Dilatation of the ductus venosus in human fetuses: ultrasonographic evidence and mathematical modeling

M. Bellotti, G. Pennati, G. Pardi, and R. Fumero

Bellotti, M., G. Pennati, G. Pardi, and R. Fumero. Dilatation of the ductus venosus in human fetuses: ultrasonographic evidence and mathematical modeling. Am. J. Physiol. 275 (Heart Circ. Physiol. 44): H1759–H1767, 1998.—Autonomic regulation of blood flow through the fetal ductus venosus has been suggested, but the existence of a sphincter at the ductal entrance in human fetuses has yet to be established. In this paper two cases of apparent ductus venosus dilatation in two growth-restricted human fetuses are reported. Prolonged ultrasonographic analysis (45 min) showed rapid and substantial changes (>80%) of ductal diameters. Pulsed Doppler analysis was used to investigate flow velocity in the ductus venosus and umbilical vein for both normal and dilated conditions. Dilated conditions caused manifest modifications of velocity tracings. Systolic peak velocity in the ductus did not change visibly, whereas velocity at the atrial contraction showed evident reduction; consequently, pulsatility indexes increased. Furthermore, the umbilical vein presented flow velocity pulsations. The mean blood flow rate through the ductus seemed to increase substantially (>70%) for high dilatation. To investigate these findings further, we performed simulations of ductal dilatation by means of a lumped-parameter mathematical model of the human fetal circulation. Model results agreed with clinical evidence and confirmed the relationship between ductal dilatation and the observed velocity alterations. Simulated systemic peak velocity slightly increased for small dilatation (>30%), whereas atrial velocity was reduced when the ductus dilated. Furthermore, the model indicated that umbilical venous pressure decreases for increasing dilatation, whereas no change occurs in the central venous pressure. The present results seem to indicate the presence of active dilatation of the ductus venosus in human fetuses.

IN RECENT YEARS technological advances in ultrasound imaging and color Doppler equipment allowed the collection of new data on the complex morphology and hemodynamics of the ductus venosus (DV) in the human fetus (13, 15, 17–21, 26, 30). Many studies demonstrated the role of the DV in shunting the well-oxygenated blood from the umbilical vein (UV) through the foramen ovale to the left atrium (LA) and to the cerebral and myocardial circulation in both animals (2, 7, 31) and human fetuses (17). In animal studies, induced hypoxemia (8, 23) or severe acute hemorrhage (22) results in a higher blood flow rate through this vessel. An increased proportion of blood flow from the intrahepatic UV to the DV was shown when umbilical blood flow decreased because of experimental cord compression (16). In human growth-restricted fetuses, the DV peak velocities are maintained within normal ranges even in the presence of impaired umbilical circulation (18). In these fetuses a reverse flow during atrial contraction in the DV has been supposed to be related to augmented atrial pressure, suggesting myocardial compromise (18, 30). The exact mechanism determining an increased flow shunt is still unknown. The anatomic findings in animals of a muscular structure along the DV and adrenergic activity suggested the presence of a sphincter that could allow the DV to change its isthmic diameter and regulate the blood flow throughout it (1, 4). Similar sphincteric activity was speculated in the human fetus (11, 24), but this occurrence is quite controversial. To the best of our knowledge, no clinical evidence of active ductal dilatation has been observed in human fetuses.

Obviously, modifications of the diameter of a vessel cause alterations in the hydraulic resistance to blood flow through the vessel. The effects of a change in a vascular parameter (i.e., flow resistance) on the hemodynamic features of blood circulation can be evaluated by means of model simulations. Huikeshoven and colleagues (14) applied a mathematical model of the fetal lamb circulation to study the effects of disturbances from the normal steady state produced by changes in DV resistance. According to their model, mean ductal and umbilical flow are substantially affected by ductal resistance changes, whereas cardiac output, central oxygen tension, and central blood pressures in fetal lambs are only slightly influenced. However, the simulated changes in DV resistance were not related to changes in its diameter. Furthermore, the influences of a resistance change on the morphology of velocity time tracings were not investigated.

We previously developed a mathematical model to simulate the Doppler tracings in the human fetal circulation (27). The model parameters are related to the anatomic dimensions of the vessels; thus the model allows us to simulate changes of the ductal diameter and to investigate the subsequent hemodynamic variations.

In this paper two clinical cases of apparent DV dilatation are presented. The ductal ultrasonographic and Doppler findings in two growth-restricted human fetuses were compared with the results of mathemati-
cal simulations of ductal dilatation to investigate a possible active dilatation of the DV in human fetuses.

**MATERIALS AND METHODS**

Clinical study: Case reports. Two fetuses (fetus A and fetus B) affected by intrauterine growth restriction (IUGR) were examined, fetus A at 24 wk of gestation and fetus B at 29 wk of gestation. Ultrasound examinations were carried out with a coaxial pulsed Doppler color flow imaging system (Esaote Biomedica AU4, Genoa, Italy) implemented with a 3.5-MHz probe. Fetal biometry was plotted against our reference values for gestational age. IUGR was defined as an abdominal circumference below the fifth percentile of our reference limits. Fetal morphology was examined to exclude structural abnormalities. Fetal karyotypes obtained after fetal blood samplings were normal (46 XY for both fetuses). Fetus A was delivered at 28 wk of gestation by cesarean section performed for fetal distress, with a birth weight of 900 g. Fetus B was delivered at 29 wk of gestation by cesarean section, weighing 910 g.

At birth no major malformations and no infectious diseases were present in the neonates. Fetus A is alive and well at 12 mo of life. Fetus B died after 15 days of life because of respiratory distress syndrome, and autopsy did not evidence anatomic malformations. Histological examinations of the two placentas revealed multiple vascular cysts for fetus A and wide chronic hypoxic areas for fetus B.

Each fetus was observed for ~45 min. During this period repeated measurements of ductal dimensions were performed (Fig. 1), studying the DV in a near-midsagittal section (Figs. A and B). Ultrasound examinations of DV (inlet section [I] and outlet section [O]), which connects umbilical vein (UV) to heart (H), were carried out with a 3.5-MHz probe. Fetal biometry was plotted against our reference values for gestational age. IUGR was defined as an abdominal circumference below the fifth percentile of our reference limits. Fetal morphology was examined to exclude structural abnormalities. Fetal karyotypes obtained after fetal blood samplings were normal (46 XY for both fetuses). Fetus A was delivered at 28 wk of gestation by cesarean section performed for fetal distress, with a birth weight of 900 g. Fetus B was delivered at 29 wk of gestation by cesarean section, weighing 910 g.

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Measurements of the diameters at the inlet \(D_{\text{isthmus}}\) and at the outlet portion of the vessel \(D_{\text{outlet}}\) were obtained by positioning the calipers at the inner walls of the vessel. Doppler investigations of the DV velocity were also performed for some relevant values of diameters. Pulsed Doppler waveforms were recorded in the absence of fetal active and breathing movements. Doppler tracings of the maximal velocities \(V_{\text{max}}\) were obtained with an insonation angle below 30°. The maximum velocity at the systolic peak \(S\) and the minimum velocity during atrial contraction \(A\) were measured at the isthmus of the DV (see Figs. 2, B and E, and 3, B and D); time-averaged maximal velocity during the cardiac cycle \(\bar{V}_{\text{max}}\) was also calculated.

With this velocity value and \(D_{\text{isthmus}}\), we estimated the blood flow rate through the DV according to the following formula:

\[
Q_{\text{DV}} = h \cdot V_{\text{max}} \cdot \pi D_{\text{isthmus}}^2 / 4
\]

where the constant \(h\) (related to the spatial velocity distribution) was assumed equal to 0.67 in agreement with a previous study (28).

To assess the fetal ventricular function, peak velocities at the aorta and pulmonary artery were obtained and compared with our normal reference ranges (10). In addition, the intrahepatic UV was sampled immediately before the ductal branching (Fig. 2, C and F). The blood flow direction was assessed using color Doppler imaging, and the exact site of the isthmical flow of the DV was evidenced by the aliasing effect, at a low pulse repetition frequency.

Angle-independent indexes were calculated at the level of the umbilical artery and the middle cerebral arteries [pulsatility index (PI) according to the Gosling formula (Ref. 12)] and the DV [DV index (DVI) = \((S - A)/S\), according to DeVore and Horenstein (Ref. 5)].

Mathematical model. The fluid dynamics of the DV was investigated by means of a mathematical model of the human fetal circulation that was primarily based on and validated using blood velocity data derived from the Doppler analysis (27). It consists of two major parts, the heart and the vascular bed (arteries and veins), that were described by means of some lumped parameters. We adopted this model approach to have a simple tool to study human fetal blood circulation and to identify the relationship between vascular features and hemodynamic behavior. The parameter values of the model refer to the final gestation period, when fetal body weight is \(\sim 3\) kg. The vascular bed is divided into 19 compliant vascular...
compartments. Figure 4 shows only the portion of the model close to the DV. The connection between the inferior vena cava and LA represents the blood flow path that crosses the foramen ovale (17). A component that allows the flow only in one direction was considered in the models of the cardiac valves and the foramen ovale.

Each compartment in the vascular model (blocks in Fig. 4) was described by means of a constant compliance $C = \delta V(t)/\delta P(t)$, where $P(t)$ is the instantaneous local pressure and $V(t)$ is the instantaneous compartmental blood volume. Each compartment was mathematically modeled by the mass conservation law, which can be expressed, according to the definition, as follows

$$\sum Q_{\text{in}}(t) - \sum Q_{\text{out}}(t) = C \cdot \frac{dP(t)}{dt}$$  \hspace{1cm} (2)

where $\sum Q_{\text{in}}(t)$ and $\sum Q_{\text{out}}(t)$ indicate the sum of the instantaneous volumetric flow rates at the inlet and the outlet of the compartment, respectively.

The momentum conservation law for each interconnection (lines in Fig. 4) between two compartments can be expressed as

$$\Delta P(t) = R_{\text{visc}} \cdot \dot{Q}(t) + K \cdot \dot{Q}(t)^2 + L \cdot \frac{dQ(t)}{dt}$$  \hspace{1cm} (3)

where $\Delta P(t)$ is the instantaneous pressure difference applied to the line ends, $Q(t)$ is the instantaneous volumetric flow rate, $R_{\text{visc}}$ is the viscous resistance, and $L$ is the inertance. The additional term $K \cdot Q(t)^2$, which depends on the flow rate, takes the local fluid dynamics into account. In particular for the DV model, this term is related to the convective acceleration and energy dissipations at the inlet of the vessel ($\beta = 2$). The inertial phenomena were considered for the cardiac valves and the large arteries close to the heart only. For the model of each vessel the instantaneous hydraulic impedance $Z(t) = \Delta P(t)/Q(t)$ can be calculated.

Mass and momentum conservation laws applied to all of the compartments and connections, combined with the heart model equations, resulted in a nonlinear algebraic differential equation system that was solved using a backward differentiation formula implicit method (3); see Pennati et al. (27) for extensive explanation and validation of the model assumptions.

Simulation of DV dilatation. In the case of the DV Eq. 3 becomes

$$P_{UV}(t) - P_{IVC}(t) = R_{\text{viscDV}} \cdot \dot{Q}_{DV}(t) + K_{DV} \cdot \dot{Q}_{DV}(t)^2$$  \hspace{1cm} (4)

where the values of $R_{\text{viscDV}}$ and $K_{DV}$ depend on the blood properties (the blood was assumed as incompressible, viscous, and Newtonian fluid with a density $\rho = 1.06$ g/ml and a viscosity $\mu = 4.0$ cP) and on the DV dimensions, particularly the diameter ($D$) and length ($l$).

As far as the resistive term related to the viscous friction along the walls of a rigid cylindrical vessel is concerned, it can be calculated according to the Poiseuille theory as

$$R_{\text{visc}} = \frac{128\mu l}{\pi D^4}$$  \hspace{1cm} (5)

The dissipative term $K_{DV}$ accounting for the energy losses caused by irregular local fluid dynamics (separation of flow and secondary flow at the abrupt changes of cross section) can be related to the flow velocity ($v$) according to traditional hydraulic formulas. Pressure drops are usually calculated as $\Delta P = k v^2/2$, where $k$ is a constant coefficient that for the DV assumes a value slightly less than 1 (28). In the model we assumed $\Delta P = K \cdot v^2$; it then follows that

$$K = \frac{8\rho l}{\pi D^4}$$  \hspace{1cm} (6)

The DV has a conical shape: its diameter increases from the inlet to the outlet. In any event, in our calculations the DV was considered as a cylindrical vessel with a diameter equal to the average of $D_{\text{st}}$ and $D_{\text{out}}$. Assuming $D = 2.1$ mm and $l = 20$ mm for a normal human fetus at 38 wk (21), $R_{\text{viscDV}} = 1.3$ mmHg·s·ml$^{-1}$ and $K_{DV} = 0.26$ mmHg·s$^2$·ml$^{-2}$.

According to Eqs. 5 and 6, a little modification in the DV mean diameter $D$ causes a large change in both parameter

| Table 1. Ultrasonographic measurements for fetus A |
|----------------------------------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| Regions/Symbols | Definitions | Measured Values | Time of Measurements |
|-----------------|-------------|-----------------|---------------------|-----------------|-----------------|
| Ductus venosus  |             |                 |                     | 10 h 47 min     | 11 h 1 min     | 11 h 13 min    | 11 h 23 min    |
| $D_{\text{st}}$ | Isthmic diameter | mm  | 1.45 | 1.40 | 0.76 | 1.03 |
| $D_{\text{out}}$ | Outlet diameter | mm  | 2.39 | 2.35 | 1.29 | 1.77 |
| $V_{\text{max}}$ | Time-averaged maximal velocity | cm/s | 24  | 23  | 36  | 27  |
| $S$ | Systolic peak velocity | cm/s | 42  | 42  | 48  | 44  |
| $A$ | Velocity at atrial contraction | cm/s | -14 | -10 | 23  | 0   |
| $(S - A)/S$ | Angle-independent index | NA | 1.33 | 1.24 | 0.52 | 1.00 |
| $Q$ | Time-averaged blood flow rate | ml/min | 15.6 | 14.4 | 9.1  | 9.2  |
| Cycle length | ms | 420 | NA | NA | NA |
| $S$ | V-A time lag | ms | 340 | NA | NA | NA |
| Umbilical vein |             |                 |                     | 10 h 47 min     | 11 h 1 min     | 11 h 13 min    | 11 h 23 min    |
| $UV_{\text{Liver}}$ | Intrahepatic umbilical vein | cm/s | Pulse | NA | No pulse | NA |
| $UV_{\text{Plac}}$ | Umbilical vein at placental end | cm/s | 340 | NA | NA | NA |
| Peripheral organs |             |                 |                     | 10 h 47 min     | 11 h 1 min     | 11 h 13 min    | 11 h 23 min    |
| $P_{\text{ima}}$ | Mean cerebral artery pulsatility index | 1.42 | NA | NA | NA |
| $P_{\text{plac}}$ | Umbilical artery pulsatility index | 1.57 | NA | NA | NA |
| Ventricular outflows |             |                 |                     | 10 h 47 min     | 11 h 1 min     | 11 h 13 min    | 11 h 23 min    |
| $V_{AA}$ | Ascending aorta systolic peak velocity | cm/s | 62  | 62  | 62  | 62  |
| $V_{PA}$ | Pulmonary artery systolic peak velocity | cm/s | 49  | 49  | 49  | 49  |

Pulse, presence of pulsations in Doppler waveform; No pulse, absence of pulsation in Doppler waveform; NA, data not available.
values \(R_{\text{viscDV}} \approx D^{-4}\) and \(K_{\text{DV}} \approx D^{-4}\) and strongly affects the local hemodynamics. In the present study we simulated a progressive increase of the mean diameter of the vessel (30, 60, 90, and 150% of the reference value), maintaining the same values for all the other model parameters. Flows and velocities through the DV as well as pressures at its ends were investigated. Furthermore, the hydraulic impedance \(Z_{\text{DV}}(t)\) of the DV was evaluated using the calculated values of \(\Delta P(t)\) and \(Q(t)\) for the DV.

**RESULTS**

Clinical study. Fetus A evidenced changes in ductal diameters within 40 min of observation, passing from wider to narrower measures (Figs. 1A and 2, A and D) and successively recovering wider dimensions. In fetus B the ductal diameters dilated abruptly within 6 min of observation (Figs. 1B and 3, A and C) and then remained almost stable. In both cases the maximal variation of the diameters exceeded 50%.

Measurements of the ductal diameters and velocities as well as calculations of angle-independent indexes and flow rates are summarized in Tables 1 and 2 for fetus A and fetus B, respectively. These tables also report the velocities at the ventricular outlets and the PI at the peripheral arteries. For fetus A UV flow velocity was also examined. Pulsations at the intrahepatic level were observed for dilated DV (Fig. 2C) but disappeared when the diameters of the DV decreased (Fig. 2F). The time lag between the maximum and minimum velocities at the UV was equal to the measured time lag between the systolic peak velocity and the atrial contraction minimal velocity recorded in the DV. Furthermore, no pulsations were seen in the UV at the placental end.

Diameter and velocity values were normalized on their respective values in absence of dilatation (when the isthmic diameter assumed its minimum value) and are examined in Figs. 5 and 6.

In fetus A, the normalized velocities in the DV showed a slight decrease for the systolic peak velocity in correspondence to larger diameters; on the other hand, the atrial contraction wave largely decreased as the dilatation increased and minimum velocity (A) became negative (Figs. 2, B and E, and 5A). As a consequence, the DVI value notably increased (Fig. 5B). The mean blood flow rate through the dilated DV increased; meanwhile, the mean velocity tended to decrease (Fig. 5A).

Similar trends of modifications are shown for fetus B (Figs. 3, B and D, and 6, A and B) except for the systolic peak velocities, which slightly increased.

Model simulations. Figure 7 shows the simulated time tracings of velocity in the DV and pressure at the vessel ends for a normal fetus. Two fetal cardiac cycles were presented for five different values of the ductal mean diameter. Ductal dilatation causes a shift toward low values of the velocity at the atrial contraction (A) and produces values near zero for highly dilated DV. On the contrary, the computed systolic peak velocities (S) substantially do not change. Umbilical venous pressure decreases as much as ductal diameter increases, whereas the pressure in the inferior vena cava present only small alterations. In addition, pulsations of the pressure, synchronous to the atrial events, appeared at the UV level when high dilatation was simulated. Figure 8 reports the changes of the blood velocities and flow through the DV and of the DVI consequent to modifications of the vessel diameter. The computed velocities show minor changes for the systolic peak and important reduction of the atrial contraction velocity for dilated diameter; ductal mean velocity decreases, even if blood flow rate is notably augmented (Fig. 8A). The related angle-independent index doubles its value when normalized diameter reaches the maximum investigated value (\(D/D^* = 2.5\), see Fig. 8 B). Table 3 summarizes absolute values of flow and velocity calculated by means of model simulations. DV dilatation causes an increase (<15% of its reference value) of the flow in the UV (\(Q_{\text{UV}}\)); nevertheless, the proportion of umbilical flow shunted to the DV significantly increases. The calculated impedance \(Z_{\text{DV}}(t)\) showed small changes during the simulated cardiac cycle (standard deviation <20% of mean value) and large variations with ductal diameter modifications. Figure 9 illustrates the relationships among normalized ductal diameter, ductal impedance (time averaged), and mean flow rates through the UV and the DV. A diameter increase of 30% (\(D/D^* = 1.3\)) causes a reduction of the ductal impedance.
over 50% of its reference value (from 0.031 to 0.013 mmHg·s·ml⁻¹) and a 78% increase of the flow rate through the ductus (from 117 to 208 ml/min); when diameter dilates further on (D/D* ↩️), the impedance of the ductus falls to <10% of the reference value and the ductal flow rate tends to equal Q˙UV (445 vs. 479 ml/min for D/D* = 2.5).

**DISCUSSION**

The ductus venosus plays an important role in shunting highly oxygenated blood to the brain and the myocardial cells, both in animals and in human fetuses (2, 6, 7, 17). Experimental studies suggested that an increased proportion of blood flow passes from the umbilical vein to the ductus venosus, in the presence of hypoxic conditions and reduced umbilical blood flow volume (2, 8, 29). Similarly, the observed maintenance of high velocities at the systolic and diastolic peak of the ductus venosus in growth-retarded human fetuses, despite reduced umbilical vein blood flow, was associated with higher flow rate through the vessel (18).

However, up to now, this hypothesis has not been supported by measurements of vessel diameter and evaluations of blood flow rate. Anatomic findings in animals suggested the presence of a sphincter at the level of the ductal isthmus (1, 4), and its muscular activity would represent the physiopathological basis of the redistribution of blood. Determination of a similar muscular activity in the human fetus is quite controversial because of the lack of anatomic evidence of such a structure and in vivo observations of diameter dilatation.

In our clinical observations on two growth-retarded fetuses examined for a prolonged period of time, we evidenced variation of the ductus venosus diameters in both fetuses. Because our reproducibility of the ductus venosus diameters showed a mean coefficient of variation within 10% (25) both at the isthmus and at the outlet, the changes of the ductus diameters measured during fetal observations are caused by an unstable condition of ductal dilatation rather than by large variability in measurements. In addition, the extent of diameter increase (as high as 100% for fetus B) was unlikely to have been caused by a passive enlargement for augmented venous pressure because the pressure should reach values inconsistent with the observed normal cardiac function. Hence, in our opinion, it is reasonable to affirm that in IUGR fetuses, active

![Fig. 5. Fetus A: changes of blood velocities and flow through DV (A) and of angle-independent index [DVI = (S - A)/S; B] consequent to modifications of isthmic diameter (D_{isthmus}). Velocity and flow are normalized to values corresponding to minimum recorded diameter value (D_{isthmus}). \( \bar{V}_{max} \) time-averaged maximal velocity; Q, time-averaged blood flow rate.](image)

![Fig. 6. Fetus B: changes of blood velocities and flow through DV (A) and of DVI (B) consequent to modifications of vessel diameter. Velocity and flow are normalized to values corresponding to \( D_{isthmus} \).](image)
Dilatation of the ductus venosus could occur and that specific Doppler waveforms are related to different diameter conditions. However, we cannot exclude the possibility of transient dilatation of the ductus venosus in normal fetuses, although such evidence of ductal dilatation should have a different pathophysiological basis. In any event, in our experience prolonged echographic examinations in normal fetuses never demonstrated dilatation of the ductus venosus with peculiar modifications of the velocity tracing. The ultrasonographic and Doppler studies cannot evaluate the anatomic basis and the physiopathological mechanism of such a dilatation. Biochemical or neurological factors could be involved in determining an active enlargement of ductal diameters, even in early gestation (4).

In dilated ductus venosus, we observed a large reduction of the velocities at the atrial contraction, leading to a reverse flow in some instances (fetus A). However, the velocities recorded at the systolic peak were maintained at normal values for both fetuses, even if slightly different trends with diameter values were noted. In any event, the DVI manifestly increased in both fetuses when ductal diameter enlarged. The values of the DVI measured for fetus A and fetus B with small diameter (DVI = 0.52 and DVI = 0.59 for fetuses A and B, respectively) fell within the normal range according to DeVore and Horenstein (5), whereas they clearly exceeded normal values in dilated conditions (DVI > 1 and DVI = 0.79 for fetuses A and B, respectively).

Mathematical simulation of ductal dilatation showed quite similar behavior of the velocity time tracings at the ductus compared with clinical observations. This good agreement, although qualitative, confirms the dependence that exists between diameter increase and alterations of Doppler velocity waveforms. Negative values for velocity at the atrial contraction were never found in the simulations with highly dilated diameters. This discrepancy with experimental data is probably caused by the different features of the model with respect to the examined fetuses. First, the model was scaled for a fetus at 38 wk of gestation (body wt = 3 kg),
Table 3. Simulation results with mathematical model for a normal fetus at 38 wk

<table>
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<tr>
<th>Symbols</th>
<th>Definitions</th>
<th>Units</th>
<th>1</th>
<th>1.3</th>
<th>1.6</th>
<th>1.9</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{max} )</td>
<td>DV time-averaged velocity</td>
<td>cm/s</td>
<td>66.2</td>
<td>69.8</td>
<td>64.7</td>
<td>56.3</td>
<td>39.7</td>
</tr>
<tr>
<td>S</td>
<td>DV systolic velocity</td>
<td>cm/s</td>
<td>77.9</td>
<td>68.1</td>
<td>86.0</td>
<td>82.1</td>
<td>71.8</td>
</tr>
<tr>
<td>A</td>
<td>DV velocity at atrial contraction</td>
<td>cm/s</td>
<td>50.6</td>
<td>50.6</td>
<td>42.7</td>
<td>31.8</td>
<td>13.9</td>
</tr>
<tr>
<td>( \bar{Q} )</td>
<td>DV time-averaged flow rate</td>
<td>ml/min</td>
<td>114</td>
<td>210</td>
<td>294</td>
<td>360</td>
<td>438</td>
</tr>
<tr>
<td>( \dot{Q}_s )</td>
<td>DV maximum flow rate</td>
<td>ml/min</td>
<td>138</td>
<td>258</td>
<td>384</td>
<td>522</td>
<td>792</td>
</tr>
<tr>
<td>( \dot{Q}_A )</td>
<td>DV minimum flow rate</td>
<td>ml/min</td>
<td>90</td>
<td>150</td>
<td>192</td>
<td>204</td>
<td>150</td>
</tr>
<tr>
<td>( \dot{Q}_{UV} )</td>
<td>Umbilical vein flow rate</td>
<td>ml/min</td>
<td>422</td>
<td>447</td>
<td>459</td>
<td>468</td>
<td>481</td>
</tr>
<tr>
<td>( %Q)</td>
<td>DV percentage flow rate</td>
<td>% ( \dot{Q}_{UV} )</td>
<td>27</td>
<td>47</td>
<td>64</td>
<td>77</td>
<td>91</td>
</tr>
</tbody>
</table>

DV, ductus venosus; D/D*, normalized diameter value.

whereas the gestational ages of fetus A and fetus B were both <30 wk (body wt < 1 kg). In addition, the model refers to normal conditions, whereas the two investigated fetuses were IUGR fetuses. In any event, the accord of trends between model and clinical data was enough so as to not be considered trivial.

A large reduction of the A wave velocity with absent or reverse flow during atrial contraction was observed in many pathological conditions (20), all suggesting an impairment of myocardial function. Furthermore, in IUGR fetuses velocities close to zero or negative, recorded at the atrial contraction, were related to probable high atrial pressures following fetal myocardial impairment (18).

In the present study we observed a large reduction of the A wave during the ductus venosus dilatation, even in the presence of normal cardiac function. Indeed, normal peak velocities both in the pulmonary artery and in the aorta were recorded, although the fetuses under study were severe, true IUGR fetuses. According to our previous study, in IUGR fetuses the peak velocity at the ascending aorta level is well correlated with normal acid-base state and myocardial function (9). The transient effect of ductal dilatation and the return to normal dimensions and normal Doppler waveforms at the isthmus of the ductus could be explained by a temporary fetal distress, in the presence of impaired placental function, as documented by the observed Doppler velocimetric indexes (high PI in the umbilical artery) and fetal cerebral vasodilatation (low PI in the middle cerebral artery) (10). Impaired placental function of both fetuses was confirmed by histological examination at birth. Furthermore, we can speculate that more severe placental diseases and related hypoxic conditions could determine a lasting dilatation of the ductus venosus in IUGR fetuses, not only transient modifications of the ductal diameters.

The mathematical simulations confirmed the hypothesis that low velocity during atrial contraction could occur without myocardial dysfunction but caused solely by an enlargement of the diameter of the ductus venosus. Indeed, simulations with progressive increase of the ductal diameter evidenced almost constant pressure values in the inferior vena cava in presence of low A velocities. According to the model, these velocity reductions were related to a reduced pressure in the umbilical vein, consequent to the lower flow resistance of the dilated ductus. The mean impedance of the ductus venosus seems to become very low for diameter dilatations similar to those detected in the investigated fetuses (increase of 40–60% in the isthmic diameter). Actually, the calculated impedance decreases below 30% of the reference value when a 50% increase in the ductal diameter is simulated. The reference value calculated for the mean ductal impedance (0.031 mmHg s ml⁻¹) is very close to the resistance (0.0355 mmHg s ml⁻¹) assumed by Huikeshoven and colleagues (14) in their model of the circulation of a 3-kg fetal lamb. It is interesting to note that in the present work the value of impedance of the ductus results from the lumped model parameters \( R_{DV} \) and \( K_{DV} \) calculated using the anatomic dimensions of the vessel and the properties of the fetal blood.

Model simulations showed that ductus dilatation causes an increase of the flow in both the umbilical vein and the ductus venosus, but the proportion of umbilical flow shunted to the ductus venosus notably increases. The trends of the volume flow rates through the umbilical vein and the ductus venosus (Fig. 9) calculated for various impedance values (i.e., various ductal diameters) are quite similar to those simulated by Huikeshoven and colleagues (14).
The blood flow rate through the ductus venosus in both fetuses under study, evaluated from the measured velocities and diameters, evidenced an increase of the mean blood flow for the maximum dilatation of the ductal diameters around 80% of the values associated to the minimum recorded diameters.

In conclusion, the present study seems to indicate that in human IUGR fetuses, an active dilatation of the ductus venosus could occur. Further investigations are required to confirm this clinical evidence. The observed dilatation suggests a compensatory effect for which a higher proportion of the umbilical flow is shunted through the ductus to the brain and the myocardium. As yet, we cannot know whether this condition is temporary in acute distress or steady in chronic placental impairment. For dilated conditions the Doppler indexes of the ductus venosus used in the clinical routine show notable augmentation.

This work was partially supported by Grant 6-FY97–0174 from the March of Dimes Birth Defects Foundation.

Address for reprint requests: M. Bellotti, Dept. of Obstetrics and Gynecology, San Paolo Biomedical Sciences Inst., Univ. of Milan, Via di Rudini 8, 20142 Milan, Italy.

Received 17 February 1998; accepted in final form 19 July 1998.

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