbon dioxide tension was 45±2 mm Hg, and pH was 7.389±0.008 (Table 1). Resting fetal heart rate was 171±7 beats per minute, and a mean arterial pressure of 44.1 mm Hg drove a blood flow of 599 ml/min through the placental circulation. These values are typical of those recorded by us16 and others17 using chronically instrumented fetal sheep. Nitroprusside decreased blood pressure, whereas angiotensin, norepinephrine, and infusions of microspheres caused pressor responses. Heart rate was depressed with norepinephrine and microsphere infusions, presumably because of a baroreflex; however, the bradycardia that accompanied the pressor response to angiotensin was not statistically significant. Norepinephrine significantly increased total placental vascular resistance but did not affect umbilical blood flow (Table 1). All other interventions decreased placental perfusion either by causing hypotension (nitroprusside) or by increasing placental vascular resistance (angiotensin II and microspheres). Only angiotensin II and infusion of microspheres sufficiently compromised placental perfusion to affect arterial blood gases significantly. Angiotensin caused hypoxia and acidosis; these changes were accompanied by hypercapnia and elevated base excess when the peripheral beds were partially occluded by microspheres.

Umbilico-placental Hemodynamics Under Resting Conditions

The fetal umbilical arteries were 44±2 cm in length from their origin at the termination of the aorta to the catheterized cotyledon. This was ~2.5 times the length of the aorta in these animals (17.5±0.5 cm). The pressure pulse traveled along these vessels with a velocity of 623±12 cm/sec, so it took ~20% of the cardiac

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**Table 1. Effect of Interventions on Cardiovascular and Respiratory Variables**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Nitroprusside</th>
<th>Norepinephrine</th>
<th>Angiotensin II</th>
<th>Emboli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>171±7</td>
<td>165±9</td>
<td>138±6*</td>
<td>143±7</td>
<td>112±10†</td>
</tr>
<tr>
<td>Umbilical flow (ml · min⁻¹)</td>
<td>599±70</td>
<td>482±42*</td>
<td>610±63</td>
<td>406±80*</td>
<td>259±24†</td>
</tr>
<tr>
<td>Mean aortic BP (mm Hg)</td>
<td>44±2</td>
<td>31±1*</td>
<td>62±4*</td>
<td>66±3*</td>
<td>60±4†</td>
</tr>
<tr>
<td>Total PVR (mm Hg · ml⁻¹ · min⁻¹)</td>
<td>0.081±0.014</td>
<td>0.068±0.009</td>
<td>0.097±0.007*</td>
<td>0.188±0.039*</td>
<td>0.213±0.020†</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td>46±2</td>
<td>47±2</td>
<td>46±2</td>
<td>49±2</td>
<td>62±3†</td>
</tr>
<tr>
<td>PaO₂ (mm Hg)</td>
<td>16.4±0.9</td>
<td>16.6±1.1</td>
<td>16.6±1.2</td>
<td>13.7±0.7*</td>
<td>9.0±0.3†</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.386±0.013</td>
<td>7.392±0.009</td>
<td>7.422±0.041</td>
<td>7.394±0.034*</td>
<td>7.110±0.060†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. bpm, Beats per minute; BP, blood pressure; PVR, placental vascular resistance.

* Change caused by drugs was significantly different from change caused by vehicle infusion (control).
† A significant change from baseline was caused by a threefold increase in total placental vascular resistance with emboli.
cycle for the pulse wave to reach the placenta from the aorta.

At rest, 30±6% of the arteriovenous pressure gradient occurred across the umbilical arteries, 55±5% occurred across the cotyledons, and 15±2% occurred across the umbilical veins (Figure 1, top panel). Since the same total flows perfuse these different levels of the placental vasculature, these values indicate the relative distribution of “segmental” vascular resistances within the circuit. Absolute resistances are shown in Figure 1, bottom panel.

Fetal lower abdominal aortic pressures recorded with Millar catheter-tip transducers consistently showed a steep rise in early systole and a relatively continuous decline in diastole, although a small second peak in pressure was sometimes observed in mid diastole (Figure 2). We never observed the smoothed profile with a prominent second maximum in diastole that is characteristic of abdominal aortic pressures of mature mammals.18 The flow waveform in the fetus was similar in shape to the pressure waveform, but it was somewhat more pulsatile. End-diastolic flow averaged 45±3% of peak systolic flow under resting conditions, and end-diastolic pressures were 62±3% of peak systolic pressure. Pressures recorded in the cotyledon arteries exhibited lower mean values (Figure 1, top panel) and also a substantially reduced pulse pressure compared with aortic pressure. Cotyledon pulse pressure was 24±11% of aortic pulse pressure, and the waveform also appeared more “damped” than aortic pressure (Figure 2).

Harmonic contents of these signals are shown in Figure 3. Amplitudes of aortic pressure, cotyledon artery pressure, and aortic flow harmonics all decreased monotonically with increasing frequency with the largest decrease, always >50%, occurring between the DC level and the first harmonic. Comparison of aortic and cotyledon arterial pressure harmonics indicated that attenuation of the pressure wave was frequency dependent. Thus, percent transmission fell rapidly between 0 and 5 Hz and then remained constant up to 15 Hz (Figure 4).

Umbilical impedance at rest exhibited two striking features (Figure 5). First, impedance modulus fell only a modest amount with increasing frequency and sometimes rose to near, or even above, placental vascular resistance at about the second harmonic (~6 Hz). In other vascular beds, impedance to pulsatile flow is normally much less than resistance to mean flow.6,18 Second, impedance phase became positive (pressure harmonics led flow harmonics) in all animals when frequency increased from zero. Impedance phase fell at

**Figure 1.** Top panel: Bar graph showing distributions of mean pressures in the umbilico-placental circulation under control conditions, during the infusion of nitroprusside (Nitro.), norepinephrine (NE), and angiotensin (A II), and after the infusion of a sufficient number of microspheres to increase total placental vascular resistance threefold (Emboli). Coty. A., cotyledon arteries; Umb. v., umbilical veins; I.V.C., inferior vena cava. Bottom panel: Bar graph showing resistances of the complete umbilico-placental circulation and “segmental” resistances of the umbilical arteries, the microcirculation within the cotyledons, and the umbilical veins for the conditions described in the top panel. *Significantly different (p<0.05) from control (dextrose infusion). #Significantly different (p<0.05) from measurements immediately before embolization.

**Figure 2.** Sample tracings of common umbilical arterial flow (top panel) and abdominal aortic and cotyledonal arterial pressures (bottom panel) under control conditions.
higher frequencies, crossing over to negative values at \(-6\) Hz, i.e., the frequency of the first maximum in impedance modulus. In other vascular beds, impedance phase is negative at low frequencies,6 except for during some exceptional experimental interventions.19

**Figure 3.** Graphs showing harmonic contents of abdominal aortic pressure (top panel), cotyledon arterial pressure (middle panel), and common umbilical arterial flow (bottom panel) under control conditions (five to seven animals per group).

**Figure 4.** Graph showing amplitude of harmonics of cotyledonal arterial pressure, under control conditions, expressed as a percentage of corresponding harmonic of abdominal aortic pressure (% transmission) versus frequency.

**Effects of Drug Infusions**

The pressor response to angiotensin did not affect cotyledon artery pressure; consequently, the pressure gradient across the umbilical artery was substantially enhanced (Figure 1, top panel). This was because the twofold to threefold increase in total placental vascular resistance was concentrated in the umbilical arteries, where the resistance increased an average of fivefold (p<0.05, Figure 1, bottom panel). A much smaller (56%) increase in cotyledon vascular resistance also proved significant.

Angiotensin greatly influenced wave transmission—reflection and pressure–flow relations. Thus, oscillations in impedance modulus, impedance phase, and percent transmission of the pressure wave were virtually eliminated (Figure 6, top left panel, and Figure 7, top panel). These are strong indications that wave-reflection effects are reduced with angiotensin. In addition, angiotensin II infusions eliminated positive impedance phases at low frequencies in all experiments.

Norepinephrine also significantly increased total placental resistance but only by about one third. Variable responses of the umbilical artery yielded no significant effect even though umbilical artery resistance increased in every animal and the majority of the change in total resistance occurred at this site. Instead, only the much smaller, but more consistent, change in cotyledon resistance (13%) was significant. Norepinephrine had no appreciable effects on impedance phase, but impedance modulus was elevated relative to resistance at most frequencies (Figure 6, top right panel). Impedance maxima occurred at \(-6\) Hz, as for control conditions, but they were
consistently above vascular resistance, occasionally by >50%.

Nitroprusside significantly decreased resistance of the umbilical arteries by ~50%, but other levels of the placental circulation were unaffected. Umbilical impedance modulus showed a greater fall as frequency increased from zero to the first harmonic (Figure 6, bottom left panel), but effects on pressure-wave propagation in the umbilical arteries were modest (Figure 7, bottom panel).

Angiotensin II and norepinephrine tended to increase and nitroprusside tended to decrease pulse-wave velocity in the umbilical artery, but none of these changes reached statistical significance.

**Effects of Microsphere Infusions**

Experimental design dictated that microsphere infusion would increase placental resistance by threefold.
Angiotensin II

Norepinephrine

Nitroprusside

FIGURE 7. Graphs showing percent transmission of harmonics of the pressure wave propagated along the umbilical artery (see Figure 4) during infusions of angiotensin II (top panel), norepinephrine (middle panel), and nitroprusside (bottom panel).

Not surprisingly, the dominant increase in resistance occurred in the microvessels, where the spheres lodged (Figure 1, bottom panel); however, there was also a small, but significant, increase in venous resistance. Large effects on pressure–flow relations resulted. Although the aortic pressure waveform was largely unaffected, apart from a broadening of the systolic peak, the cotyledon artery pressure waveform was dramatically altered (Figure 8). Cotyledon artery pulse pressure, as a percent of aortic pulse pressure, increased from 35±8% before embolization to 90±8% after embolization. Fourier analysis of the two pressure signals showed that percent transmission of pressure harmonics was substantially above control values, especially at low frequencies (Figure 9 versus Figure 4). Oscillations in percent transmission of the pressure wave with frequency were enhanced. The input flow waveform also became much more pulsatile. Thus, flow in the common umbilical artery fell to zero, or near zero, in diastole and then frequently showed a modest late diastolic rise. The well-defined second maximum in diastole shown in Figure 8 was not consistently seen.

Microsphere infusions also caused marked changes in impedance spectra (Figure 10). Impedance modulus fell substantially as frequency increased from zero to a well-defined minimum at 2–4 Hz before oscillating.

FIGURE 8. Sample tracings of common umbilical arterial flow (top panel) and abdominal aortic and cotyledonal arterial pressures (bottom panel) after infusion of microspheres. Note that cotyledonal arterial pulse pressure now exceeds abdominal aortic pulse pressure. In addition, common umbilical arterial blood flow is much more pulsatile than under control conditions (Figure 2), falling to zero in early diastole.

FIGURE 9. Graph showing percent transmission of harmonics of the pressure wave propagated along the umbilical artery after embolization produced by microsphere infusions.
reflection effects were relatively modest in the umbilicoplacental circulation. Primary manifestations of wave reflections in mature arterial systems include relative amplification of the pressure wave at more peripheral recording sites, because reflected and outgoing waves add constructively near the source of reflections and destructively at more distant sites. In addition, highly reflecting systems exhibit a dramatic fall in impedance modulus as frequency increases from zero. Thus, input impedance to the systemic circulation falls to values typically below 5% of resistance to steady flow. In contrast to this behavior, umbilical arterial pressure waves were attenuated during propagation, and umbilical impedance modulus was normally over half of placental vascular resistance and sometimes exceeded resistance. These findings suggest that wave-reflection effects are less significant, not greater, in the umbilical system. On the other hand, they are not totally absent. Umbilical impedance modulus and phase versus frequency exhibited clear maxima and minima, well-established by-products of reflections. We considered it most appropriate to compare umbilical impedance at rest with total systemic impedance of adults, rather than with impedance of specific vascular beds, because the former exhibit fluid mechanical “similarity” with respect to wave propagation; i.e., their lengths are ~15–25% of a wavelength for the first harmonic of the pulse wave. However, if comparisons are made with adult beds that are positioned near the aortic termination, e.g., the femoral bed, then some contrasts become even more striking. Thus, femoral impedance to pulsatile flow falls to ~2% of resistance to mean flow, which is far below the 50% level seen in the placental circulation. It could be argued that the fetal placenta should be compared with the adult pulmonary system, since both must meet the full gas exchange requirements of the organism. Pulmonary input impedances in both neonates and adults do indeed fall less with increasing frequency than systemic impedance. However, they still rapidly reach 20–30% of resistance to mean flow, a substantially greater decline than that seen in the umbilical artery. Furthermore, impedance phase in pulmonary systems, as in systemic beds, is negative at low frequencies.

Interesting comparisons can also be made with studies of hemodynamics in the aorta of the python, another very long conduit artery. Impedances and percent pressure-wave transmission measured in this vessel also failed to display large oscillations with increasing frequency. However, strong evidence was presented that this was due to the very wide distribution of reflecting sites at different distances along the aorta and not to weak wave reflection. Clearly distributed reflection sites are not a major factor in the relatively unbranched umbilical arteries.

The modest wave-reflection effects in the umbilical circulation merit particular attention. Reflections arise in wave-propagation systems at sites where impedance of the system changes. Thus, arterial beds are common sources of reflections because impedances of conduit arteries are normally small compared with those of resistance vessels. In this context, two factors probably contribute to reduced wave-reflection effects in the umbilical placental circulation. First, the umbilical arteries terminate in a low-resistance placental microvas-
culature that receives 40% of the combined output of both ventricles. Low resistance terminations minimize reflection effects in vascular beds because they are normally better matched to the low impedance of supply arteries. Indeed, virtually the only impedance moduli that resemble those of the umbilical circulation have been recorded in the maximally dilated femoral bed and in the renal artery, which, like the umbilical artery, feeds a very low resistance bed (see page 303 of Reference 6). Second, the long, relatively narrow umbilical arteries are higher impedance vessels than most conduit arteries. High impedances are indicated by a significant pressure drop between the aorta and the cotyledon artery seen in this and our previous study. High impedances of feed arteries, like low impedance of peripheral beds, reduce impedance mismatch and reduce reflections. The umbilical arteries are also very thick-walled muscular vessels, so they should exhibit a high degree of viscous damping. Viscous damping reduces the amplitude of reflected waves returning to the aorta, and this would further reduce the effect of reflections on umbilical impedance. The special properties of the umbilical arteries were also apparent from our measurements of pulse-wave velocities, which were high for fetal vessels distended under low pressure; i.e., they were 50–100% greater than those of the fetal aorta (authors' unpublished observations, 1991). According to the Moens-Korteweg equation (Nichols and O'Rourke), pulse-wave velocity is proportional to the square root of the Young's modulus times the wall thickness/radius ratio. It is probable that the very high wall thickness/radius ratio of umbilical arteries (0.5–1.0, authors' unpublished data, 1988) is largely responsible for the high pulse-wave velocity in these arteries.

A further very striking aspect of umbilical impedance was the positive impedance phase (pressure oscillations leading flow oscillations) that was observed as frequency increased from zero. This phenomenon, always seen under resting conditions, is not exhibited by other vascular beds; instead, impedance phase normally falls to negative values (flow harmonics lead pressure harmonics) then increases to cross zero. The only exception to this pattern we are aware of was recorded in the femoral artery of dogs when the muscle supplied by this artery was stimulated to contract cyclically in phase with systole. In those experiments, impedance phase at the frequency of the first harmonic was consistently positive. Although a number of possibilities were considered, it would appear most likely that compression of the vasculature by muscle contraction largely obstructed systolic flow and forced a delay in the flow rise until diastole. Since most of systole was involved, the first harmonic of flow must lag behind the corresponding harmonic of pressure. We believe that it is not feasible to pursue this phenomenon further in terms of wave transmission models because large, cyclic variations in resistance violate the assumptions of linearity implicit in these models.

The impedance phase pattern seen in most beds (negative phase at low frequencies) is readily explained in terms of reflections from purely resistive terminal beds. In this case, the crossover frequency occurs when the distance from recording site to the peripheral beds is one-fourth wavelength. One possible explanation for positive umbilical impedance phases is that the same model applies but that the lowest harmonics are consistently above the first crossover frequency. However, this explanation is not consistent with our data. Pulse-wave velocity was 6–8 m/sec, and an umbilical artery length was ~50 cm, so one-fourth wavelength will span this vessel when frequency is 3–4 Hz, which is above the heart rates we recorded. The most probable alternative is that the assumption of a purely resistive termination is false and that significant compliance resides on the arterial side of the placental microvasculature. Recent modeling studies showed that introducing compliances into terminations causes crossovers to occur at lower frequencies, presumably because they introduce phase shifts into reflected pressure and flow waves. Compliance in peripheral beds could explain another feature of umbilical impedance. Oscillations in impedance modulus and phase are tightly coupled in adult vascular beds, with maxima and minima in impedance modulus coinciding with zero crossovers in phase. This is a feature of systems with resistive terminations. In the umbilical circulation, maxima and minima in impedance modulus did not consistently coincide with phase crossovers, behavior that is mimicked by models with a peripheral compliance. Peripheral compliance could also partially explain why the peripheral pressure signal is attenuated compared with the aortic waveform. A phase shift of the reflected pressure wave would reduce constructive interference with outgoing waves at peripheral sites.

Increases in peripheral resistance usually enhance reflection effects by increasing impedance mismatch between conduit arteries and the terminal beds. Such effects were clearly in evidence in the umbilical circulation when microspheres were infused to selectively increase placental microvascular resistance. The cotyledon artery pulse pressure increased and often exceeded aortic pulse pressure, a well-recognized manifestation of wave reflections. In addition, flow became more pulsatile and exhibited a waveform distinctly different from pressure, falling nearly to zero throughout most of diastole. Impedances recorded after embolization demonstrated that these coordinated changes in pressures and flows again were consistent with much increased reflections from peripheral beds. Impedance modulus fell to low levels when frequency increased from zero, and oscillations in modulus and phase followed patterns characteristic of reflecting systems. Interestingly, impedance phase converted to a pattern typical of a system with a resistive termination. Impedance phases were negative at low frequencies, and zero crossovers in phase were more consistently linked with maxima and minima in impedance moduli. Lodging of the 50-μm microspheres may have isolated some of the cotyledonal compliance from the arterial circulation, in addition to increasing resistance.

The changes in umbilical blood flow waveforms observed after placental embolization are similar to changes in blood velocity waveforms of human fetuses exhibiting intrauterine growth restriction. In these infants, peripheral placental vascular resistance appears to be elevated by hypovascularization. Our findings suggest that altered pulse-wave reflections play an important role in the genesis of these waveforms.

Effects of altering peripheral resistance in adult arterial beds are normally examined by infusing vasoac-
tive agents. Vasoconstriction, like microsphere infusions, normally increases reflection effects, whereas vasodilation has the opposite effect. However, vasomotor substances do not preferentially affect the periphery in the umbilical circulation. The umbilical arteries are highly vasoactive vessels that contribute a significant proportion of the total resistance of the system at rest (~30%). We have shown that angiotensin preferentially constricts the umbilical arteries and that this coincides with reduced wave-reflection effects: impedance modulus shows little decline with increasing frequency, and neither impedance spectra nor pressure-wave transmission exhibits substantial oscillations with increasing frequency. A decrease in wave-reflection effects probably occurs because constriction of the umbilical arteries decreases, rather than increases, mismatch between the characteristic impedance of this vessel and the terminal impedance. In addition, angiotensin increases wave attenuation in umbilical arteries, which would limit the effects of any reflected waves on input impedance spectra. The conversion of impedance phase at low frequency from positive to negative values with angiotensin was surprising. It is possible that the modest constriction of the peripheral placental beds reduced compliance and converted them to a mainly resistive termination.

Reflection phenomena were somewhat enhanced with nitroprusside, since impedance modulus fell to relatively lower levels at low frequencies; however, other manifestations of reflections were not greatly affected. Modest enhancement may result from the selective dilation of the umbilical artery that was induced by this drug. Feed artery dilation, like peripheral vasoconstriction, increases impedance mismatch at the periphery and enhances reflections. The modest effects of norepinephrine on the placental circulation, at the doses we used, were in accord with little change in impedance patterns or pressure-wave propagation.

In summary, we have explored the hemodynamics of the umbilical circulation of chronically instrumented fetal sheep near term. Umbilical impedance and pulse-wave propagation effects were assessed under control conditions and during interventions that were designed to preferentially affect different levels of this circulation. These assessments revealed characteristics that were unexpected and unique to this system. First, reflection effects were more modest than in typical mature systemic beds, despite a localized source of coherent reflections. The primary reason for weak reflections is probably the low peripheral resistance of the placenta, although other factors may be involved. Second, vascular impedance data did not fit the models that have been successfully applied to other mammalian vascular beds. In the present study, impedance phase was positive (pressure harmonics led flow harmonics) at low frequencies, whereas negative phases have occurred at low frequencies in systems previously studied. Third, angiotensin reduced and nitroprusside enhanced wave reflections in the umbilical circulation. These effects are opposite those of vasomotor substances in adult beds because these drugs selectively acted on the umbilical arteries and had only modest effects on the peripheral arteriolar beds in the placenta. When peripheral vascular resistance was increased by embryolization with microspheres, hemodynamic adjustments mimicked those of peripheral vasoconstriction in mature beds.

These findings indicate that the umbilical circulation imposes a unique load on the fetal cardiovascular system that is not comparable to any mature vascular bed yet studied. The large share of cardiac output delivered to the placenta suggests that central cardiovascular function is highly sensitive to changes in this bed. Indeed, it is likely that systemic input impedance is largely influenced or even dominated by placental hemodynamics. If this is so, then the coupling between the heart and the arterial system is clearly different from that pertaining to the adult circulation. Furthermore, the loss of the placenta at parturition undoubtedly initiates a phase of major readjustment of the impedance to pulsatile flow that is imposed on the neonatal heart. Defining these readjustments awaits data on central impedances in the fetus and the changes these impedances undergo at birth.

Acknowledgments

We are grateful to Dr. Larry Mo and Ms. Sari Pichtianarar for writing the Fourier transform program and to Mr. Will Gibson, who performed the electronic calibration of the electromagnetic flowmeter.

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Circ Res. 1992;70:761-772
doi: 10.1161/01.RES.70.4.761

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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