Role of ductus venosus in distribution of umbilical blood flow in human fetuses during second half of pregnancy

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The ductus venosus (DV), first described in the human fetus by anatomist Giulio Cesare Aranzio in the sixteenth century, is a narrow, trumpet-shaped vessel in the fetal liver. It directly connects the umbilical vein to the inferior vena cava in the proximity of the right atrium. This vessel plays a critical role in the fetal circulation because it shunts highly oxygenated and nutrient-rich umbilical venous blood to the brain and myocardium instead of the fetal liver (32, 34). This role has been demonstrated by experiments on fetal primates (3), fetal sheep (6, 7, 33), and even in previable human fetuses (36). Edelstone et al. (7) showed that this shunting can account for 53% (±9%) of umbilical flow.

It has been estimated that, during induced hypoxia or reduced umbilical flow in fetal sheep, the blood flow shunted through the DV increases and could reach as much as 70% of the umbilical blood flow (3, 8). The active dilatation of the DV (2, 11) and the increased shunting was also observed for the first time by Bellotti et al. (4) in two human fetuses with intrauterine growth retardation (IUGR).

Since the introduction of color Doppler imaging in 1991–1992, this small venous vessel has become the object of extensive clinical research in the human fetus, and the velocity waveform in the DV has been proposed as a relevant indicator of fetal well-being (14–19, 29, 31). However, in contrast to velocity measurements, blood flow through the DV in the human fetus has not been extensively investigated (28, 39) because of the technical difficulties involved. The anatomic features of this trumpet-shaped vessel as well as the unusual geometry of the DV branching from the intrahepatic umbilical vein are responsible for complex hemodynamics (30). These conditions suggest that caution should be exercised in the clinical interpretation of simple Doppler velocimetric indexes (29).

In several recent publications, we (4, 27, 29, 30) investigated the hemodynamics of the umbilical vein-DV branching by means of a mathematical approach based on sophisticated computational simulations. We examined the velocity profiles in the DV by model simulations, and the velocity shape coefficients were calculated as a function of vessel geometry. In this way, we were able to define and validate a new method to calculate blood flow through the DV (28).

The geometry of the DV, particularly its isthmus or inlet diameter, appears to be the major determinant of...
the extent of umbilical blood flow shunting in IUGR fetuses (4). Similarly, we hypothesize that ductal dimensions principally determine DV flow during normal gestation. Anatomic features of the DV in normal fetuses were investigated by Kiserud et al. (20). Nevertheless, the possible correlation between the changes in umbilical flow repartition at the DV branching observed during normal pregnancy (39) and ductal diameters has not yet been investigated.

Furthermore, it has been impossible to assess ductal flow and its changes during gestation in any animal species. There are many reasons for this, but it heightens the importance of these studies for the human fetus.

The aims of the present work were to 1) evaluate blood flow in the DV in the human fetuses during normal pregnancy using a validated methodology, 2) assess the changes in the distribution of umbilical venous blood flow between the DV and hepatic circulation, and 3) to examine the possible relationship between DV flow changes and the diameters of the DV.

MATERIALS AND METHODS

Study group. One hundred and thirty-seven uneventful singleton pregnancies were included in this cross-sectional study. Gestational age (GA) was confirmed by ultrasound biometry within 20 wk of gestation. Each fetus studied underwent a single Doppler examination between the 20th and 38th weeks of gestation. All infants were delivered at term (mean week of gestation ± SD = 39 ± 1) and were of normal birth weight (mean weight ± SD = 3,330 ± 325 g). This study was approved by the appropriate review committee for our institution and the mothers of the fetuses gave informed consent.

Methods. Ultrasound examinations were performed with high-resolution equipment with digital imaging, color Doppler, and pulsed-wave Doppler modes (AU4 Esaote Biomedica, Genoa, Italy). A 3.5-MHz convex transducer carrying a 2.8-MHz Doppler unit was used. The spatial peak temporal average intensities were <20 mW/cm² for the imaging mode and <100mW/cm² for the Doppler mode.

Each fetus was appropriate for GA in size (between 10th and 90th percentile growth curves for local standards) at the time of Doppler examinations, as assessed by ultrasound measurements of fetal biometry. Fetal weight at the time of the Doppler examination was estimated using formulas based on abdominal and head circumference and femur length (13).

Echo-Doppler measurements. Doppler examinations were performed during a fetal quiet state in the absence of fetal breathing movements. Each fetus had a single Doppler evaluation between the 20th and 38th weeks of gestation.

Velocities and vessel diameters were measured at four different sites, as shown in Fig. 1. The DV was studied in a midsagittal section using methodology previously described by Kiserud et al. (16). The intrahepatic umbilical vein was studied in cross-sectional planes of the abdomen. Diameters were always measured on sections perpendicular to the vessel at the highest magnification possible, with calipers placed on the inner edges of the brightest image of the vessel walls. Inlet and outlet ductal vessel diameters were measured by positioning the calipers on the narrowest portion of the vessel and at the connection with the inferior vena cava, respectively. Furthermore, to define the DV shape completely, its length from the isthmus to the outlet was evaluated. Color Doppler imaging was always used to visualize vessels at their best insonation angle. Pulse repetition frequency was set to show aliasing phenomena for the high velocities at the inlet of the ductus. Pulsed-wave Doppler was used to measure velocities in the vessels as shown by color Doppler. The angle of insonation was as low as possible and always <30°. The sample volume was set to cover the entire lumen of the vessel under investigation. Umbilical vein Doppler sampling was performed on the same segments of the vessel in which diameter measurements were obtained, that is, the intrahepatic vein was insonated in the segment immediately upstream of the DV branching (UVin) and at the amniotic vein (UV) in a free and approximately straight segment. Doppler waveform measurements at the isthmus and at the outlet of the DV were performed in each fetus within 2 min. The above techniques replicate those used in our previous validation study (28).

Blood flow calculations. Blood flow at the ith measurement site (Qi) was calculated according to the following formula

\[ Q_i = h_i \cdot V_{\text{max}_i} \cdot \pi \cdot \frac{D_i^2}{4} \]

where \( h_i \) is the coefficient related to the spatial flow velocity profiles of the vessel under investigation, \( V_{\text{max}_i} \) is the time-averaged maximum velocity, and \( D_i \) is the diameter.

The \( h_j \) coefficients for the DV were calculated by means of previous mathematical simulations (28); their values at the inlet \( (h_{\text{DVin}}) \) and at the outlet \( (h_{\text{DVout}}) \) depend on the ductal conicity according to a second-order polynomial relationship

\[ h_{\text{DVin}} = -0.03 \cdot DR^2 + 0.189 \cdot DR + 0.43 \]
\[ h_{\text{DVout}} = 0.066 \cdot DR^2 - 0.448 \cdot DR + 0.899 \]

where \( DR \) is the ratio between the diameter at the inlet and at the outlet \( (D_{\text{DVout}}/D_{\text{DVin}}) \). The \( h_i \) coefficients for the umbilical vein were assumed to equal 0.5, according to the hypothesis of parabolic velocity profile in this vessel (18).

Hence, the formulas used to calculate ductal blood flows at the inlet and outlet were, respectively

\[ Q_{\text{DVin}} = (-0.03 \cdot DR^2 + 0.189 \cdot DR + 0.43) \cdot V_{\text{max}_{\text{DVin}}} \cdot \pi \cdot \frac{D_{\text{DVin}}^2}{4} \]

\[ Q_{\text{DVout}} = 0.066 \cdot DR^2 - 0.448 \cdot DR + 0.899 \cdot V_{\text{max}_{\text{DVout}}} \cdot \pi \cdot \frac{D_{\text{DVout}}^2}{4} \]
The calculations were generally carried out by taking the natural logarithm of the variables to linearize the data (slope equals exponent of independent variable in power curve model). The coefficients of the regression lines were obtained by the least-squares method, and their significance was tested with the $F$-test. Curves were compared, when necessary, with the $t$-test (differences were considered significant at $P < 0.05$).

**RESULTS**

Ductal flow was measured in all 137 fetuses, UVhe flow in 90 fetuses, and UV flow in 53 fetuses. All three measurements were obtained at the same time in only 35 fetuses.

The regression calculated (82 fetuses) for the difference between inlet and outlet flows versus the average of the two flows was not significant ($F = 0.17$ against a critical level at 5% equal to 3.96, $P = 0.68$). Similar findings were found for the difference expressed as a percentage of the average flow ($F = 2.33$, $P = 0.13$). The gestational trend of the inlet ductal flow was compared against the gestational trend of the average flow by means of a $t$-test; these trends did not differ significantly either for the slope ($t = 0.040$, $P = 0.96$) or for the intercept ($t = -0.086$, $P = 0.93$).

According to these analyses, flow measured at the inlet can be used to represent the actual ductal flow, simplifying its measurement. Hence, we adopted this estimate for all cases

$$Q_{DV} = Q_{DVin}$$

**Flows.** Figure 2A presents the blood flow through UV, UVhe, and DV from 20 to 38 wk of gestation. The blood flow (ml/min) increases significantly with advancing GA in all three parts of the venous circulation ($P < 10^{-8}$ for each). The increases in flow in the UV and in the UVhe approximate a power curve to the third power (exponents equal to 2.804 and 2.632, respectively); this was not the case for ductal flow (exponent equal to 1.398). The slopes (i.e., the power exponents) of UV and UVhe flow were not significantly different ($P = 0.31$), but they were significantly higher ($P < 10^{-5}$) than that of ductal flow.
Figure 2B presents the blood flow per kilogram of estimated fetal weight (ml·min⁻¹·kg⁻¹) for the three vessels. The negative slope of the weight-specific flow of the DV is significantly steeper than the negative slopes of the weight-specific flow of UV and UV_he. In fact, from 20 to 38 wk of gestation, the weight-specific ductal flow showed a significant decrease of 69% (from 60 to 17 ml·min⁻¹·kg⁻¹, P < 10⁻⁵), whereas the UV_he weight-specific flow decreased only 30% (from 88 to 61 ml·min⁻¹·kg⁻¹, P < 0.01) and the UV weight-specific flow only 11% (from 123 to 109 ml·min⁻¹·kg⁻¹). The slight decrease of the weight-specific flow of UV is not significant (P = 0.42).

Umbilical vein flows (both UV and UV_he) were measured on the same occasion as DV flow in 35 fetuses, and the blood flow to the hepatic circulation was calculated. The absolute flow to the liver (ml/min) from the placenta increased significantly versus GA (Q˙liver = 0.0189 × GA².352, R² = 0.703) and versus AC (P < 10⁻²) as well as versus GA (P < 10⁻¹), assumed as a marker of liver growth (Fig. 3A). In contrast, the weight-specific flow from the placenta to the liver did not change significantly with increasing GA or increasing AC (84.0 ± 32.6 ml·min⁻¹·kg⁻¹, P = 0.14). Furthermore, both right and left hepatic flows (Fig. 3B) increased significantly with advancing gestational age (P < 10⁻⁶ and P < 0.001 for right and left lobes, respectively).

Umbilical flow distribution. The percentage of umbilical flow shunted through the DV decreased significantly (P < 0.005) as gestation advanced from ~40% at 20 wk to ~15% at term (Fig. 4). The percentage of flow to the liver increased significantly (P < 0.05) from ~60% at 20 wk to ~85% at term (Fig. 4), particularly the right lobe, in which flow increased from ~20% to ~45% (P < 0.05). In contrast, the percentage of umbilical flow toward the left lobe did not change significantly (P = 0.74) during gestation, assuming a value of ~40%.

Morphometry. Figure 5 shows increasing diameters of the UV, the UV_he (Fig. 5A), and the DV at the inlet and outlet (Fig. 5B) versus EFW. The regressions for each vessel are statistically significant (P < 10⁻¹⁴ for each).

The power exponents of the curves of the UV (0.338) and the UV_he (0.316) are not significantly different (P = 0.92). Their values indicate that umbilical diameters increase approximately as the cubic root (0.333) of the fetal body weight.

The power exponents of the regression analysis at the inlet (0.178) and at the outlet (0.213) of the DV are virtually identical (P = 0.21) as well, but their values are significantly lower (P < 10⁻⁴) than those for the umbilical diameters. In contrast, the DV length (Fig. 5C)
increases significantly with gestation ($P < 0.01$) according to a power exponent (0.328) not significantly different than those for the umbilical diameters ($P = 0.17$).

DISCUSSION

The present data provide the first estimates of DV flow and the repartition of umbilical venous flow collected on a large series of normal human fetuses throughout gestation using a validated Doppler methodology.

In animal models, the DV holds a prominent position in the fetal circulation because of its role in shunting highly oxygenated blood to the brain and the myocardium. A compensatory mechanism, supported by transient dilatation, is supposed to increase oxygenated blood flow through the DV during hypoxia or reduced umbilical flow (2, 4, 8, 9). To understand the adaptation to hypoxia in the human fetus, it is important to quantify the blood flow through this venous system and the repartition of umbilical flow through the DV.

However, most of the DV Doppler studies in the human fetus are related to velocimetry measurements alone (14, 16–19, 29, 31) because of major problems in calculating the volume flow by means of ultrasound techniques. This is because of the inaccuracy of ultrasound techniques in measuring mean spatial blood velocity and ductal diameters. According to Kiserud and colleagues (22, 23) the limitation in diameter measurement is so high that unless a set of 10 measurements is obtained and averaged, the confidence limit of a single measurement can be as high as 0.23 mm, which is almost a 30% random error in diameter estimate. This pessimistic view is not reflected in our previous results. In our experience, the coefficients of variation of inlet and outlet measurements are 9.5% and 6.7%, respectively (28). Mean spatial blood flow velocity estimates require a complex methodology. The automatic mean velocity, calculated by ultrasound units, is usually unreliable because of the interference of the lower velocities of the neighboring vessels. The mean velocity can be more accurately derived from the maximum velocity, multiplied by a coefficient related to the shape of the velocity profile. The conical nature of the DV sets an absolute condition that velocity waveforms will change along the course of the vessel in each fetus as a function of the inlet and outlet diameter variation. In 1996, we (29, 30) published a fluid dynamic model validated by experimental findings. This model allowed us to simulate the flow, to analyze the velocity profile along the DV, and to calculate for each fetus the shape coefficients that vary continuously from the inlet to the outlet (28). Our results were in good agreement with experimental data on fetal sheep by Kiserud and colleagues (21). In their study, the shape-related mean coefficient at the DV inlet was equal to 0.69, which compares well with the mean value of 0.68 derived with our model. Furthermore, the high correlation we found between the measured inlet and outlet ductal flow (28) further validates the correctness of the method derived from the model. Thus, in the present study, we used the volume flow calculated only at the DV inlet, instead of the average of the two measurements, because no significant difference was observed between the two methods for evaluation of the ductal flow in a subgroup of 82 fetuses of the present series.

The values of ductal blood flow observed from the 20th to the 38th week of gestation were compared with blood flow measured in the amniotic umbilical vein (UV) and in the intrahepatic umbilical vein (UVhe) sampled after the branching of the left hepatic vein. The absolute blood flow (ml/min) increases significantly with advancing GA in all three parts of the venous circulation examined in this series (Fig. 2A). However, the calculation of the flow per unit body weight (ml·min$^{-1}$·kg$^{-1}$) indicated that the increase in the blood flow is proportional to body size only for the UV blood flow. In fact, the weight-specific umbilical flow does not change significantly during gestation

![Diagram](http://ajpheart.physiology.org/Downloadedfromhttp://ajpheart.physiology.org/)

Fig. 5. A: changes of the UV (○) and UVhe (●) diameters vs. EFW. B: changes of the DV diameters (inlet DVin, ■; outlet DVout, ▲) vs. EFW. C: changes of the ductal length ($L_{DV}$) vs. EFW. Best-fitting power curves are also reported ($D_{UV} = 0.057 \times EFW^{0.316}, R^2 = 0.814; D_{UVhe} = 0.047 \times EFW^{0.316}, R^2 = 0.69; D_{DVin} = 0.04 \times EFW^{0.178}, R^2 = 0.239; D_{DVout} = 0.053 \times EFW^{0.213}, R^2 = 0.348; L_{DV} = 0.122 \times EFW^{0.326}, R^2 = 0.48$).
(mean ± SD = 120 ± 44 ml·min⁻¹·kg⁻¹). In contrast, ductal flow decreases significantly from 60 ml·min⁻¹·kg⁻¹ at 20 wk of gestation to 17 ml·min⁻¹·kg⁻¹ at 38 wk of gestation (Fig. 2B), notwithstanding the slight decrease of umbilical venous Po₂ during gestation in normal pregnancies (5). The mild vasodilatation in the cerebral arteries observed in normal human fetuses during gestation (41) could be explained as a compensatory effect of the decreased flow and oxygenation through the DV to the brain. These data support the hypothesis that the DV shunt plays a relatively less important role in supplying well-oxygenated blood to the brain and myocardium in late gestation, probably reflecting the slower rate of growth of the brain compared with the liver in late gestation. In agreement with this observation, Rudolph et al. (37) demonstrated that experimental obstruction of DV in fetal sheep at term did not change oxygen delivery to the vital organs.

The trends of the venous flows observed in the present study are similar to those previously published by Tchirikov et al. (39) in a smaller series of human fetuses, but the measured flow values are profoundly different. The mean values of the human ductal flow reported by Tchirikov et al. (90.9 ± 42.2 ml/min) are approximately threefold the mean flow value calculated in the present work (33.3 ± 18.1 ml/min). The main reason for this discrepancy lies in the fact that the inlet diameters that they reported (2.5 ± 0.5 mm) are consistently larger (~1 mm) than the values reported by other authors (20) and our present findings (1.4 ± 0.4 mm). Furthermore, Tchirikov and colleagues used an automatic calculated modal velocity (intensity-weighted mean velocity) instead of the mean velocity and accepted measurements with a Doppler insonation angle of <60°. The automatic modal velocity, i.e., the velocity that is recorded most frequently within the sample volume, can be appropriately used only in the case of an almost flat velocity profile, for instance at the outflow cardiac valves (26). In all other hemodynamic situations with different spatial velocity profiles, this calculation provides an unpredictable value that has no relation to the actual mean value. In addition, some errors caused by very high insonation angles could have affected the accuracy of the velocity measurements (26). The umbilical vein flow reported in that study, calculated using the same method, probably suffers these limitations as well. Moreover, the reported flow values (214.9 ± 109.7 ml/min) are higher than our present results (142.6 ± 80.2 ml/min) and also higher than the results we obtained previously in normal human fetuses with the same methodology (1). In any case, our umbilical flow data are in agreement with measurements by other authors (12, 38).

Possible comparisons with animal data are even more difficult, because of the different proportion of brain and hepatic mass in animal and human fetuses and the great variability observed in different studies when highly invasive techniques are applied (7, 32–35). Furthermore, the studies of the ductal circulation in the sheep fetus have been very limited and confined to late gestation. The assessment of the changing role of the DV during gestation is emphasized by the reduction of blood flow shunted through it. According to our data, the percentage of umbilical blood flow shunted through the DV significantly decreases during gestation from 40% at 20 wk of gestation to 15% at 38 wk of gestation. In previable human fetuses, Rudolph et al. (36) reported a mean percentage of UV flow shunted through the DV equal to 52% with a very wide range (8–92%). These data were found in exteriorized fetuses under non-physiological conditions, and they are not comparable with in vivo measurements. Other Doppler studies on human fetuses reported different values of estimated shunting of the umbilical venous flow through the DV, varying from 25 to 50% (9, 39, 40). Obviously, some discrepancies of the results in the human fetuses are related to the methodological problems previously discussed. The blood flow shunted through the DV increases during hypoxia or hypovolemia both in animal (3, 6, 8) and human (4, 39) fetuses, suggesting an important role of blood flow evaluation in assessing fetal adaptation to nutrient and oxygen deprivation. However, the blood flow calculation should be applied with caution for clinical purposes because of the magnitude of the error in the measurements of vessel diameters as previously described.

The analysis of the pattern of growth of the vessel diameters is of great interest in understanding the mechanisms involved in the distribution of the umbilical blood flow. Our findings clearly demonstrate that the increase in umbilical vein diameters at both sites of measurement (UV and UVhe) and in ductal length as well, is proportional to body size, following approximately the third root of body weight (i.e., body weight¹/³). Ductal diameters do not follow the same proportionality to body size (i.e., body weight¹/²). These different patterns of growth are the anatomic determinants of the changes of the umbilical blood flow shunted through the DV during uncomplicated pregnancy. However, we cannot exclude the influence of differing neural and endocrine regulation of ductal diameters during gestation. Experimental studies suggested that the DV could function as a regulator of the flows to the fetal liver and heart. Different mechanisms could be implied in the repartition of the umbilical blood flow through the DV. Variations of ductal isthmic diameter, in the same fetus, have been hypothesized on the basis of anatomic and biochemical observations (2, 11). In chronic hypoxic conditions, ductal dilatation and increased flow through the ductus were observed in human fetuses (4), suggesting a compensatory mechanism of the higher shunting of umbilical blood flow as evidenced in animal studies. Hemodynamic characteristics could also influence the repartition of the UV blood flow through the DV; for example, blood viscosity acts on the vascular resistance in the fetal liver circuit. During in vitro studies, Kiserud et al. (24) demonstrated that the hepatic resistance dramatically increases in relation to an increased hematocrit, leading to a reduction in liver flow. Under physiological conditions, as in our present control group of normal preg-
nant women, we could hypothesize that the relatively small hematocrit changes do not affect the ductal shunt to a detectable degree.

Our data provide the first estimate of the quantitative flow to the liver, both right and left lobes, in human fetuses during gestation, by measuring intrahepatic umbilical vein flow in addition to amniotic umbilical venous and ductal flows. Umbilical flow to the liver showed a significant increment during gestation. If we use abdominal circumference as an indirect reflection of hepatic size, the absolute blood flow to the liver increases proportionally to the hepatic mass, approximately as the third power of the abdominal circumference (Fig. 3A). The comparison between the percentage of umbilical flow to the liver and through the DV clearly showed opposite trends for ductal shunting and liver perfusion. This fits with the fact that the abdominal-to-head circumference ratio is also increasing with gestational age.

The increased fetal hepatic flow seems to be caused exclusively by the right lobe flow, which increases from ~20% to 45% throughout gestation. In animal models, the right lobe is supplied by well-oxygenated umbilical vein blood (~75% of umbilical flow), portal blood (~15%) with a low oxygen saturation, and ~10% from the hepatic artery. The left lobe receives ~90% of its blood flow from the highly oxygenated umbilical vein and ~10% from the hepatic artery (7). Thus the increased umbilical venous flow to the right lobe should determine a higher oxygen supply to the right lobe in late pregnancy. The differences of oxygen supply between the two lobes could be related to different functional activities in fetal life. For example, both in animal and human fetuses, the right lobe has greater hemopoietic activity than the left lobe, in response to a lower oxygen saturation in early gestation (32) and a progressive diminution in the hemopoietic tissue in the parenchyma of the fetal liver during the last few months of pregnancy (10). Other fetal hepatic functions, such as amino acid uptake and synthesis, do not seem related to the different lobes in the fetal liver. In fact, in fetal sheep in late pregnancy, no differences were found in the patterns of amino acid concentration for the right and left lobes of the liver (25), probably reflecting little impact of the different patterns of liver perfusion on amino acid metabolism. In sheep, only a small quantity of portal flow (<10%) from the right lobe passes through the DV (7). Although in human fetuses it is impossible to evaluate the portal flow for technical reasons, we can postulate that in three cases of the present study, in which the right hepatic flow, calculated as $Q_{RHLO} = Q_{UVfe} - Q_{DV}$, was negative (Fig. 3B), the DV also received blood from the portal system through the umbilical sinus. All these cases occurred before the 23rd wk of gestation, when ductal shunting is greatest.

In conclusion, the present study provides normative data on ductal and umbilical venous blood flows throughout gestation. It demonstrates that the magnitude of the ductal shunt changes during gestation, and it highlights the importance of the inlet or isthmus diameter. Because the ductal shunt should increase during fetal hypoxia, these data provide an incentive to examine the magnitude of the ductal shunt in high-risk pregnancies, e.g., IUGR pregnancies.

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