Abnormal arterial flows by a distributed model of the fetal circulation

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Abstract

DOPPLER INSIONATION TECHNIQUES allow for identification of characteristic blood velocity profiles in the fetal arterial tree during gestation (11). Abnormal velocity waveforms in umbilical arteries, i.e., absent or reversed velocities during diastole, have been associated with adverse perinatal outcome (20, 25, 41, 67). In addition, abnormal development of the fetal circulation has been associated with cardiovascular disease in postnatal life (8, 9, 12, 30). Commonly, blood velocity profiles are most often described by the pulsatility index (PI) (15), defined as the difference between the maximum and minimum velocities divided by the mean velocity. Abnormal PI in the umbilical artery (UA) and middle cerebral artery (MCA) are clinically significant because they are associated with adverse pregnancy outcomes (25, 66).

Absence of forward flow in diastole in the UA, with increased PI, is hypothesized to result from an increased placental resistance (3, 31, 35, 36, 51). Additionally, decrease of the PI in the cerebral arteries due to an increased diastolic flow has been suggested to result from a dilated cerebral vasculature, a compensatory response to hypoxia (18, 41, 42, 66). However, it is unclear how abnormalities in several other parameters, e.g., the Young’s modulus (arterial stiffness) or blood viscosity affect the PI. Since the influence of these parameters cannot be studied in an experimental animal model, because arterial stiffness cannot easily be varied and individual variation of a single parameter while other parameters remain unchanged is difficult, computational modeling of pulsatile flow in the fetal arterial circulation has become important.

The existing models have contributed significantly to our understanding of the fetal circulation because they allow investigation of the influence of various individual parameters on the flow pulse waveform (7, 16, 21, 26, 31, 36, 38, 46, 48, 50). However, these models have limitations in that they either considered a small range of gestational ages, lacked variation of anatomical or rheological parameters, or only included the umbilicoplacental circulation rather than attempting to include the fetal arterial tree.

Our aim in this study was twofold. First, we attempted to construct a mathematical model of the pulsatile fetoplacental arterial circulation from 15 to 40 wk, particularly including the clinically most relevant umbilical and cerebral arteries. The arteries were modeled by including Womersley’s oscillatory flow theory (68) and adding viscoelastic arterial wall properties. Abnormal PI in the umbilical artery and decreases in the cerebral arteries, as a result of increasing placental resistance or decreasing brain resistance. Both changes in resistance decrease the flow through the placenta. An increased arterial stiffness increases the PI in the entire fetoplacental circulation. Blood viscosity and peripheral bed compliance have limited influence on the flow profiles. Bradycardia and tachycardia increase and decrease the PI in all arteries, respectively. Umbilical arterial length has limited influence on the PI but affects the mean arterial pressure at the placental cord insertion. The model may improve the interpretation of arterial flow pulsations and thus may advance both the understanding of pathophysiological processes and clinical management.

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Modeling the propagation of blood pressure and flow along the fetoplacental arterial tree may improve interpretation of abnormal flow velocity waveforms in fetuses. The current models, however, either do not include a wide range of gestational ages or do not account for variation in anatomical, vascular, or rheological parameters. We developed a mathematical model of the pulsating fetoplacental arterial circulation using Womersley’s oscillatory flow theory and viscoelastic arterial wall properties. Arterial flow waves are calculated at different arterial locations from which the pulsatility index (PI) can be determined. We varied blood viscosity, placental and brain resistances, placental compliance, heart rate, stiffness of the arterial wall, and length of the umbilical arteries. The PI increases in the umbilical artery and decreases in the cerebral arteries, as a result of increasing placental resistance or decreasing brain resistance. Both changes in resistance decrease the flow through the placenta. An increased arterial stiffness increases the PI in the entire fetoplacental circulation. Blood viscosity and peripheral bed compliance have limited influence on the flow profiles. Bradycardia and tachycardia increase and decrease the PI in all arteries, respectively. Umbilical arterial length has limited influence on the PI but affects the mean arterial pressure at the placental cord insertion. The model may improve the interpretation of arterial flow pulsations and thus may advance both the understanding of pathophysiological processes and clinical management.

pulsatility index; fetal pulsating arterial blood flow; mathematical model
**METHODS**

**Distributed model of the fetal arterial circulation.** We adapted our previous model of pressure and flow transfer of the adult arterial circulation (60), scaled it to fetal dimensions from 15 to 40 wk, and included the umbilical circulation. We included 13 arterial segments and nine peripheral vascular beds representing various organs. The anatomical basis of the model is given in Fig. 1A. This choice of arteries and organs describes the vascular pathways to the brain and placenta. Obviously, these organs have the greatest clinical relevance in the assessment of fetal arterial flows. The parameters used are summarized in Table 1. The fetal arteries were considered as viscoelastic tubes (61, 63). For the organs, three-element Windkessels were used, which best characterize the vascular bed of organs (57, 62).

From the input flow waveform, the equivalent Fourier transform, i.e., the frequency components, is determined, and each frequency component of flow (with its corresponding amplitude and phase) is treated separately in terms of its propagation and attenuation along the arterial tree. Figure 1A illustrates this by showing a different Fourier spectrum amplitude between the cardiac output and the flow through the abdominal aorta. Details on the method used to describe the fetal circulation in terms of its pressure and flow relations in the frequency domain can be found in the **APPENDIX**. In the model, 25 harmonics of the normal fetal heart rate are used to compute the frequency spectrum of the input flow. In the time domain, the input flow was chosen as shown in Fig. 1A. The model equations are written in Mathematica 4.0 (Wolfram Research, Champaign, IL).

**Anatomical parameters.** We used published data to define vessel length (l), radius (r), and wall thickness (16, 19, 36, 45), and because these data are incomplete, we extrapolated them to cover the full gestational period (Table 2). We assumed that radius and lengths of arteries increase proportionally to gestational age (19, 45, 54). Details are as follows: arterial radii (r) and lengths (l) depending on gestational age in weeks (t) are described by

\[ r = r_0 \cdot t + r_0 \]

(1)

\[ l = l_0 \cdot t/40 \]

(2)

Details on \( r_0, r_0 \), and \( l_0 \) are given in Table 2. Arterial wall thickness was assumed to be 15% of the arterial radius, except for the UA, in which wall thickness was assumed to be 20% of UA radius. Similar to other models (36), the umbilical arteries were assumed to be uniform, i.e., without tapering.

The static Young’s modulus (\( E_s \)) was determined from the thoracic aorta pulse wave velocity (PWV) together with the wall thickness (h), blood density (\( \rho \)) taken as 1.05 g · cm\(^{-3}\) and \( r \). First, we used the relation for the increase of PWV during gestation measured by Gardiner et al. (13) combined with the normal PWV at term in the thoracic aorta, which is 250 cm/s (17, 36), yielding

\[ PWV = 5.4 \cdot t + 34 \]

(3)

Next, we used the Moens-Korteweg equation for the PWV and the vessel characteristics and solved for \( E_s \) as

\[ E_s = \frac{\rho \cdot 2\pi \cdot PWV^2}{h} \]

(4)

Because all parameters are known throughout pregnancy, Young’s modulus for the thoracic aorta follows as

\[ E_s = 3.8 \cdot 10^5 \cdot r^2 + 4.7 \cdot 10^7 \cdot t + 1.5 \cdot 10^4 \]

(5)

The Young’s moduli for the additional arterial segments were estimated from that of the thoracic aorta, combined with slight fitting to yield normal PI values and PWVs. The Young’s moduli of the ascending aorta, abdominal aorta, iliac arteries, and UAs are taken as 0.5, 2.22, 6.66, and 6.66 times the thoracic aorta’s Young’s modulus, which is similar to other values (36). The Young’s moduli of the carotid artery and cerebral arteries were estimated as 1.5 and 2.5 times that of the thoracic aorta. These relations are taken age independent. Figure 1C shows the different segmental Young’s moduli for three gestational ages. This rapid increase in arterial Young’s moduli during gestation (about 60%) corresponds to clinical results (6), which found rapid increase of both elastin and collagen content of the human arterial wall during gestation. In addition, the increase in Young’s modulus toward the distal segments is consistent with clinical measurements of human arteries (28).

The fetal heart rate (HR) was taken from Struijk et al. (45) and is given by

\[ HR = \left( -0.67 \cdot t + 162 \right)/60 \]

(6)

(in beats per second). The fetal cardiac output was taken from our previous model (32, 53). The fetal blood viscosity was taken from Welch et al. (59) as

\[ \eta = (1.15 + 0.075 \cdot t)/100 \]

(7)

**Peripheral vascular bed parameters.** The three-element Windkessel is used to describe the peripheral vascular bed of organs. The model of a Windkessel is presented in Fig. 1B and the pertaining equation is given in the **APPENDIX** by Eq. A8. The Windkessel is connected to the feeding artery by a resistance (\( R_c \)). In the model, \( R_c \) is chosen to equal the characteristic impedance \( Z_{char} \) of the feeding artery, see Eq. A6, at high frequencies (62), implying that reflection is absent at high frequencies. For relatively low frequencies, the Windkessel impedance decreases already strongly as a consequence of the term \( \omega^3 \cdot C_W \cdot R \) when \( C_W \) is large. As a result, reflections from organs, in the normal fetus are low.

When several parallel arteries and vascular beds are present, e.g., at the position of the kidneys, the \( R_{es} \) of the two Windkessels are connected to the known \( Z_{char} \) of the thoracic aorta. We use that these resistances are in parallel with the abdominal aorta, where \( 1/Z_{char}^{thor} = 1/Z_{char}^{abdom} + 2/R_{es}^{abdom} \). Because the two characteristic impedances are known, this relation defines renal Windkessel \( R_c \).

The distribution of the cardiac output was estimated from literature values (16, 36). It is assumed that 0.5% of the cardiac output enters the fetal brain (36), 3% of the cardiac output enters each kidney (16), 10% enters the right or left side of the lower body (16, 36), and 15% enters each UA (36). In addition, it is assumed in the ascending aorta that 5% of the cardiac output leaks into the thorax (e.g., coronary arteries), 10% and 5% leaks out of the thoracic and abdominal aorta, respectively (e.g., into the intercostal and mesenteric arteries). The carotid, cerebral, and umbilical arteries are considered without significant leaks into the surrounding tissue.

The total Windkessel resistance (\( R_c + R_p \)) of all Windkessels was determined from assessing the total arterial tree resistance to nonpulsatile flow in two ways. First, the mean arterial pressure and cardiac output (32) at the appropriate gestational age gives the numerical value of the overall total vascular resistance. Here, we use that mean arterial pressure increases linearly from 0 at 5 wk to 60 mmHg at 40 wk (52, 53). Second, circuit analysis of the vascular tree defines the resistance of the vascular tree segments and the peripheral resistance, which is the organ bed resistance, from mean flow distribution. In the case of the thoracic aorta connecting to the abdominal aorta in parallel with the two kidneys, 61% of the cardiac output exits from the thoracic aorta and is divided over the abdominal aorta (55%) and the kidneys (3% each) (Fig. 1A). Using that the pressure at the entrance of the kidneys and the abdominal aorta is equal and that mean flow is inversely proportional to resistance, it follows that the resistance of one kidney is 55/3-fold the resistance of the vascular tree beginning at the abdominal aorta. Additionally, the abdominal aorta can be considered in parallel with two resistances, each of 55/3 times the abdominal aorta’s vascular tree resistance. This resistance is the sum of the abdominal aorta resistance and the parallel resistances of the two iliac arteries, which each consist of the sum of the iliac artery...
Fig. 1. A: schematic overview of the fetal arterial circulation, consisting of 22 segments. The 13 conduit arteries are 1, ascending aorta (Asc Ao); 2 (left and right), carotid arteries (Car As); 3 (left and right), middle cerebral arteries (MCAs); 4 (left and right), anterior cerebral arteries (ACAs); 5, thoracic aorta (Thor Ao); 6, abdominal aorta (Abdo Ao); 7 (left and right), iliac arteries (Iliac As); and 8, two umbilical arteries (UAs). The 9 Windkessels represent the fetal brain (B, 4 Windkessels), kidneys (K, 2 Windkessels), lower body (L, 2 Windkessels), and the placenta (1 Windkessel). Percentages indicate the percentage of the cardiac output that enters or exits the vascular tree segment. In the case of segments 1, 5, and 6, the leak (through small arteries) from the vascular segment into the body as part of the cardiac output is indicated by the arrow.

B: schematic drawing of a three-element Windkessel, where $R_C$ denotes the organ resistance matched to the characteristic resistance of the feeding artery at high frequencies, $R_P$ is the organ peripheral resistance, and $C_{WK}$ is the organ compliance. Both resistances are drawn as tubes with internal walls. The compliance is considered a partly fluid-filled compartment.

C: segmental Young’s moduli used in the model for 22, 28, and 40 wk.
resistance and the parallel circuit of UAs plus placenta and the lower body Windkessels. This type of analysis can be continued. In the end, the placental ($R_c + R_p$) can be expressed as a function of the total arterial tree resistance so its numerical value can be determined. Finally, working backward, the numerical value of the other Windkessel ($R_k$) evaluated in the placental, adapted from Struijk et al. (45), adapted from Guettouche et al. (16), adapted from Struijk et al. (45), estimated.

Table 2. Details on artery length ($l$) and radius ($r$), given by $l = l_r \cdot t / 40$ and by $r = r_0 + r_o$ (Eqs. 1 and 2)

<table>
<thead>
<tr>
<th>Artery</th>
<th>$l$</th>
<th>$r_0$</th>
<th>$r_o$</th>
<th>Reference Length</th>
<th>Reference Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta</td>
<td>5.0</td>
<td>0.027</td>
<td>0.33</td>
<td>Fig 1 from (19)</td>
<td>0.21 at 13 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.42 at 20 wk (19)</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>2.0</td>
<td>0.0085d</td>
<td>0.0075d</td>
<td>5.1 at 28 wk (36)</td>
<td>0.21 at 28 wk (36)</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>2.0</td>
<td>0.0077b</td>
<td>0.0068b</td>
<td>1.5 at 27.5 and 28 wk (16, 36)</td>
<td>0.21 at 28 wk (36)</td>
</tr>
<tr>
<td>Iliac artery</td>
<td>1.3</td>
<td>0.0055b</td>
<td>0.0049b</td>
<td>1.0 at 27.5 and 28.0 wk (16, 36)</td>
<td>0.15 at 28 wk (36)</td>
</tr>
<tr>
<td>Umbilical artery</td>
<td>60.0</td>
<td>0.0047b</td>
<td>0.0041b</td>
<td>40.0 at 28 wk (36)</td>
<td>0.28 at 27.5 wk (16)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>4.0</td>
<td>0.0085c</td>
<td>0.0075c</td>
<td>50.0 at 27.5 wk (16)</td>
<td>0.23 at 27.5 wk (16)</td>
</tr>
<tr>
<td>Cerebral arteries</td>
<td>2.0</td>
<td>0.0031c</td>
<td>0.0027c</td>
<td>1.0 at 27.5 wk (16)</td>
<td>0.34 at 27.5 wk (16)</td>
</tr>
</tbody>
</table>

Values are in centimeters. Numbers in parentheses are References. Adapted from Halley Castillo et al. (19), adapted from Myers and Capper (36), adapted from Guettouche et al. (16), adapted from Struijk et al. (45), estimated.
From the flow transfer functions, all distal flows can be obtained that yield the distal pressures when multiplied by the distal input impedances. Finally, inverse Fourier transformation of these output spectra yields, for each segment, the distal blood flow pulse in the time domain (Figs. 1A and 2).

We increased the placental resistance (2), Young’s modulus (14), and blood viscosity (59) to a maximum of fivefold. Brain resistance (59) was decreased maximally by fivefold. Heart rate and the length of the UA (5) were increased and decreased maximally by a factor of two and three, respectively. These changes were taken to represent the upper limits of the physiological range (2, 5, 14, 59), however, maximal decrease in brain resistance in the human fetus is not known, so the factor of five was chosen arbitrarily.

Model input and output. The values of the vessel segment lengths, radii, Young’s moduli, and the Windkessel resistances and compliances were entered as input parameters in the model. A normal flow waveform at the entrance of the ascending aorta was chosen, in which the end of the ejection time, similar to clinical measurements (43), was 40% of the cardiac period, corresponding to an ejection time of 178 ms at 40 wk. At increased or decreased
heart rates, ejection time was maintained as a constant, whereas the relaxation time was varied.

Since flow distribution in the model results from the influence of the different segmental impedances, the relative flow as a percentage of the cardiac output, and therefore the PIs, are not influenced by the magnitude of the cardiac output. Additionally, the model is linear in pressure and flow, i.e., pressure and flow are related proportionally along the arterial tree. Because the mean arterial pressure in the ascending aorta was modeled to remain unaltered, the cardiac output decreases proportionally to the increase of the input impedance for nonpulsatile flow.

**RESULTS**

In the normal fetus, at 40 wk, results for flow waveforms are given in Fig. 2, and results for PIs compared with clinical results for three gestational ages are in Table 3.

An increase in placental resistance increases the amplitude of the placental Windkessel impedance. The result is an increased PI of the UA, thoracic and abdominal aorta, and iliac arteries (Table 4), and a reduced percentage of the cardiac output flowing through the placenta (Table 4) (when placental resistance increases 200%, placental flow is reduced by almost 50%). Also, the PIs of the carotid and MCAs (Table 4) are reduced. Further, a threefold increase in placental resistance causes absent end-diastolic flow in the UA, and a further increased placental resistance subsequently causes severe reversal of end-diastolic flow.

Decrease of brain resistance increases the PIs of the thoracic and abdominal aorta and iliac arteries (Table 5) and reduces the percentage of the cardiac output flowing through the placenta (Table 5). In contrast, a decreased brain resistance decreases the PIs of the carotid and MCAs (Table 5) at an increased percentage of cardiac output entering the brain (Table 5). When brain resistance decreased to 20% of its normal value, placental flow decreased by 50%, and brain flow increased by 140%.

The combined effect of an increase in placental resistance and a decrease in brain resistance showed an increased PI in the distal UA and a decreased PI in the MCA. A typical example of this combination is shown in Fig. 3, where the placental resistance was increased by 300% (*left*), combined with a 60% increase in placental resistance.

### Table 3. Pulsatility indices for a normal fetus at different gestational ages as compared to values in literature

<table>
<thead>
<tr>
<th>Anatomical segment</th>
<th>Reference PI</th>
<th>Model PI</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aorta</td>
<td>2.0 at 24 wk</td>
<td>3.25 at 22 wk</td>
<td>Adapted from Konje et al. (27)</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td>2.0 at 22 wk</td>
<td>1.84 at 22 wk</td>
<td>Arduini et al. (4)</td>
</tr>
<tr>
<td>Abdominal aorta</td>
<td>1.6 at 28 wk</td>
<td>1.71 at 22 wk</td>
<td>Myers et al. (36)</td>
</tr>
<tr>
<td>Iliac artery</td>
<td>1.3 at 28 wk</td>
<td>1.68 at 22 wk</td>
<td>Myers et al. (36)</td>
</tr>
<tr>
<td>Proximal umbilical artery†</td>
<td>1.2 at 28 wk</td>
<td>1.72 at 28 wk</td>
<td>Adapted from Acharya (1)</td>
</tr>
<tr>
<td>Distal umbilical artery†</td>
<td>0.9 at 40 wk</td>
<td>1.31 at 40 wk</td>
<td>Myers et al. (36)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>1.7 at 22 wk</td>
<td>2.46 at 22 wk</td>
<td>Arduini et al. (4)</td>
</tr>
<tr>
<td>Middle and anterior cerebral arteries</td>
<td>1.9 at 22 wk</td>
<td>2.08 at 22 wk</td>
<td>Arduini et al. (4)</td>
</tr>
</tbody>
</table>

Pulsatility indices (PIs) for all arteries except UA are given for distal sites. †The range of normal values of the UA PI is approximately ±0.5 of the indicated reference values (4).

### Table 4. Effect of placental resistance, for a normal fetus at 40 wk

<table>
<thead>
<tr>
<th></th>
<th>On Flow PIs</th>
<th>On Flow Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asc Ao</td>
<td>Thor Ao</td>
</tr>
<tr>
<td>0.5</td>
<td>2.23</td>
<td>1.51</td>
</tr>
<tr>
<td>1</td>
<td>2.23</td>
<td>1.62</td>
</tr>
<tr>
<td>2</td>
<td>2.23</td>
<td>1.75</td>
</tr>
<tr>
<td>3</td>
<td>2.23</td>
<td>1.82</td>
</tr>
<tr>
<td>4</td>
<td>2.23</td>
<td>1.87</td>
</tr>
<tr>
<td>5</td>
<td>2.23</td>
<td>1.90</td>
</tr>
</tbody>
</table>

R^n_plac, placental resistance; Asc Ao, ascending aorta; Thor Ao, thoracic aorta; Abdo Ao, abdominal aorta; Iliac A, iliac artery; UA prox, proximal umbilical artery; UA dist, distal UA; Car A, carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral arteries.
brain resistance decrease (middle) and a 300% increased Young’s modulus (right).

Normal PWVs at 40 wk for the ascending, thoracic, and abdominal aorta, and iliac, umbilical, and carotid arteries and the cerebral arteries are 177, 250, 372, 645, 722, 306, and 395 cm/s, respectively. Increase of the Young’s modulus increases the PIs of all arteries (Table 6 and Fig. 3). The increase of PWVs is proportional to the square root of the static Young’s modulus $E_S$. An increased Young’s modulus did not alter the flow distribution over the various peripheral vascular beds, and neither reduced the cardiac output.

Increase of fetal blood viscosity leaves the flow distribution and blood density unaltered but increases the longitudinal impedance of the fetal arteries and organ beds proportionally. We varied the blood viscosity between a 0.2- and 5-fold normal, roughly corresponding to hematocrit variations between 10 and 90% (59). As a result, the PIs of the ascending, and abdominal aorta, iliac, and carotid artery and the proximal UA all slightly increased (the proximal UA gave the largest response, i.e., a maximal increase of 19%), whereas the arteries directly connected to organ beds, i.e., thoracic aorta, distal UA, and the MCA had a slightly decreased PI (the MCA gave the largest response, i.e., a maximal decrease of 20%). Because an increase in blood viscosity increases the mean resistance to flow, the cardiac output is proportionally decreased.

Decrease of the placental compliance increases the amplitude of the Windkessel impedance and decreases the PI of the distal UA, the carotid artery, and the MCA. Both an increased or decreased placental compliance within physiologically realistic values (compliance was increased and decreased 1,000-fold) fail to significantly change the PIs in all arteries in the model (the distal UA had the largest response and decreased only by 30% when placental compliance was 0.1% of its initial value).

An increase or decrease of the fetal heart rate increases or decreases the PIs, respectively, in all arteries in the model as is illustrated in Table 7, at an unchanged flow distribution over the peripheral vascular beds and cardiac output (halving the heart rate approximately doubled the PIs, whereas increasing the heart rate by almost 50% reduced the PIs ~40%).

Increase in UA length, while keeping all additional vascular parameters identical, effectively increases the distal resistance to flow. As a result, the PI of the proximal UA is increased, whereas the PI of the distal UA and the placental flow is decreased (Table 8). An additional interesting observation is that this results in a decreased pressure in the distal UA. In the normal case at 40 wk, the UA length is taken as 60 cm, and mean distal pressure is 47.6 mmHg. In the case of a cord length of 30, 120, or 180 cm, the mean distal UA pressure is 52.7, 39.8, or 34.3 mmHg, respectively.

**DISCUSSION**

In this study, we simulated the pulse flow wave propagation of the fetal arterial circulation. Our studies confirmed many previous findings (7, 26, 31, 36, 46, 48) but, in addition, we have extensively evaluated how the PIs are affected by abnormalities in blood viscosity (39), vessel wall stiffness (Young’s modulus) (14, 30), blood flow redistribution (18), UA length (5), and fetal heart rate (34). To our knowledge, this is the first fetal model that includes not only Womersley’s theory of pulsatile flow (33, 68) and viscoelastic arterial walls but that also evaluates the individual effects of abnormalities in all these parameters on the PIs of all arteries included in the model.

Womersley’s theory (23, 68) and vessel wall viscoelasticity (63) are important constituents of the model. This is illustrated by different model results when longitudinal impedance is approximated by the sum of the Poiseuille resistance and the inerterance (See Eq. A3 of the APPENDIX). In this case, the longitudinal impedance may have a 10 to 20% lower amplitude than according to Eq. A1 for the Fourier spectrum frequencies used in the model. Also, the complex Young’s modulus can be replaced by the static Young’s modulus, in $E_A$, which decreases the amplitude of the transverse impedance. We found that either of these approximations underestimates the $\text{Z}_{\text{Char}}$, and results in increased PIs of the carotid, MCAs, and UAs, as much as 1.9-fold as in the distal UA when both approximations are made. In addition, Womersley’s theory indicates a nonsteady parabolic flow is present in the ascending, thoracic, and abdominal aorta, and carotid artery (65).

The simulated PIs at 22, 28, and 40 wk (Figs. 1A and 2 and Table 3) not only show a decrease with gestation but are also in good agreement with the range of clinical results used for a normal fetus. We found a threefold increase of placental resistance (Table 4) is required to simulate an increased PI with absent end-diastolic flow in the proximal UA. When UA length and radius are both increased, so that placental perfusion remains normal, the PIs are virtually unchanged. The absence of UA PI change when UA length is increased, suggests lack of specificity of this parameter in distinguishing what may be a hazardous flow condition (5).

The mechanism of increased PI when the peripheral organ resistance, $R_p$, is increased is the result of two effects. First, there is decreased flow through the segment connected to the organ bed. Second, for low frequencies, there is an increased
Fig. 3. Flow waveforms in the model representing a 40-wk-old fetus. **Left:** predicted flow waveforms after a fourfold increased placental resistance. **Middle:** predicted flow waveforms after a fourfold increased placental resistance and a fourfold increased brain resistance. **Right:** predicted flow waveforms after a fourfold increased Young’s modulus. Normal flows are indicated by dotted lines. Labels in the left column [Ascending Aorta (A), etc.] apply horizontally across the middle and right columns.
impedance amplitude of the peripheral bed. As a result, the reflection resulting from the impedance mismatch between the tube and organ bed is increased, which reduces the systolic peak and the diastolic flow levels and hence also the average flow. Since the PI is the difference between these flows divided by the mean flow (15), the reduction in mean flow effectively leads to an increased PI.

Increase of all PIs through an increased Young’s modulus results from the increased transverse impedance amplitude (Eq. A4). As a result, the propagation coefficient is reduced while the characteristic impedance is increased in their amplitudes. A reduced propagation coefficient amplitude accounts for reduced damping of waves along the arterial tree. The increased characteristic impedance amplitude, however, provides better impedance matching for the lower frequencies compared with a normal Young’s modulus. Therefore, the reflection coefficient is decreased. As a result, the PI is increased.

The small changes in PI when blood viscosity is increased are due to a complex interaction of mechanisms. An increased blood viscosity increases the organ bed resistance ($R_C + R_P$), which increases the reflection coefficient but decreases the mean flow through the organ bed. However, because the organ bed resistance increases proportionally with viscosity, whereas the characteristic impedance amplitude increases with the square root of viscosity, the PI of the vessel connected to the Windkessel decreases, i.e., in the thoracic aorta, distal UA, and cerebral arteries. Because the mean flow decreases proportionally with the increase of the Windkessel resistance and the PI decreases to a smaller extent with the increase in viscosity, the PIs of the other arteries are increased. The overall effect of viscosity on the PIs, however, is small and similar to clinical findings in the UA (47).

Changes in fetal heart rate at identical cardiac output follow directly from the unaltered model outcomes in which a lower fetal heart rate increases the PI and vice versa (34). An important model limitation, however, is the assumption of identical cardiac output. In a real fetus, cardiac output is influenced by its heart rate (49).

Absent and/or reversed end-diastolic flow in the UA are clinical markers for fetal compromise (25). In our model, both are a consequence of increased placental resistance. For the proximal UA, it occurs when placental resistance is increased at least threefold, implying the proportion of cardiac output flowing to the placenta is approximately halved. This was also found in other models (31, 36). Clinical situations of increased placental resistance may result from placental compression due to polyhydramnios (10). In case of twin-twin transfusion syndrome, a serious complication of monochorionic twinning (55), polyhydramnios occurs in the recipient twin’s sac but the donor twin may experience an additional increased placental resistance due to its endogenous production of vasoconstrictive hormones (29) and a decreased maturation of the placental villi (48, 58). Absent end-diastolic flow in the proximal UA, as a consequence of an increased flow to the brain only, in our model, occurs when brain resistance is less than one-fifth of normal. At these settings, the model simulates only half the normal flow entering the placenta, and more than double the normal flow entering the fetal brain. Increase of Young’s modulus within the ranges tested does not produce absent end-diastolic flows in the UA.

In our model, the organ bed compliance hardly affects PI. The organ bed impedance approaches the characteristic impedance of the artery to which the organ bed is connected already for low frequencies. Increasing the organ bed compliance therefore does not further affect the impedance for high frequencies. In addition, even reducing the placental organ bed compliance to an unrealistic 1/1,000 of its normal value, only halves the distal UA PI.

Table 6. Effect of Young’s modulus on flow PIs for a normal fetus at 40 wk

<table>
<thead>
<tr>
<th>E/ENormal</th>
<th>Asc Ao</th>
<th>Thor Ao</th>
<th>Abdo Ao</th>
<th>Iliac A</th>
<th>UA prox</th>
<th>UA dist</th>
<th>Car A</th>
<th>MCA AKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.91</td>
<td>1.21</td>
<td>0.88</td>
<td>0.87</td>
<td>1.08</td>
<td>0.50</td>
<td>1.33</td>
<td>1.11</td>
</tr>
<tr>
<td>1</td>
<td>2.23</td>
<td>1.62</td>
<td>1.06</td>
<td>1.05</td>
<td>1.31</td>
<td>0.70</td>
<td>1.63</td>
<td>1.46</td>
</tr>
<tr>
<td>2</td>
<td>2.53</td>
<td>2.11</td>
<td>1.25</td>
<td>1.24</td>
<td>1.53</td>
<td>0.92</td>
<td>1.96</td>
<td>1.81</td>
</tr>
<tr>
<td>3</td>
<td>2.74</td>
<td>2.48</td>
<td>1.35</td>
<td>1.33</td>
<td>1.63</td>
<td>1.05</td>
<td>2.13</td>
<td>2.02</td>
</tr>
<tr>
<td>4</td>
<td>2.89</td>
<td>2.75</td>
<td>1.41</td>
<td>1.40</td>
<td>1.70</td>
<td>1.14</td>
<td>2.32</td>
<td>2.18</td>
</tr>
<tr>
<td>5</td>
<td>2.99</td>
<td>2.96</td>
<td>1.46</td>
<td>1.45</td>
<td>1.75</td>
<td>1.20</td>
<td>2.45</td>
<td>2.32</td>
</tr>
</tbody>
</table>

Table 7. Effect of heart rate on flow PIs for a normal fetus at 40 wk

<table>
<thead>
<tr>
<th>HR, beats/min</th>
<th>Asc Ao</th>
<th>Thor Ao</th>
<th>Abdo Ao</th>
<th>Iliac A</th>
<th>UA prox</th>
<th>UA dist</th>
<th>Car A</th>
<th>MCA AKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>4.70</td>
<td>3.27</td>
<td>2.18</td>
<td>2.15</td>
<td>2.71</td>
<td>1.46</td>
<td>3.34</td>
<td>2.95</td>
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<tr>
<td>135</td>
<td>2.23</td>
<td>1.62</td>
<td>1.06</td>
<td>1.05</td>
<td>1.31</td>
<td>0.70</td>
<td>1.63</td>
<td>1.46</td>
</tr>
<tr>
<td>200</td>
<td>1.52</td>
<td>1.11</td>
<td>0.66</td>
<td>0.65</td>
<td>0.80</td>
<td>0.42</td>
<td>1.05</td>
<td>0.95</td>
</tr>
</tbody>
</table>

HR, heart rate.
relevance because it may allow us to develop improved methods of detecting the influences on flow pulsations in the fetal circulation and thus improve both our understanding of pathological processes and clinical management.

**Perspectives**

The propagation of blood flow and pressure along the fetal arterial tree relates to complex interactions between numerous anatomical, physiological, and rheological parameters. These interactions are still incompletely understood for a normal developing fetus, let alone for abnormal cardiovascular function. In this paper, we combined Womersley’s theory of pulsating flow through a rigid tube, relating the tube’s longitudinal impedance with anatomical and rheological parameters, with the use of a viscoelastic arterial wall, relating the artery’s transverse impedance with anatomical and mechanical parameters. We acknowledge that Womersley’s theory is an approximate solution of the Navier-Stokes differential equations. However, this is an appropriate approximation in view of the low Reynolds numbers in the fetal circulation. We designed an arterial tree that consists of numerous arterial segment tubes and used three-element Windkessel circuits to represent the function of organ beds.

We submit that the strength of our work is the systematic variation of anatomical, rheological, and mechanical parameters, representing various forms of pathological fetal development, and the study of their individual influence on the temporal behavior of the blood flow pulses during propagation. Such information cannot easily, if at all, be obtained from human or animal study. Our approach may aid in identifying the pathophysiological mechanisms that affect blood flow pulse waveforms, to such a degree that diagnosis is either possible or impossible. The latter outcome may perhaps be as important as the former.

Examples of clinical areas that may benefit from our analysis are the twin-twin transfusion syndrome (55), a severe complication of monochorionic twin pregnancies with considerable intrauterine mortality and postnatal complications, where anemia and stiff arteries develop in the smaller twin and simultaneously polycythemia and hypertrophic arteries in the other (37, 14). A second and rarer complication of monochorionic twinning is an acardiac twin pregnancy (56), where one twin lacks cardiac action, but nevertheless grows because it is being perfused by the other (the pump twin) through arterioarterial and venovenous anastomoses located on the placenta. Here, growth of the acardiac twin mass strongly influences the cardiac function of the pump twin. Finally, our approach may also stimulate finding a more specific parameter than the currently used PI for earlier prognosis of adverse fetal outcome.

**APPENDIX**

**Arterial segment equations.** The frequency domain relation between pressure and flow for a tube includes the longitudinal impedance ($Z_L$) and the transverse impedance ($Z_T$). In the formulas that follow, the prime denotes per meter vessel length. See Table 1 for a list of parameters. For each segment, the longitudinal impedance is obtained from Womersley’s oscillatory flow theory (33, 68), which is given by

$$Z_L = \frac{i \cdot \eta \cdot r^3}{\pi \cdot r^4} \cdot \frac{1}{F(\alpha)}$$

(A1)

where $\alpha = r \cdot \sqrt{\omega \rho / \eta}$ and $F(\alpha)$ is given by

$$F(\alpha) = 1 - \frac{2 \cdot J_1(\alpha \cdot i^{3/2})}{\alpha \cdot i^{3/2} \cdot J_0(\alpha \cdot i^{3/2})}$$

(A2)

where $J_0, J_1$ are the zero and first order Bessel functions (23, 33, 68), $\rho$ is the blood viscosity, and $i = \sqrt{-1}$. In a simplified lumped model of a rigid tube, longitudinal impedance is given by the sum of the Poiseuille resistance and the inertance

$$Z_L' \approx \frac{8 \cdot \eta}{\pi \cdot r^4} + i \cdot \omega \cdot \frac{\rho}{\pi \cdot r^4}$$

(A3)

The transverse impedance is obtained from the viscoelastic wall material (23, 33)

$$Z_T' = \frac{1}{i \cdot \omega / \pi \cdot r^4} \cdot \frac{E \cdot h}{(1 - s^2)}$$

(A4)

where $s$ stands for the Poisson ratio, which is taken as one-half, indicating biological tissue retains its volume, i.e., its cross-sectional area is halved when extended to twice its length.

In general, vascular tissue exhibits elastic capacitance (compliance) and viscous properties of resistance to stretch (63, 65). As a result, the Young’s modulus depends on $\omega$ and is described by the complex Young’s modulus $E$. The relation between the static Young’s modulus $E_s$, which describes the steady state and thus does not depend on frequency, and $E$ was given by Westerhof and Noordergraaf (63) as

$$E = E_s \cdot \frac{a \cdot b}{\omega \cdot c + d} \cdot \frac{\omega + c}{\omega + a} \cdot \frac{\omega + d}{\omega + b}$$

(A5)

where the values for $a, b, c, d$ for the set of large compliant arteries are 5, 50, 6, and 70 Hz, respectively, and where the set of smaller and stiffer arteries differs for $a$, which equals 4 Hz. At high frequencies, the modulus of the ratio of $E/E_s$ approaches $ab/cd > 1$ and the argument approaches zero. Therefore, high frequencies observe an increased Young’s modulus and a small phase shift that tends to go to zero.

---

**Table 8. Effect of umbilical artery length for a normal fetus at 40 wk**

<table>
<thead>
<tr>
<th>UA Length/Normal</th>
<th>On Flow Plts</th>
<th>On Flow Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>Asc Ao</td>
<td>Thor Ao</td>
</tr>
<tr>
<td>1/2</td>
<td>2.23</td>
<td>1.60</td>
</tr>
<tr>
<td>1</td>
<td>2.23</td>
<td>1.62</td>
</tr>
<tr>
<td>2</td>
<td>2.21</td>
<td>1.63</td>
</tr>
<tr>
<td>3</td>
<td>2.20</td>
<td>1.67</td>
</tr>
</tbody>
</table>

Values are cm³/s⁻¹.
The characteristic impedance ($Z_{\text{char}}$) is the impedance encountered by pulsatile flow when the vessel is terminated by its own impedance so that there is no reflection of pressure or flow. It is defined as (33, 65)

$$Z_{\text{char}} = \frac{Z_i \cdot Z_i^*}{1 + i \cdot \omega \cdot C_{\text{WK}} \cdot R_p} \quad (A6)$$

The propagation coefficient also depends on longitudinal and transverse impedances (33) and is defined as

$$\gamma = \sqrt{Z_i/Z_i^*} \quad (A7)$$

Here, $\gamma$ consists of a real part, describing the damping of waves due to viscous friction, and an imaginary part $i\beta$, describing the phase delay. The PWV is related to the angular frequency and the phase delay via $\beta$ (33). Thus for each vascular segment, the $Z_{\text{char}}$ and $\gamma$ can be calculated as a function of all frequencies. Details can be found in the literature (23, 33, 65).

**Peripheral vascular bed parameters.** The model includes nine peripheral vascular beds that are modeled with three-element Windkessel units, see Fig. 1. A and B, consisting of two resistances $R_c$ and $R_p$ and a compliance $C_{\text{WK}}$ (62). The total Windkessel impedance ($Z_{\text{WK}}$) follows as

$$Z_{\text{WK}} = R_c + \frac{R_p}{1 + i \cdot \omega \cdot C_{\text{WK}} \cdot R_p} \quad (A8)$$

**Reflection coefficient.** The reflection coefficient for a vascular segment with $Z_{\text{char}}$ and load impedance ($Z_{\text{load}}$) of the distal vascular tree connected to the segment, is defined as

$$\Gamma = \frac{Z_{\text{load}} - Z_{\text{char}}}{Z_{\text{load}} + Z_{\text{char}}} \quad (A9)$$

indicating zero reflection when the load impedance equals the characteristic impedance and full reflection of one when the load impedance is infinite (33, 65).

**Transfer functions of flow and pressure.** The transfer function is defined as the spectrum of pressure or flow at the distal site of the vascular segment divided by the spectrum of proximal pressure or flow, respectively (65). The pressure transfer function ($T_{\text{Pressure}}$) (44) is defined as

$$T_{\text{Pressure}} = \frac{p_{\text{Distal}}}{p_{\text{Proximal}}} \quad (A10)$$

The net flow and pressure consist of the sum of the forward and backward components, where the backward flow results from reflections from distal impedance mismatches. Therefore, the pressure transfer function can be written as a function of forward and backward pressures. Since the relation between proximal and distal pressure includes the propagation coefficient $\gamma$ (33), i.e., $p_{\text{Proximal}} = p_{\text{Forward}} \cdot \exp(\gamma t)$ and $p_{\text{Distal}} = p_{\text{Backward}} \cdot \exp(-\gamma t)$, these relations can be substituted in Eq. A10, using Eq. A9, which gives

$$T_{\text{Pressure}} = \frac{1 + \Gamma}{1 + \Gamma \cdot e^{-2\gamma r}} \cdot e^{-\gamma l} \quad (A11)$$

The transfer function for flow can be derived similarly, including that the reflection coefficient has a negative sign (65).

$$T_{\text{Flow}} = \frac{1 - \Gamma}{1 - \Gamma \cdot e^{-2\gamma r}} \cdot e^{-\gamma l} \quad (A12)$$

The input impedance ($Z_{\text{IN}}$), which is the total impedance starting from the proximal part of the segment under consideration to the final distal segment (the placenta), is obtained by division of the transfer function of flow by the transfer function of pressure of the segment considered, multiplied by the $Z_{\text{Load}}$ resulting from all subsequent connected segments (60).

$$Z_{\text{IN}} = \frac{T_{\text{Flow}}}{T_{\text{Pressure}}} \cdot Z_{\text{Load}} \quad (A13)$$

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