Ductus venosus shunting in the fetal venous circulation: regulatory mechanisms, diagnostic methods and medical importance

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KEYWORDS: blood flow volume; ductus venosus; DV shunting; fetal growth regulation; liver perfusion

ABSTRACT

The fetal liver is located at the crossroads of the umbilical venous circulation. Anatomically, the ductus venosus (DV) and the intrahepatic branches of the portal vein are arranged in parallel. The actual DV shunting rate, i.e. the percentage of umbilical blood flow entering the DV measured by Doppler velocimetry, seems to be lower than that estimated using radioactively-labeled microspheres. In human fetuses the DV shunting rate is about 20–30%. Increases in the DV shunting rate are a general adaptational mechanism to fetal distress. Hypoxia results in a significant increase in the DV shunting rate, most probably in order to ensure an adequate supply of oxygen and glucose to vitally important organs such as the brain and heart. The mechanism of blood flow redistribution between the fetal liver and the DV is still a matter of debate. The isthmic portion of the DV contains less smooth muscle tissue than the intrahepatic branches of the portal vein, which in vitro react more forcefully in response to catecholamines than the DV.

In growth-restricted human fetuses DV shunting is increased and the umbilical blood supply to the fetal liver is reduced. The long-term reduction of the hepatic blood supply may be involved in fetal growth restriction. The occlusion of the DV leads to a significant increase in cell proliferation in fetal skeletal muscle, heart, kidneys and liver, and possibly to an increase in insulin-like growth factor (IGF)-I and -II mRNA expression in the fetal liver. These findings hint at the possible role of the perfusion of the fetal liver in the control of the growth process.

The quantification of DV shunting by Doppler velocimetry may improve the early recognition of fetal compromise in prenatal medicine. In this Review we summarize the published data on the anatomical structure and histology of the DV, the mechanisms of regulation of DV shunting, its role in fetal survival and growth and the possible use of the measurement of DV shunting in clinical practice. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

The fetal liver is located at the crossroads of the umbilical venous (UV) circulation. Anatomically, the ductus venosus (DV) and the affluent hepatic veins – the intrahepatic branches of the portal vein – are arranged in parallel (Figure 1). This is important because the ratio of flow through the DV and the liver will be inversely related to the ratio of flow resistances, regardless of whether the resistance values actually decrease or increase. In fetal sheep, under normal conditions two-thirds of the UV blood flow supplies the liver (equivalent to about 70% of total hepatic blood flow)1,2, with about one-third passing through the DV3–7 (as measured by the radioactively-labeled microsphere technique). The actual DV shunting rate (i.e. the percentage of umbilical blood flow that enters the DV) when measured with Doppler velocimetry seems to be lower than that estimated with radioactively-labeled microspheres8–12. Hypoxia results in a significant increase in the DV shunting rate, most probably in order to ensure an adequate supply of oxygen and glucose to vitally important organs such as the brain and heart5,7–9,13. The mechanism of redistribution of blood flow between the fetal liver and the DV is still a matter of debate.

It is assumed that an increase in DV shunting rate is important for fetal survival during stress situations. In other words, an increase in DV/UV flow ratio is an indicator that the fetus is compromised. The early recognition of distressed fetuses is important in obstetrics.
Ductus venosus shunting in the fetus

In growth-restricted human fetuses DV shunting is increased and the umbilical blood supply to the fetal liver is reduced\(^8,12\). This may influence cell proliferation in fetal organs because the liver synthesizes many growth factors\(^14–19\).

In clinical practice at present, analysis of the blood flow velocity profile of the DV also serves as an indicator of circulatory decompensation\(^20,21\). Reversed blood flow in the DV during atrial contraction is strongly associated with poor fetal outcome\(^21,22\).

In this review we summarize the published data on the anatomical structure and histology of the DV, the mechanisms of regulation of DV shunting, its role in fetal survival and growth and the possible use of the measurement of DV shunting in clinical practice.

ANATOMICAL STRUCTURE AND HISTOLOGY OF THE DUCTUS VENOSUS IN HUMANS AND ANIMALS

The ductus venosus Arantii is a venous shunt between the intra-abdominal umbilical vein and the inferior vena cava (IVC)\(^23–25\). As an organized vascular structure, the DV is present in the fetuses of most mammalian species. Amphibians and other lower-order vertebrates do not have a DV\(^26\). The DV has been described in fetuses of mice\(^27,28\), rats\(^29\), dogs\(^30–33\), cats\(^34,35\) and many other mammals. However, guinea pig and horse fetuses do not have a DV at term\(^36–38\). In pig fetuses, the DV disappears during intrauterine life\(^39,40\) while in sheep fetuses the DV increases in size up to birth as a short-circuit for re-oxygenated blood returning from the placenta\(^36\).

In humans, the development of the DV can be divided into two stages\(^41\). The first stage involves the establishment of the DV as a major vessel in the bilateral symmetrical arrangement of the hepatic sinusoids. From the yolk sac blood flows through the omphalo-mesenteric veins and the liver to the sinus venosus, while blood from the chorionic villi bypasses the liver and empties into the sinus via the right and left UVs. In the second stage the symmetry of the first stage is transformed into the asymmetric definitive condition, in which the DV connects the left UV with the right hepato-cardiac vein, later destined to become the inferior vena cava (IVC). In late embryonic and fetal stages this general arrangement of the DV and main venous vessels remains substantially unaltered\(^41\).

In rhesus monkeys, the DV drains into a dilated ampullary area – the collectus venosus – which is connected to the IVC (Figure 2)\(^42\). This venous structure also receives blood entering on the right side from the umbilical vein.

Figure 1 Principle of venous blood circulation in the fetal liver. Blood flow directions in the liver are indicated by arrows. The vessels/vascular bed resistances to blood flow involved in the regulation of the ductus venosus shunting rate are marked by the boxes. DV, ductus venosus; IVC, inferior vena cava; LHV, left hepatic vein; LPV, left branch of the intrahepatic portal vein; PV, portal vein; RHV, right hepatic vein; RPV, right branch of the intrahepatic portal vein; UV, umbilical vein.

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abdominal vena cava and from effluent hepatic veins. The DV courses to the posterior wall of the venous collector. In some primate fetuses the DV terminates in the left hepatic vein.

The presence of a ‘sphincter’ in the isthmic portion of the DV is controversial. For the following discussion it may be useful to make a distinction between a ‘morphological’ sphincter, and a ‘functional’ sphincter. In 1942 Barron described the sphincter at the inlet of the DV in his short report, while 2 years later Barclay et al. identified, with cineangiography, a ridge located at the inlet of the fetal lamb DV which projected slightly into the DV lumen. In agreement with later investigators, Barclay et al. postulated that this ridge functioned as a sphincter mechanism. In 1984 Coceani et al. also described in histological sections a smooth muscle sphincter in fetal sheep. The development of the DV sphincter in humans was described by Chacko and Reynolds in 1953. However, as described in their 1966 report Meyer and Lind were unable to identify a muscular sphincter between the UV and the DV in human fetuses. Mavrides et al. in 2002 could not identify the sphincter of the DV in human fetuses at 13–17 weeks using scanning electron microscopy and immunohistochemical methods. We found that in fetal sheep the isthmic portion of the DV mainly contained connective tissue and small amounts of smooth muscle tissue but no completely circular layer of muscle cells. In contrast, the media of hepatic affluent veins contained well-organized muscle tissue.

In non-human primate fetuses a small layer of muscle tissue was observed throughout the DV wall just below the endothelium (Figure 3). A non-completed circular layer, 3 to 7 cells thick, formed a contractile element at the DV inlet. This smooth muscle structure frequently took the form of a lip or a ‘horseshoe’ protruding into the lumen at the junction of the DV and UV. However, this condensation of smooth muscle generally represented a thin band of muscle fibers and did not constitute a complete sphincter.

The diameter of the DV in marmoset fetuses at a gestational age (GA) between 100 and 124 days (term, 144 days) is frequently about half the diameter of the UV (mean diameters 0.7 ± 0.1 mm and 1.7 ± 0.4 mm, respectively).

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Figure 3: Histological structure of (a) the ductus venosus (DV) and (b) the intrahepatic branch of the portal vein (BPV), in the baboon fetus. (a) The DV. I: Hematoxylin eosin staining of the ductus venosus. A, the contractile element of the DV as an asymmetrical lip at the isthmic portion of the shunt; B, the umbilical vein. II: Masson’s trichrome staining. The vessel wall of the isthmic portion of the DV consists of a network of collagenous tissue in the subendothelial zone. A, the contractile element of the DV; B, the umbilical vein. III: Histological structure of the isthmic portion of the DV using antibodies against α-smooth-muscle actin. A few muscle cells in the DV inlet are present only in the lip portion. (b) Right intrahepatic BPV. I: Histological structure of the branches of the portal vein (hematoxylin eosin staining). II: Masson’s trichrome staining. The media of the vessel wall is well seen. III: The same level stained to show α-smooth-muscle actin. Muscle cells in the media of the BPV are more plentiful than in III (a). (Reproduced from Tchirikov M, Schlabritz-Loutsevitch NE, Hubbard GB, Schröder HJ, Tardif S, Nathanielsz PW. Structural evidence for mechanisms to redistribute hepatic and ductus venosus blood flows in non-human primate fetuses. Am J Obstet Gynecol 2005; 192: 1146–1152. Copyright © 2005 Mosby, Inc.)
respective). In baboon fetuses at a GA between 90 and 144 days (term, 185 days) the DV is 1.1 ± 0.2 mm and the UV is 3.1 ± 0.5 mm. Abundant nerve bundles and nerve fibers with small arteries could frequently be observed in the region of the DV inlet.

### Contractile capacities of the ductus venosus and central venous vessels

The function of the DV depends largely on its contractile abilities. In 1944 Barclay et al. postulated that the sphincter of the DV could control the amount of blood which traverses the liver sinusoids, but that its main function was to occlude the ductus at birth, while in 1951 Reynolds considered that the function of the DV was to maintain the pressure in the UV, thus preventing collapse. He suggested that, in addition to keeping the veins distended, the DV sphincter, by constriction or relaxation, acts as a valve that everts out pressure changes.

Writing in 1956, Dickson was of the opinion that the main function of the DV is to control the intravascular pressure in the UV. In 1980 Edelstone postulated that when UV flow and pressure fluctuated widely, the DV could react passively, to ensure an adequate venous return to the fetal heart.

The available information on the contractile capabilities of the DV is controversial, which may, in part, be owing to different experimental DV conditions, as well as the methods applied. The response of the isthmic portion of the DV is to control the intravascular pressure in the UV.

### In vitro

In vitro, isolated DV rings contract in response to catecholamines and electrical stimulation. Prostaglandins H₂ and I₂ lead to relaxation of the indomethacin-constricted DV and thromboxane A₂ evokes DV contraction.

In our experiments the intrahepatic branches of the portal vein developed more force in reaction to catecholamines than vascular rings obtained from the isthmic portion of the DV (Figure 4). α-adrenergic receptors were present in the structured media of the intrahepatic branches of the portal vein, but were less frequently observed in the wall of the DV. The same situation was demonstrated in non-human primate fetuses (Figure 3). Because fetal hypoxia provokes a profound rise in plasma catecholamine levels, it is conceivable that the increase in the DV shunting rate is caused by the more forceful response of the intrahepatic branches of the portal vein to catecholamines when compared to the DV.

In vivo, the main DV reaction in response to hypoxic situations seems to be vessel dilatation. Using ultrasonographic observations, Bellotti et al. – in 1998 and 2004 – were able to demonstrate an increase in the diameter of the DV in growth-restricted human fetuses, and Kiserud et al. in 2000 also demonstrated a substantial increase in the diameter of the DV in response to induced hypoxemia in fetal sheep; however, the α₁-adrenergic agonist phenylephrine did not have any effect on the diameter of the DV in this experiment. The application of sodium nitroprusside dilated the DV as expected. In 1944 Barclay et al. showed by cineangiography that vagal nerve stimulation in neonatal lambs had no effect on the diameter of the DV, but Arstila et al. in 1965 were able to demonstrate dilatation of the DV in lambs in response to stimulation of the left and right vagal nerves. In 1964 Peltonen et al. dilated the DV by injecting acetylcholine, epinephrine and norepinephrine into the umbilical or jugular veins of newborn lambs. Prostaglandin E₁ can also open the DV in newborn lambs.

The dilatation of the DV during acute hypoxia in vivo may reflect the passive reaction of the shunt to increased pressure in the central venous system. We hypothesize that changes in blood content of the liver may evoke alterations to the vascular geometry of the DV, which might also affect its resistance to flow.

In our opinion, the forceful contractional capabilities of the intrahepatic branches of the portal vein, as opposed to the isthmic portion of the DV, are mainly responsible for the regulation of DV shunting.

### UMBILICAL BLOOD FLOW SHUNTING THROUGH THE DUCTUS VENOSUS

Under normal conditions and during acute or chronic hypoxia, hemorrhage and in response to vasoactive substances

The blood flow in the UV was directly measured for the first time by use of a ‘stromuhr’, placed in an umbilical artery in fetal sheep. Direct measurement of the blood flow volume in the DV is difficult because the DV is usually located within the liver parenchyma. The four methods most frequently used to determine quantitatively blood flow rates in the DV and the UV and/or the DV/UV ratio were: (1) cineangiography; (2) indicator dye-dilution; (3) radioactively-labeled microspheres; and (4) blood flow volume measurement using Doppler velocimetry.
accuracy of these techniques in measuring flow ratios or flow rates differs considerably. To our knowledge, no experimental data on direct flow rate measurements of both vessels with electromagnetic or Doppler velocimetry probes were available.

Cineangiography was used to study fetuses, delivered by Cesarean section, in which radio-opaque substances were injected into the UV. Barclay et al. found that at least one ninth (and probably more) of the umbilical blood passed directly to the posterior caval vein via the DV.

The second method resulted in the occurrence of double peaks of dye concentration in peripheral fetal arteries after the injection of dye into a UV. The first peak represented the umbilical venous blood through the DV, whereas the second peak resulted from the slow passage of umbilical blood through the hepatic vasculature. In 1975 Power and Longo thus measured a DV shunting rate of 42.5 ± 5.2% (mean ± SD), 36% after correction for the removal of dye by liver parenchyma (Table 1).

Rudolph and Heymann made the first quantitative measurements of DV blood flow rates, in 1967, by using the radioactively-labeled microsphere technique on acutely-catheterized fetal sheep (0.7–0.9 of gestation). The DV shunting rate varied considerably (Table 1). In 1979 Edelstone and Rudolph were also able to demonstrate that DV-derived blood was preferentially distributed to upper body organs, including the brain and heart.

Using the radioactively-labeled microsphere technique, DV shunting in fetal Macaca mulatta was determined to be 53 ± 14.3% of 208 ± 20 mL/min/kg UV blood flow, and in 1973 Paton et al. described a similar DV shunting ratio in anesthetized near-term baboon fetuses (Papio spp.), using the antipyrene equilibrium technique together with the radioactively-labeled microsphere technique. Rudolph et al. estimated DV shunting in heavily compromised exteriorized human fetuses (0.3–0.5 of gestation, Table 1).

The most frequent experimental condition to provoke changes in the DV shunting rate was induced maternal hypoxia, which was followed by fetal hypoxia. This maneuver usually resulted in a significant increase in the DV shunting rate (Table 1). Other techniques (cord and aortic occlusion, fetal hemorrhage, reduction of uterine blood flow), besides their respective circulatory effects, will also influence the state of fetal oxygenation.

Reduction of blood pressure and flow in the UV, by partially occluding the descending aorta in fetal sheep, resulted in a significant increase in DV shunting. The authors postulated that at each reduction of UV pressure there must have been a relatively high resistance to blood flow through the liver as compared to flow through the DV. This would explain why the proportion of DV shunting increased with corresponding decreases in blood pressure. In 1987 Iskovitz et al. investigated the

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**Table 1 The proportion of umbilical blood shunting through the ductus venosus in control fetuses and in fetuses under distress conditions**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Control (%)</th>
<th>Distress group (%)</th>
<th>Distress situation</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudolph and Heymann (1967)</td>
<td>34–91</td>
<td>90 ± 9</td>
<td>Hypoxia</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Behrman et al. (1970)</td>
<td>53 ± 14.3</td>
<td>65 ± 12</td>
<td>Hypoxia</td>
<td>Human (RM)</td>
</tr>
<tr>
<td>Rudolph et al. (1971)</td>
<td>51.6 (8–92)</td>
<td>67.2 ± 3</td>
<td>Hemorrhage</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Paton et al. (1973)</td>
<td>55.4 ± 16.4</td>
<td>54.9 ± 4.9</td>
<td>Cord compression</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Power and Longo (1975)</td>
<td>36 (10–73)</td>
<td>62.4 ± 0.2</td>
<td>Hypoxia</td>
<td>Baboon (RM)</td>
</tr>
<tr>
<td>Edelstone et al. (1980)</td>
<td>44.9 ± 8.3</td>
<td>73.5 ± 6.6</td>
<td>Norepinephrine (1 µg/kg/min)</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Reuss and Rudolph (1980)</td>
<td>57 ± 12</td>
<td>62 ± 7.5</td>
<td>Epinephrine (2 µg/kg/min)</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Iskovitz et al. (1982)</td>
<td>57.7 ± 4.8</td>
<td>62 ± 7.5</td>
<td>Vasopressin (4 µU/kg/min)</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Paulick et al. (1990)</td>
<td>50.5 ± 8</td>
<td>62.9 ± 7</td>
<td>Angiotensin (100 ng/kg/min)</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Paulick et al. (1991)</td>
<td>60.8 ± 6.8</td>
<td>75.4 ± 7</td>
<td>Reduction of uterine blood flow</td>
<td>Sheep (RM)</td>
</tr>
<tr>
<td>Jensen et al. (1991)</td>
<td>44.6 ± 18.6</td>
<td>53 ± 19.8</td>
<td>IUGR</td>
<td>Human (Doppler)</td>
</tr>
<tr>
<td>Tchirikov et al. (1998)</td>
<td>43 ± 9</td>
<td>62 ± 8</td>
<td>Hypoxia</td>
<td>Sheep (Doppler)</td>
</tr>
<tr>
<td>Tchirikov et al. (1998)</td>
<td>36 ± 5</td>
<td>53 ± 6</td>
<td>SGA</td>
<td>Human* (Doppler)</td>
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<td>Kisnerud et al. (2000)</td>
<td>32 and 18</td>
<td>17 ± 9</td>
<td>Hypoxia</td>
<td>Sheep (Doppler)</td>
</tr>
<tr>
<td>Bellotti et al. (2000)</td>
<td>40 and 15</td>
<td>29 ± 5</td>
<td>Fetoscopic coagulation of one umbilical artery</td>
<td>Sheep (Doppler)</td>
</tr>
<tr>
<td>Tchirikov et al. (2001)</td>
<td>22 (13–41)</td>
<td>56 (17–97)</td>
<td></td>
<td>Baboon (Doppler)</td>
</tr>
<tr>
<td>Haugen et al. (2004)</td>
<td>25 (13–47)†</td>
<td>90 (59–117)‡</td>
<td>IUGR</td>
<td>Human (Doppler)</td>
</tr>
<tr>
<td>Bellotti et al. (2004)</td>
<td>29 (21–35)‡</td>
<td>41 (18–76)‡</td>
<td>Marmoset (Doppler)</td>
<td></td>
</tr>
<tr>
<td>Tchirikov et al. (2005)</td>
<td>28 ± 1 (18–76)‡</td>
<td></td>
<td></td>
<td>Baboon (Doppler)</td>
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*DV shunting in early and late pregnancy. †Median, 10th and 90th centiles. ‡Median, 25th and 75th centiles. DD, indicator dye-dilution method; Doppler, blood flow volume measurement using the Doppler ultrasound technique; IUGR, intrauterine growth restriction; RM, radioactively-labeled microsphere technique; SGA, small for gestational age.
distribution of blood flow in response to cord compression in fetal sheep. Hepatic blood flow decreased after cord compression and the proportion of DV shunting and O₂ delivery from the DV blood to upper body organs increased. In 1991 Jensen et al. found no reduction in umbilical blood flow in response to a graded reduction in uterine blood flow after the constriction of the common uterine artery. However, the brain and heart obtained significantly more blood derived from the DV. The proportion of UV return that bypassed the liver through the DV significantly increased following fetal hemorrhage, resulting in maintenance of the DV blood flow, despite a marked decrease in the UV return. The combined cardiac output and the umbilical blood flow were distinctly reduced. The DV blood flow remained constant, implying a significant decrease in umbilical blood supply to the liver.

The DV shunting rate may also depend on blood viscosity. In 1997 Kiserud et al. investigated the flow distribution in isolated livers of fetal sheep, which were perfused with blood with different levels of hematocrit. The authors found that reduced UV pressure and increased hematocrit favor an increase in the fraction of blood flow through the DV (red boxes, Figure 1).

In 1980 Reuss and Rudolph demonstrated that, despite a 40% reduction in total available oxygen in the umbilical blood of fetal sheep during hypoxia, oxygen delivery to the myocardium was significantly increased and maintained to the placenta and the brain. Paulick et al., in 1990, also found an elevated DV shunting during hypoxemia, which was associated with an increase in the plasma norepinephrine (11-fold) and epinephrine (55-fold), as compared with controls. The authors discussed the role of catecholamines in umbilical blood flow distribution. One year later, the same group published results of a study in which infusion of catecholamines increased the vascular resistance of the UV and the intrahepatic branches of the portal vein, resulting in an increase in DV blood flow (Table 1). Catecholamines may be responsible for an increase in DV shunting during fetal hypoxia which is in agreement with our in vitro results (red boxes, Figure 1).

The idea of preferential UV blood flow through the DV and foramen ovale to the left side of the heart and the brain was well documented by Dawes et al. in 1954, while Cross et al. (1959) studied O₂ saturation in anesthetized fetal sheep.

The radioactively-labeled microsphere technique is considered to be more accurate than the other methods discussed above. However, this technique is invasive and requires preparation of the fetal or placental vessels for injection of the microspheres. In our opinion, the fetus, after the surgical preparation of the fetal vessels in acutely or chronically catheterized fetal sheep, cannot be regarded as being completely under normal physiological conditions. The DV shunting ratios measured by the microsphere technique thus may be influenced by the short- or long-term effects of surgical stress and of the implanted catheters, which will undoubtedly block parts of the fetal circulation.

Non-invasive, transcutaneous Doppler velocimetry measurements in the UV and DV have been performed in humans, as well as in experimental animals. The DV shunting rate has been estimated in human fetuses under normal conditions, in fetuses with intrauterine growth restriction and in multifetal pregnancies. Absolute blood flow volume through the DV increased with gestational age, whereas blood flow normalized for estimated fetal body weight (ultrasound morphometry), decreased with gestational age. The proportion of UV return passing through the DV was significantly increased in growth-restricted fetuses as well as in multifetal pregnancies when compared with the control group. Accordingly, the calculated umbilical blood supply to the liver was significantly decreased in growth-restricted fetuses and in multifetal pregnancies. As a consequence of these findings, estimation of the proportion of DV shunting may serve as an indicator of early fetal distress in a clinical setting. The finding was confirmed by other research groups using Doppler velocimetry (Table 1).

In sheep fetuses, we found a significant increase of DV shunting during late hypoxemia induced by maternal hypoxia. The DV blood flow volume rate was not significantly increased (88 ± 29.6 mL/min to 101.7 ± 30.1 mL/min); however, the placental perfusion was decreased from 238.7 ± 47.3 mL/min to 194.4 ± 58.4 mL/min, while umbilical blood supply to the liver was reduced by 39%. In these experiments, fetal plasma catecholamine levels were elevated.

We investigated the influence of reduced placental perfusion, after coagulation of one umbilical artery, on DV shunting using fetoscopy in acutely anesthetized fetal sheep. The blood flow volume rate through the DV remained constant (94 and 92 mL/min/kg) during the reduction of placental flow from 408 to 173 mL/min/kg. The DV shunting rate increased from 22% to 56% and the estimated umbilical blood supply to the liver was reduced by 70%.

Recently, Bellotti et al. found a dilated DV in growth-restricted human fetuses that also increased the DV shunting rate. We investigated the influence of DV dilatation on the placental and hepatic circulations in fetal sheep. The DV diameter was increased up to 5 mm by implantation of a stent. DV dilatation was associated with a significant increase in DV shunting from 30.1% (range, 23.8–36.4%) to 59.2% (range, 49.3–69.0%) in a randomized study.

In conclusion, the increase in the proportion of umbilical blood that bypasses the liver tissue through the DV following or during fetal distress may facilitate fetal adaptation by preferentially supplying important fetal organs, such as the brain and heart, with oxygen and nutrients. It requires changes of resistance to flow in the DV and/or in those parts of the hepatic vascular bed. Regardless of which vessel or group of vessels is involved, the ratio of DV resistance to intrahepatic venous resistance must decrease to allow blood to flow preferentially through the DV (Figure 1). Umbilical flow will also depend, of course, on the arteriovenous pressure...
The diagnosis of increased DV shunting using non-invasive Doppler velocimetry may improve the early recognition of fetal compromise.

**Methodology of the Doppler measurement of the DV shunting**

For UV blood volume flow measurement, a straight segment of the intra-abdominal part of the UV upstream of any hepatic branches should be selected, with the Doppler gate positioned so as to completely cover the vessel’s diameter. The UV flow volume can also be measured in the umbilical cord. We suggest measuring blood flow volume following the ‘maximum principle’, which aims to determine the maximum diameter of the vessel, the maximum intensity weighted mean velocity (or time-averaged mean velocity, TAV) at the maximum vessel length in a straight longitudinal section. The inner vessel diameter is determined to the nearest tenth of a millimeter by placing the calipers at right angles to the vessel axis on a frozen B-mode image (without color). This is followed by the TAV measurement at the same vessel portion with a small angle of insonation (less than 30°). The blood volume flow rate is calculated from diameter (D) and TAV as flow rate = TAV × π × (D/2)² mL/min. We recommend repeating flow measurements at least three times (including the determination of diameters) to improve precision. Doppler evaluations must be carried out in the absence of fetal breathing and body movements.

Doppler velocimetry is increasingly being used in prenatal medicine to estimate blood flow volume rates. However, the precision of the method is still a matter of debate, with accurate measurement of the vessel diameter being regarded as a major problem. For example, our first measurements, 9 years ago, of the DV shunting rate in humans seem to have been higher when compared to later investigations owing to the large diameter of the DV isthmic portion measured with the ultrasound equipment available at the time. Flow measurements and thus calculation of the DV shunt rate should be regarded with caution, especially when determined in small fetuses. The requirements to measure precisely the true vascular diameters and TAMXVs are difficult to fulfill; however, no alternative non-invasive measurement technique is currently available. The progressive development of functional nuclear magnetic resonance and positron emission tomography imaging, and three-dimensional ultrasound techniques may improve the quality of blood flow measurements in the near future.

**Liver blood perfusion and DV umbilical blood shunting in the regulation of fetal growth**

The liver is privileged amongst fetal organs in that it receives well-oxygenated, nutrient-rich blood directly from the placenta. The anatomical position of the liver also determines its role in controlling the distribution of nutrients to other fetal organs. The liver produces proteins, lipids and carbohydrates and is involved in their metabolism. In addition, the liver synthesizes insulin-like growth factors (IGFs), IGF binding proteins (IGF-BPs), and other growth factors, which may influence cell proliferation in fetal organs.

We developed a method in a fetal sheep model, with twin pregnancies, in which the DV was either occluded with an embolization coil or dilated with a wide-bore coronary stent. A catheter with a guide wire was inserted into the right external jugular vein of the fetus and advanced under ultrasound guidance through the right atrium and the IVC to the DV. The embolization coil was then placed in the DV to occlude the vessel in one twin. The sibling fetuses served as controls. The fetuses survived the DV occlusion for up to 3 weeks. A wide-bore coronary stent was used, instead of the embolization coil, to increase the diameter of the DV using the same method of DV catheterization.

Occlusion of the DV led to a significant increase in relative liver weight from 3.4 ± 0.8% to 4.3 ± 0.8%. In fetal skeletal muscles, heart and kidneys, the elevated umbilical blood supply to the liver led to a 2- to 3-fold increase in cell proliferation (pKi-67), with a corresponding 6-fold increase in cell proliferation in the fetal liver. The index of proliferate cell activity in the placenta was not different between groups. The occlusion of the DV was associated with an apparent increase in mRNA for IGF-I and IGF-II in the fetal liver. However, we could not determine any significant differences between twins in either body weight, or in the concentration of amino acids, free fatty acids, catecholamines and IGFs in the fetal plasma. It is likely that the supply and consumption of amino acids and free fatty acids in fetuses with an increased blood supply to the liver were well-balanced owing to the placenta not being affected. On the other hand, other growth factors and parameters, such as IGF-BPs, insulin, leptin, the epidermal growth factor and interleukins may be involved in the regulation of fetal growth.

Stent implantation in the DV significantly decreased umbilical blood supply to the liver by around half, from 499 ± 371 to 278 ± 219 mL/min, occasionally inducing reversed blood flow in the hepatic veins with pulsations in the UV. Reduced hepatic blood supply in the stent group appeared to be associated with a 50% decrease in cell proliferation in the liver and in the heart and skeletal muscle. However, in some cases DV dilatation increased total placental blood perfusion; thus, in spite of a distinctly increased DV shunting rate, hepatic blood supply was not diminished (unpublished observation). It seems possible that the combined resistances to flow of the DV and the hepatic vasculature may also influence placental perfusion.

**CONCLUSIONS**

The present review summarizes the results of clinical and experimental research on the DV in the fetal circulation.
Ductus venosus shunting in the fetus

The isthmic portion of the DV contains less smooth muscle tissue than the intrahepatic branches of the portal vein, which in vitro react more forcefully in response to catecholamines than the DV. More α-adrenoreceptors were found in the vessel wall of affluent hepatic veins than in the DV, which may also contribute to the functional difference. In humans, about three-quarters of the UV blood supplies the fetal liver in late gestation, with the remainder passing through the DV. The DV shunting rate increases under fetal stress situations, in particular with acute hypoxia of varying origin. This implies a decrease in the umbilical blood supply to the fetal liver, provided that total umbilical blood flow does not increase. The increase in DV shunting rate is a general adaptational mechanism to fetal distress and is observed in growth-restricted human fetuses as well as twin pregnancies. The late-gestational increase in the proportion of umbilical blood that supplies the liver, as deduced from the decrease in the DV shunting rate, may indicate that fetal maturation in late gestation leads to an increasing demand for hepatic metabolism. The relatively low non-stress shunt rates may also allow a wide margin of DV shunt increases when necessary in a temporary stress situation. The Doppler velocimetric quantification of DV shunting may improve the early recognition of fetal compromise in prenatal medicine. A long-term reduction in hepatic blood supply may be involved in fetal growth restriction. The occlusion of the DV leads to a significant increase in cell proliferation in fetal skeletal muscles in the heart, kidneys and liver and possibly to an increase in mRNA for IGF-I and IGF-II in fetal skeletal muscles in the heart, kidneys and liver and possibly to an increase in mRNA for IGF-I and IGF-II in the fetal liver. These findings hint at the possible role of the perfusion of the fetal liver in the control of the growth process.

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REFERENCES


