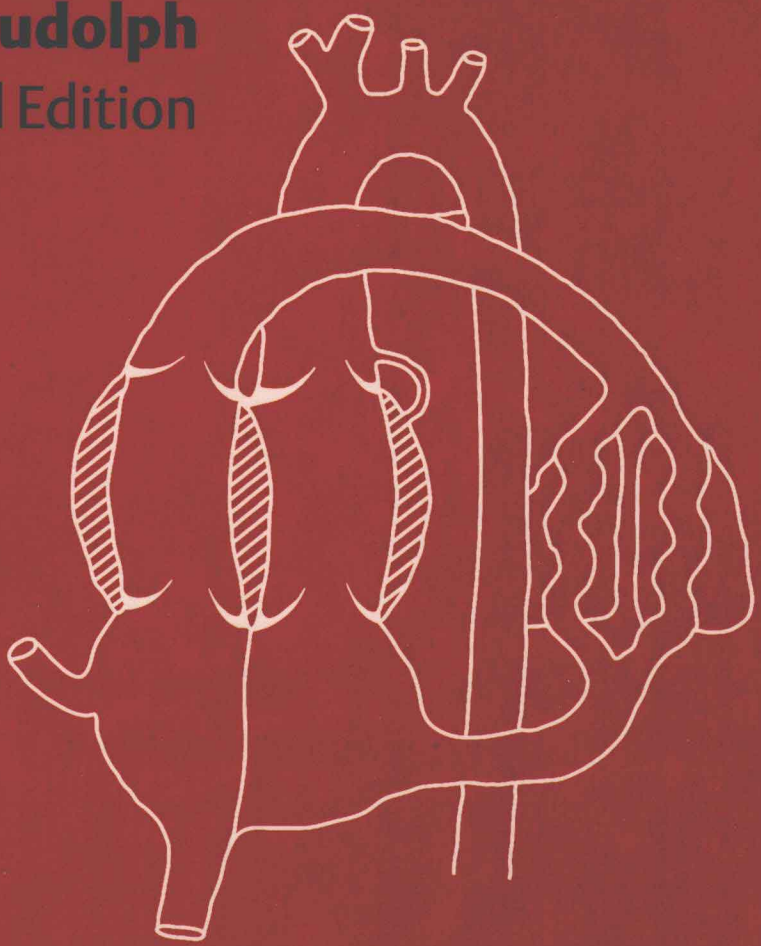
Congenital Diseases of the Heart

Clinical-Physiological Considerations

Abraham M. Rudolph

Third Edition



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Clinical-Physiological Considerations

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Preface

The second edition of *Congenital Diseases of the Heart* was published in 2001. Since then, there have been remarkable advances in our understanding of many aspects of etiology, pathophysiology, clinical manifestations and management of congenital cardiovascular malformations.

Although the association of congenital cardiac lesions with many chromosomal anomalies had been recognized, specific gene defects responsible for cardiovascular anomalies have now been identified. One example is the NOTCH 1 gene mutation found in individuals with bicuspid aortic valve, as well as in those with hypoplastic left heat syndrome and aortic coarctation.

The extensive use of ultrasound examination for prenatal screening has facilitated diagnosis of congenital cardiovascular malformations in fetuses in utero. Previously it was thought that these lesions had little adverse effect during fetal life. However, the ultrasound studies are defining the influences of these anomalies on blood flow patterns and on development of the cardiac chambers and great vessels. This has stimulated efforts to relieve obstruction of the aortic valve to attempt to prevent the development of hypoplastic left ventricle. Furthermore, the effects of normal changes in the circulation during fetal development, on the hemodynamic changes associated with congenital cardiac lesions, are being defined.

Management of many congenital cardiovascular malformations has changed dramatically in recent years. Interventional cardiac catheterization techniques with percutaneous approach have largely replaced surgical thoracotomy to relieve obstructions and, in many instances, to close communications between the left and right sides of the heart. The low risk of these procedures and avoidance of thoracotomy has resulted in the temptation to close small defects and relieve minor obstructions, raising issues regarding the indications for these procedures.

These advances, as well as increasing knowledge of the hemodynamic changes associated with fetal and postnatal development, prompted me to embark on the preparation of this *Third Edition.* As in the previous editions, I have not attempted to provide a detailed discussion of all aspects of congenital cardiovascular disease, but have discussed the anomalies from the perspective of their impact at various stages of development – from fetus to neonate to child and adolescent. Because ultrasound examination and other techniques are largely replacing cardiac catheterization for diagnosis, I was tempted to drastically reduce the discussion of the procedure. However, at the urging of many of my colleagues I have retained these sections, because they felt they added to the understanding of the pathophysiology.

I am most grateful to Dr Norman Silverman, with whom I frequently have discussions about effects of congenital cardiac malformations on the fetus. His vast experience with echocardiography of fetuses has contributed enormously to assisting me to appreciate fetal hemodynamics. I also greatly appreciate the contributions of Dr. Charles Kleinman; he reviewed the manuscript and his comments, criticisms and suggestions have been most helpful.

I dedicate this edition to my wife, Rhona. She died soon after I embarked on this venture. She had always been most supportive and I sensed her enthusiastic encouragement throughout the preparation of this book.

Contents List

CHAPTER 1
The fetal circulation

The circulation in the fetus differs from that in the adult. Knowledge of the course and distribution of the fetal circulation is important to our understanding of the manner in which various congenital heart lesions influence the normal circulation. The circulation undergoes continuous maturation during gestation, both morphologically and functionally, and these changes during development may be greatly influenced by congenital cardiac lesions. Furthermore, we now recognize that the clinical manifestations of congenital heart disease are intimately related to postnatal changes in the circulation. At birth, dramatic changes occur as the gas exchange function is transferred from the placenta to the lungs.

The presence of congenital heart lesions may profoundly affect the alterations in the circulation necessary for adaptation and postnatal survival. In this chapter I review current knowledge of the fetal circulation and its distribution and the changes that occur postnatally. The pulmonary circulation and the changes it undergoes after birth are described in Chapter 5 and fetal function and perinatal changes of the ductus arteriosus are discussed in Chapter 6.

Most of the information regarding the fetal circulation has been derived from the sheep, which has a gestational period of about 150 days as compared with the human of about 280 days. However, with the advent of ultrasound techniques, knowledge of the circulation of the normal fetus and of fetuses with congenital heart lesions has been increasing. It cannot be assumed that development in different species is the same at similar stages of gestation. This is not only because of inherent species differences but also because there are wide variations in the degree of maturity at the time of birth. The rat and the rabbit are relatively immature at birth, whereas the guinea pig is very mature at birth; the lamb is relatively mature and the human infant somewhat less mature. Furthermore, in considering distribution of the circulation, there are marked differences in body proportions. Whereas the brain in the mature lamb fetus is only about 3% of body weight, the human brain comprises about 12% of body weight in the term fetus. Despite these differences, observations we have made in previable human fetuses and ultrasound studies in the human fetus indicate that the course and distribution of the circulation are similar to those in the fetal lamb. However, as discussed below, the quantities of blood ejected by the ventricles and the volumes distributed to various organs differ considerably in human and lamb fetuses.

Because gestational period varies in different species, it is convenient, in making comparisons, to express gestation as a fraction of the normal period for the species. Thus, in the lamb with a 150-day gestation, 100 days is denoted as 0.66 gestation.

Postnatal circulation

Postnatally, respiratory gases enter and leave the body through the lungs, and energy sources are provided from the gastrointestinal tract, entering the portal venous system to be distributed to the liver. The adult circulation is characterized by serial flow of venous blood into the right atrium (Figure 1.1). It is ejected by the right ventricle into the pulmonary circulation to be oxygenated in the lungs and returns to the left atrium and ventricle to be ejected into the aorta for distribution to body organs. Carbon dioxide is removed and oxygen taken up in the lungs; a variable proportion of oxygen is extracted, and carbon dioxide and

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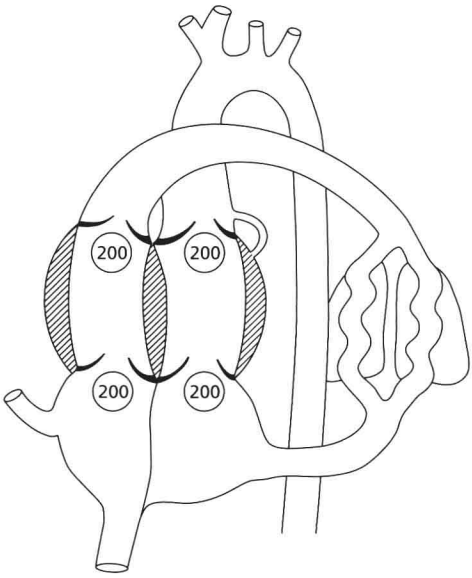


Figure 1.1 Course of blood flow in the adult circulation. The volumes of blood ejected by each ventricle and returning to each atrium are similar postnatally.

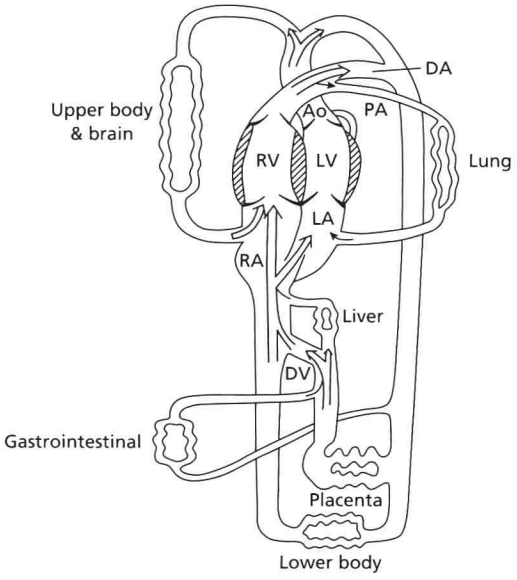


Figure 1.2 The general course of the mammalian fetal circulation. Ao, aorta; DA, ductus arteriosus; DV, ductus venosus; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

metabolites are added to blood by the tissues. Apart from minor amounts of bronchial venous blood that may enter the pulmonary vein and coronary venous blood that may empty directly into the left ventricular cavity, there is essentially no mixing of pulmonary venous and systemic arterial blood with poorly oxygenated systemic venous and pulmonary arterial blood. Postnatally, metabolic substrates, absorbed from the gastrointestinal tract into the portal venous system, are first delivered to the liver and then enter the systemic venous system and pass through the lungs before being delivered to tissues by the arterial circulation.

Circulation in the fetal lamb

Course of blood flow

The course of the circulation in the fetus is shown in Figures 1.2 and 1.3. Blood is oxygenated in the placenta and returns to the fetus through the umbilical veins, which enter the body through the umbilicus and join the portal vein. Umbilical venous blood has a Po_2 of about 32–35 mmHg when the mother is breathing ambient air and its oxygen saturation is about 80–85%. The umbilical vein

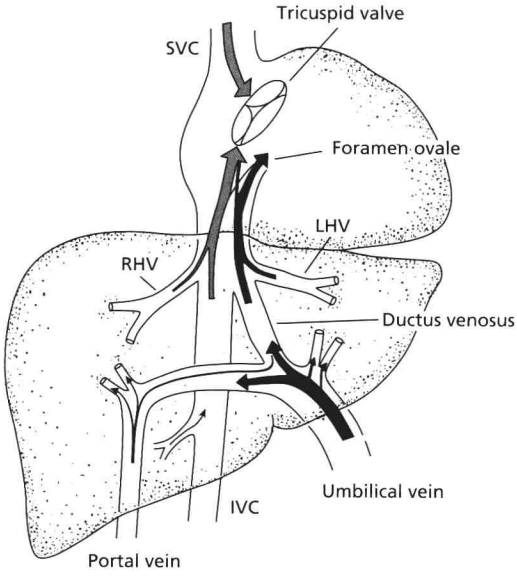


Figure 1.3 Course of blood flow in the region of the porta hepatis. Umbilical venous blood is distributed to the left lobe of the liver. The ductus venosus arises from the umbilical vein, which then arches to the right to join the portal vein. Portal venous blood is largely distributed to the right liver lobe and only a small proportion passes through the ductus venosus. IVC, inferior vena cava; LHV, left hepatic vein; RHV, right hepatic vein; SVC, superior vena cava.

passes from the umbilicus to the hilum of the liver; it provides branches to the left lobe of the liver and then divides into the ductus venosus and a large arcuate branch, which courses to the right in the hilum, where it is joined by the portal vein (Figure 1.3). Branches to the right lobe of the liver arise beyond this junction. The ductus venosus passes dorsally and cephalad through the liver parenchyma to join the inferior vena cava immediately beneath the diaphragm. The left hepatic vein joins the ductus venosus at its entry into the inferior vena cava, so there is a common entry orifice. In the sheep fetus this orifice is partly covered by a thin, valve-like membrane on its caudal edge [1]. The right hepatic vein enters the inferior vena cava separately, and the orifice is partly covered by a valve-like structure caudally. The function of these valve-like membranes is not known, but we have conjectured that they may facilitate directional flow of the various venous streams entering the inferior vena cava at this site. Previously, it was generally believed that umbilical and portal venous blood mixed in the porta hepatis and was then distributed to the left and right liver lobes and through the ductus venosus. However, Lind et al. [2] obtained umbilical venous angiograms in human fetuses immediately after delivery and suggested that umbilical venous blood passes preferentially to the left liver lobe and through the ductus venosus.

Using radionuclide-labeled microspheres, we were able to define not only the patterns of blood flow in the fetal liver but also the quantities of blood flowing through various channels in the fetal sheep [3]. Umbilical venous blood is distributed to the left lobe of the liver, through the ductus venosus, and via the arcuate branch, to the right liver lobe. Almost all portal venous blood is distributed to the right liver lobe. Only a small proportion, about 5–10% or less, passes through the ductus venosus and none is delivered to the left lobe. Thus the left lobe of the fetal liver receives well-oxygenated umbilical venous blood and a small supply from the hepatic artery. The right lobe receives a mixture of poorly oxygenated portal venous and umbilical venous blood, as well as a small amount from the hepatic artery. This accounts for the fact that the oxygen saturation of left hepatic venous blood is higher than that of right hepatic venous blood [4] (Figure 1.4).

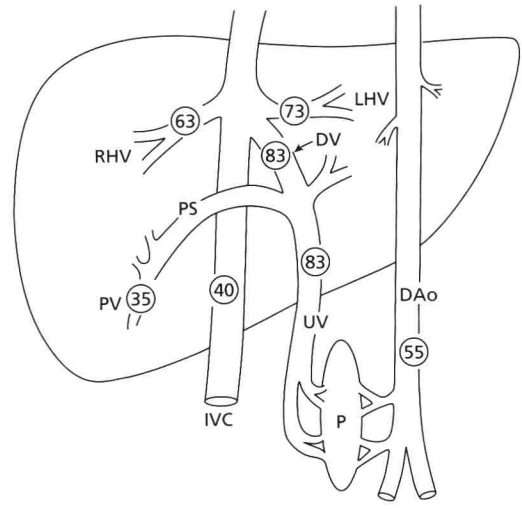


Figure 1.4 Blood oxygen saturations are shown in vessels in the region of the liver in the fetal lamb. DAo, descending aorta; DV, ductus venosus; IVC, inferior vena cava; LHV, left hepatic vein; P, placenta; PS, portal sinus; PV, portal vein; RHV, right hepatic vein; UV, umbilical vein.

The distributions of ductus venosus blood, blood from the distal inferior vena cava, and blood from the left and right hepatic veins have also been examined using radionuclide-labeled microspheres in fetal sheep [5]. Umbilical venous blood passing through the ductus venosus into the inferior vena cava is preferentially directed across the foramen ovale into the left atrium and left ventricle; only a small proportion passes into the right atrium and through the tricuspid valve. Abdominal inferior vena cava blood, in contrast, preferentially streams across the tricuspid valve into the right atrium and right ventricle and only a relatively small proportion crosses the foramen ovale to the left atrium. Blood from the left hepatic vein tends to follow the course of the ductus venosus stream, being preferentially distributed across the foramen ovale, whereas right hepatic venous blood preferentially streams across the tricuspid valve, following the course of abdominal inferior vena cava blood (see Figure 1.3). This preferential distribution of blood to the foramen ovale or the tricuspid valve suggests that there is streaming within the inferior vena cava between the liver and the heart. This can be observed directly in the fetal lamb when a right thoracotomy is performed. Observation of the

thoracic portion of the inferior vena cava reveals well-oxygenated and poorly oxygenated blood streams. The anterior and right portion of the vessel is seen to have a poorly oxygenated stream, but blood flowing in the posterior and left portion is clearly well oxygenated. The streaming patterns in the inferior vena cava have also been observed by color flow Doppler studies. The ductus venosus stream has a velocity of about 55 cm/s and is directed largely through the foramen ovale, whereas distal inferior vena cava blood has a considerably lower velocity of about 15 cm/s and streams across the tricuspid valve. It is likely that the high velocity of the ductus venosus stream contributes to maintaining its preferential distribution across the foramen ovale. Ultrasound examination of human fetuses have also shown similar differences in ductus venosus and distal inferior vena cava velocities, and similar preferential streaming patterns.

The inferior margin of the atrial septum separates the entrance of the inferior vena cava from the left atrium, but the crescentic edge of the superior portion of the atrial septum, the crista dividens, overlies the inferior vena cava (see Figure 1.3). The posterior left portion of the inferior vena cava thus connects directly through the foramen ovale to the left atrium. During phases of the cardiac cycle, the eustachian valve and the lower portion of the atrial septum move in unison, either to the left to facilitate movement of blood through the foramen ovale, or to the right to enhance flow through the tricuspid valve [6]. The preferential streaming of ductus venosus and left hepatic venous blood through the foramen ovale distributes blood of higher oxygen saturation to the left atrium and ventricle and thus into the ascending aorta. Blood of lower oxygen saturation from the abdominal inferior vena cava and the right hepatic vein is preferentially distributed into the right ventricle and pulmonary artery.

The ductus venosus serves as a partial bypass of the hepatic microcirculation for umbilical venous blood. It may reduce the impedance to umbilical venous return by avoiding the need for all the blood to pass through the liver. Although it does facilitate passage of well-oxygenated blood to the left side of the heart, the proportion of umbilical venous blood that passes through the ductus varies greatly, both in the lamb and the human fetus, from about 20 to 90% [3,7]. In some species, such as the horse and the pig, the ductus venosus is not detectable in the latter part of gestation. The importance of the ductus venosus in the fetus is thus questionable, but it may be important in initiating some of the effects of aortopulmonary transposition on development of the pulmonary circulation (see Chapter 18).

Superior vena cava blood is largely directed by the tubercle of Lower to the tricuspid valve and is distributed into the right ventricle. Only about 5%, or less, flows through the foramen ovale into the left atrium in the normal fetus. Ultrasound examination of the fetal lamb indicates that the small amount of superior vena cava blood that enters the foramen ovale does so indirectly, by first flowing retrograde into the upper portion of the inferior vena cava and then entering the foramen. This phenomenon is markedly accentuated during fetal hypoxemia [6].

Right ventricular blood is ejected into the pulmonary trunk, and the larger proportion passes through the ductus arteriosus to the descending aorta, with the remainder entering the pulmonary circulation (Figure 1.5). Blood that passes from the pulmonary trunk through the ductus arteriosus is directed to the descending aorta; none passes retrogradely across the aortic isthmus to the ascending aorta and its branches. The left atrium receives blood from the foramen ovale and pulmonary veins, and then empties into the left ventricle, which ejects into the ascending aorta. Most ascending aortic blood is distributed to the coronary circulation, head and cerebral circulation, and upper extremities; only a small proportion passes across the aortic isthmus into the descending aorta. The major proportion of descending aortic blood is distributed to the umbilical–placental circulation and the remainder to the abdominal organs and the tissues of the lower trunk and lower extremities.

Admixture of oxygenated and systemic venous blood

In the adult circulation, there is essentially no mixing of oxygenated pulmonary venous and systemic venous blood. In the fetus, there are several sites of mixing. Portal and umbilical venous bloods enter the vessels in the porta hepatis. Blood from the ductus venosus, left and right hepatic veins, and abdominal inferior vena cava all enter the thoracic portion of the inferior vena cava. Admixture occurs

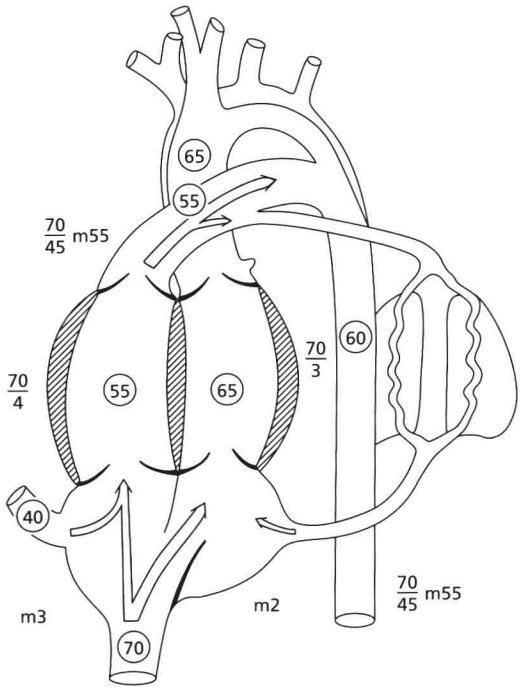


Figure 1.5 Course of the circulation in the heart and great vessels in the late-gestation fetus. The figures in circles within the chambers and vessels represent percent oxygen saturation levels. The figures alongside the chambers and vessels are pressures in mmHg related to amniotic pressure level as zero. m, mean pressure. The aortic arch and its branches are shown for both the human and the lamb. In the lamb, a single vessel, the brachiocephalic trunk, gives rise to carotid and subclavian arteries. In the human, the innominate and left carotid and subclavian arteries arise separately.

in the left atrium, where blood entering the foramen ovale from the inferior vena cava is joined by pulmonary venous blood. As mentioned above, the preferential streaming of blood partly separates the well-oxygenated and poorly oxygenated blood, favoring distribution of oxygenated blood into the left ventricle and ascending aorta and providing blood with a higher oxygen content to the heart, brain, and other upper body tissues. Systemic venous blood is preferentially directed into the right ventricle, pulmonary trunk, and ductus arteriosus to the descending aorta and its branches to the lower body, as well as to the placenta.

Because umbilical venous and vena cava blood is mixed, the blood delivered to the fetal body and the placenta contains varied proportions of oxygenated and systemic venous blood. Hence some umbilical venous blood is returned to the placenta after passing through the ductus venosus and foramen ovale or ductus arteriosus shunts without first being delivered to fetal tissues to permit oxygen uptake. This situation is equivalent to that occurring postnatally with some congenital heart lesions (e.g., atrial or ventricular septal defect), in which oxygenated blood passes from the left atrium or left ventricle into the right side of the heart to be recirculated to the lung. This, termed a *left-to-right shunt*, imposes an additional workload on the heart. Similarly, with congenital heart lesions in which systemic venous blood is shunted through an abnormal communication into the left side of the heart to be distributed back to the body tissues without passing through the lung, a *right-to-left shunt* occurs. The blood returning to the heart from the superior and inferior vena cava that is distributed to the fetal tissues without first being delivered to the placenta for oxygenation is effectively a right-to-left shunt. This effective right-to-left shunt contributes to inefficiency of the fetal circulation. In the sheep fetus under normal conditions, right-to-left shunt represents about 45% of superior vena cava and 53% of inferior vena cava blood [8]. Umbilical venous blood that passes through the ductus venosus and foramen ovale or ductus arteriosus and which is distributed back to the placenta is an effective left-to-right shunt. This represents about 22% of umbilical venous blood, and the combined left-to-right and right-to-left shunts constitute about 33% of the combined ventricular output of the fetal heart.

Intravascular pressures in the fetus

In the postnatal animal or human, it is customary to express pressures with reference to atmospheric pressure as the zero. However, the fetus is surrounded by amniotic fluid in the uterus within the abdomen, and all pressures are subjected to an increase from the environmental pressure. This changes if the intraabdominal pressure is increased by straining, distension with gas or feeding, and also by postural change; uterine contraction also produces an increase in all fetal intravascular pressures. It is therefore now customary to relate all fetal pressures to intraamniotic rather than to atmospheric pressure. The pressures shown in Figure 1.5 are expressed in relation to intraamniotic pressure. In the quietly standing ewe, intraamniotic pressure

usually is about 8–10 mmHg above atmospheric pressure. When considering effective filling pressures of the cardiac ventricles, it is more appropriate to measure transmural pressure, or intraventricular minus pericardial pressure. Pericardial pressure is generally similar to intrapleural pressure, which is negative (i.e., lower than atmospheric pressure) postnatally. Mean pressure in the superior and inferior vena cava and the right atrium is about 2–3 mmHg. The *a* and *v* waves are about 4–5 mmHg, with the *a* wave only slightly higher. Left atrial pressures have a phasic contour similar to that of the right atrium, and the mean pressure is only 1–2 mmHg lower than right atrial pressure. Mean pressure in the portal sinus is 5–6 mmHg. Umbilical venous pressure is about 7–8 mmHg near the umbilical ring, and 2–3 mmHg higher near the placenta. Systemic arterial pressure increases with gestational age in the lamb fetus, from a mean level of 25–30 mmHg at about 60 days' gestation to 55–60 mmHg close to term. Figure 1.5 shows the pressures measured in various cardiac chambers in the late gestation fetal lamb *in utero*. The ductus arteriosus, connecting the pulmonary trunk with the descending aorta, has a diameter that, through most of gestation, is large enough to equilibrate pressures in the great arteries. The similarity of the systolic and diastolic pressures in the aorta and pulmonary artery has been observed in fetal lambs as young as about 60 days' gestation and to near term at about 145 days' gestation [9]. However, there is a tendency for systolic pressure in the pulmonary trunk to exceed that in the aorta by 5–8 mmHg during the last 10–14 days of gestation, presumably as a result of mild ductus arteriosus constriction. Left and right ventricular systolic pressures are similar to those in the ascending aorta and pulmonary trunk, and end-diastolic pressures are similar to the height of the *a* waves in the left and right atrium respectively.

Blood gases and oxygen saturation

Maternal arterial blood in the pregnant ewe has a Po_2 of 90–100 mmHg and a Pco_2 of about 35 mmHg. There is a large Po_2 gradient across the placenta, with a Po_2 of 32–35 mmHg in umbilical venous blood. Umbilical venous blood Pco_2 is about 40 mmHg and pH is 7.40. Because the P_{50} (the Po_2 at which hemoglobin is 50% saturated with oxygen) for fetal blood in the sheep is considerably lower (~19 mmHg) than that of adult blood (~31 mmHg), umbilical venous blood has an oxygen saturation of 80–85% (see Chapter 3). The left lobe of the liver receives blood from the umbilical vein with an oxygen saturation of 80–85%, and about 10% of its blood supply is derived from hepatic arterial blood with a saturation of 50–55% (see Figure 1.4). The right lobe of the liver receives its supply from the umbilical vein, the portal vein with a blood oxygen saturation of about 35%, and a small amount from the hepatic artery. The fact that the right lobe of the liver receives blood of considerably lower oxygen saturation probably explains the frequent presence of a larger number of hemopoietic cells in the right as compared with the left lobe of the liver. The oxygen saturation of blood in the right hepatic vein is about 65%, whereas that in the left hepatic vein is about 75%.

Superior vena cava blood and inferior vena cava blood distal to the entrance of the ductus venosus and hepatic veins both have a Po_2 of about 12–14 mmHg and an oxygen saturation of 35–40%. The Po_2 of right ventricular and pulmonary arterial blood is 18–20 mmHg and oxygen saturation is about 50%. Left ventricular and ascending aortic blood have a Po_2 of about 25–28 mmHg and an oxygen saturation of about 65%, whereas descending aortic blood has a Po_2 of 20–23 mmHg and an oxygen saturation of about 55%. Systemic arterial blood has a Pco_2 of 43–45 mmHg and a pH of about 7.38–7.39. The values for blood gases and oxygen saturations in the human fetus *in utero* are not well defined but are discussed below.

Effects of administering oxygen to the mother

Administering 100% oxygen to the ewe raises arterial oxygen saturation to 100% and the Po_2 to more than 400 mmHg. Fetal arterial Po_2 increases to only 30–35 mmHg with an oxygen saturation of about 80%. Umbilical venous blood Po_2 increases to 40–50 mmHg and oxygen saturation reaches 95–100% (see Chapter 3).

Cardiac output and its distribution

In the adult, the circulation passes in series through the right atrium, right ventricle and pulmonary artery, returning to the left heart and being ejected into the aorta and peripheral circulation. The

cardiac output in the postnatal individual is expressed as the volume of blood flowing through the heart per unit time, and represents the volume of blood ejected by each ventricle. In the fetus, blood distributed to the various parts of the body and to the placenta is derived from the systemic venous return as well as the umbilical venous return, and the ventricles effectively act in parallel; blood to many organs is derived from both ventricles. Also, the outputs of the left and right ventricles are different in the fetus. It has therefore become customary to express the output of the heart as combined ventricular output (CVO), the sum of the volumes ejected by the two ventricles.

The CVO has been studied in human fetuses using ultrasound techniques, but measurements vary considerably (see below). Most reliable information is from studies in the sheep. In chronically instrumented fetal lambs during the latter months of gestation (term is about 145 days), CVO is about 450–500 mL/min per kg fetal body weight [9]. Umbilical–placental blood flow is about 200 mL/min per kg body weight, and blood flow to the fetal body is about 250–300 mL/min per kg. The right ventricle ejects about two-thirds and the left ventricle about one-third of CVO in the fetal lamb (Figures 1.6 and 1.7).

The umbilical–placental flow of about 200 mL/min per kg represents 40–45% of CVO. Umbilical venous blood entering the porta hepatis is distributed either to the liver or through the ductus venosus. Although the proportions vary, on average about 55% (range 20–90%) passes through the ductus venosus and 45% through the hepatic circulation. Thus about 110 mL/min per kg passes through the ductus venosus. The liver receives about 90 mL/min per kg fetal body weight of blood from the umbilical vein. Portal venous blood flow is about 30 mL/min per kg; most of this blood enters the right lobe of the liver. Inferior vena cava blood distal to the entrance of the hepatic veins and ductus venosus (abdominal inferior vena cava) is

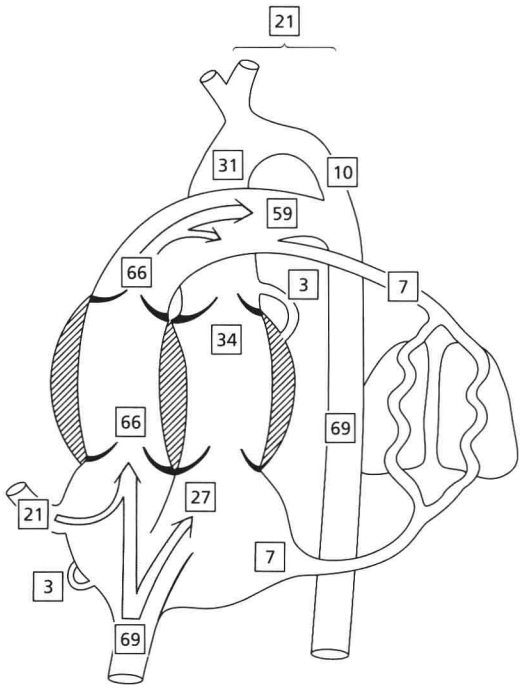


Figure 1.6 Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures represent values for late-gestation lambs.

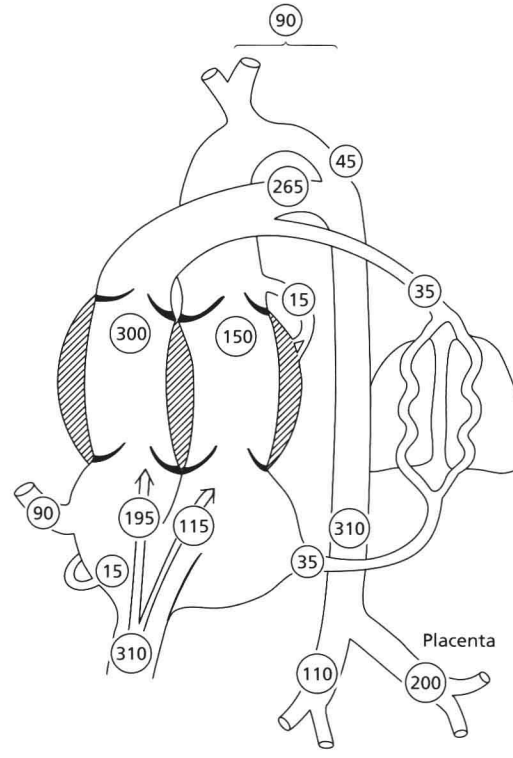


Figure 1.7 Volumes of blood (mL/min per kg body weight) flowing through cardiac chambers and great vessels in the late-gestation fetal lamb.

Table 1.1 Percent of combined ventricular output (%CVO) and actual blood flows distributed to organs in late-gestation lambs *in utero*.

Blood flow	*%CVO*[1]	*mL/100 g tissue*	*mL/kg fetal weight*
Brain	4.2	100	20
Heart	3.3	200	16
Liver	25.2	380	120
Kidney	2.9	190	14
Gut	5.2	55	25
Lung	5.2	95	25
Skin, muscle, bone	29.4	20	140
Placenta	39.4		180

1 Totals of %CVO are greater than 100 because a large proportion of liver blood flow is derived from umbilical–placental flow via the umbilical vein.

derived from the lower body organs and the lower extremities as well as the lower portion of the trunk. In the fetal lamb, this represents about 30% of CVO or about 140–150 mL/min per kg.

The blood entering the heart from the inferior vena cava includes ductus venosus, left and right hepatic venous, and abdominal inferior vena cava blood and constitutes about 70% of CVO, or about 315–350 mL/min per kg (Figures 1.6 and 1.7). About 115–125 mL/min per kg or about 25% of CVO passes through the foramen ovale to the left atrium; this blood is derived predominantly from the ductus venosus. Venous return from the superior vena cava is 90–95 mL/min per kg and represents about 21% of CVO. Most of this blood, as well as about 200 mL/min per kg of inferior vena cava blood passes through the tricuspid valve into the right ventricle. In addition, coronary venous blood enters the right ventricle. The right ventricle ejects about 300–325 mL/min per kg or about 66% of CVO. Only about 10–15% of the blood ejected by the right ventricle into the pulmonary trunk enters the pulmonary circulation; this constitutes about 8% of CVO or about 35–40 mL/min per kg fetal weight. The remainder, about 265–300 mL/min per kg, or about 60% CVO, passes through the ductus arteriosus.

The left ventricle receives about 115 mL/min per kg of blood passing through the foramen ovale and the 35 mL/min per kg from pulmonary venous return. It ejects about 150–170 mL/min per kg, or about 33% of CVO. Less than one-third of the blood ejected by the left ventricle passes across the aortic isthmus to the descending aorta. This represents about 10% of CVO or about 45 mL/min per kg. About 3% of CVO enters the coronary circulation and about 20% of CVO or about 90–100 mL/min per kg is distributed to the head, brain, upper extremities, and upper portion of the trunk. The proportions of CVO traversing the major arteries are reflected in the relative diameters of these vessels. The pulmonary trunk is very large, and the ascending aorta somewhat narrower; the descending aorta is also very wide, whereas the isthmus of the aorta is much narrower than the ascending or descending aorta and the ductus arteriosus. These features are discussed in Chapter 12. The blood flows to various fetal organs is shown in Table 1.1.

Hepatic flow is derived from the umbilical vein, portal vein and hepatic artery; flow to the left lobe is about 350 mL/min per 100 g tissue weight, whereas the right lobe receives about 450 mL/min per 100 g [4]. The proportions of the CVO distributed to the fetal organs and the placenta change with advancing gestation (Figure 1.8). There is a gradual reduction in the proportion of CVO directed to the placenta, from about 45% at 75–90 days (0.5–0.6 gestation) to 38–40% at term. The percentage of CVO distributed to the brain increases progressively, from about 2.2% at 0.5 gestation to 3% at term. The percentages of combined output to the lungs and gastrointestinal tract are fairly constant until about 120 days (0.8) gestation, but then increase rapidly [9]. The changes in actual blood flow per unit mass of tissue are shown in Figure 1.9. There are quite striking increases in flow per 100 g organ weight to the brain, gut and lungs, starting at

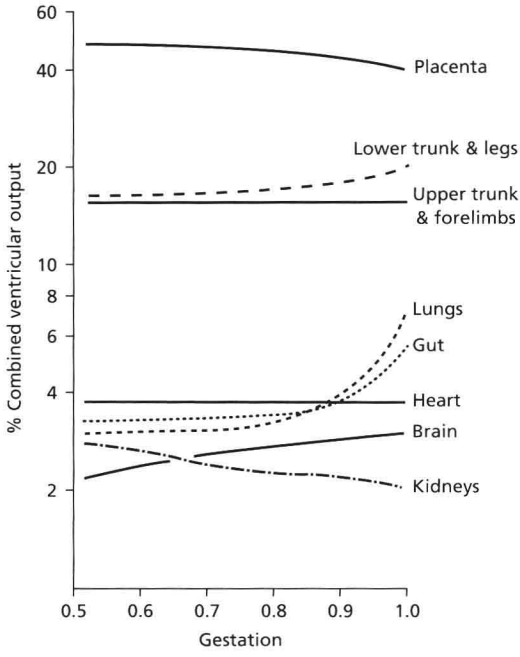


Figure 1.8 Changes in the percentage of fetal combined ventricular output distributed to various organs, body and limbs and the placenta at different gestational ages in the fetal lamb.

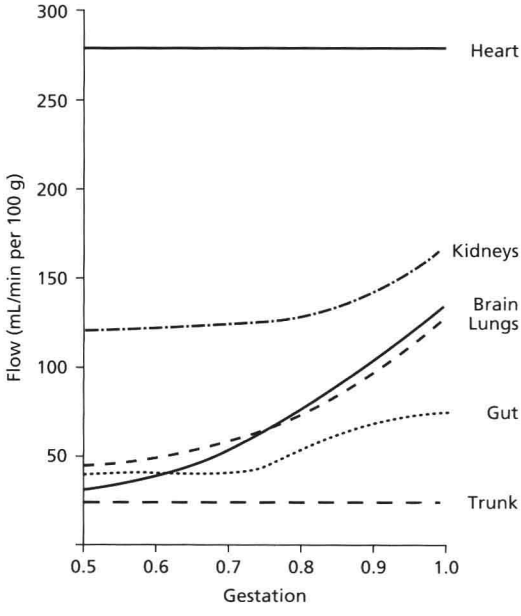


Figure 1.9 Changes in actual blood flow to various organs in the lamb during the latter half of gestation.

about 0.75 gestation (110 days). The cause of the increase in flow to these organs is not known; it could be related to increase in the size of the vascular bed, due to growth of new vessels, or to increased metabolic activity with vasodilatation, or a combination of these factors.

Oxygen delivery and oxygen consumption

One of the important functions of the circulation is to provide oxygen to the tissues. In the adult, oxygen delivery to the body is the product of arterial oxygen content and systemic blood flow, or cardiac output. In the fetus, calculation of oxygen delivery to the body is more complex. Umbilical–placental blood flow represents the volume of blood being presented to the site of oxygenation, whereas CVO minus umbilical–placental blood flow is the volume of blood delivered to the whole fetal body. Umbilical–placental blood flow determines oxygen uptake, and fetal body blood flow determines oxygen delivery to the fetus. However, the oxygen content of blood distributed to the organs supplied from the ascending aorta and to those supplied from the descending aorta are different. Oxygen delivery to an organ or tissue is determined by the oxygen content and the blood flow (see Chapter 3). In the fetus, pressures in the aortic and pulmonary arteries are almost identical, so blood flow to various fetal organs and to the umbilical–placental circulation is determined by local vascular resistance. This is influenced by the size, or cross-sectional area, of the vascular bed and by the degree of vascular constriction or dilatation. Oxygen delivery and oxygen consumption in various organs and tissues in the late-gestation lamb fetus are shown in Table 1.2.

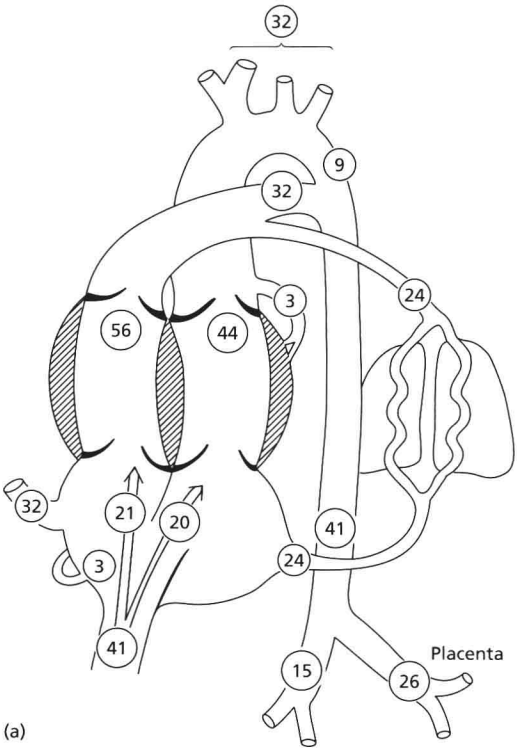
Circulation in the human fetus

Studies in previable human fetuses have demonstrated that the general course of the circulation in the human fetus is similar to that in the lamb [7]. Figure 1.10 and Table 1.3 show average values for distribution of CVO and volumes of blood flow in the human fetal circulation, based on numerous studies [11–17].

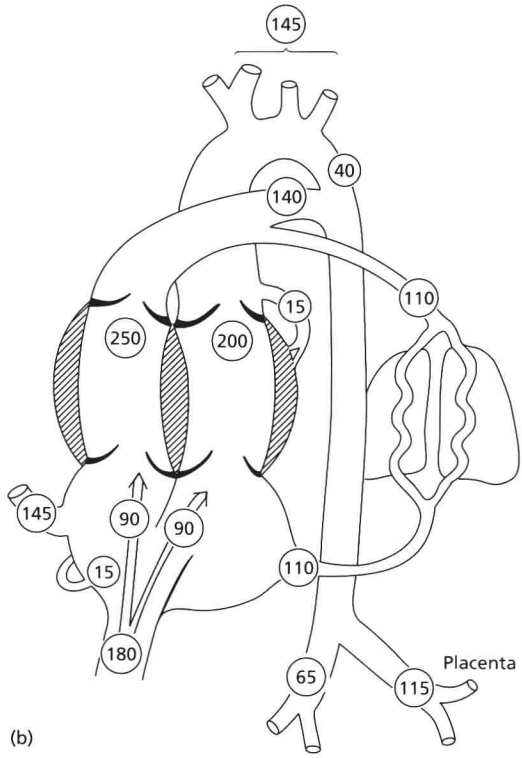
Using ultrasound techniques, blood flow has been estimated in human fetuses based on measurement

Table 1.2 Oxygen consumption by tissues and organs in the late-gestation fetal lamb as a percentage of total consumption, as consumption per 100 g tissue weight, and as consumption per kg fetal weight.

Blood flow	*Percent of total*	*mL/100 g tissue*	*mL/kg fetal weight*
Brain	12	4.0	2.4
Heart	12	8.0	0.8
Liver	23	4.0	1.35
Kidney	4	2.6	0.5
Gut	5	0.4	0.4
Lung	4	0.6	0.25
Skin, muscle, bone	40	0.4	2.8
Total			8.5



(a)



(b)

Figure 1.10 (a) Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels for the late-gestation human fetus. (b) Volumes of blood flowing through cardiac chambers and great vessels for the late-gestation human fetus (mL/min per kg body weight).

of blood flow velocities and vessel diameter. There is considerable potential for error in these measurements and this may explain the variation in reported values for blood flows in published reports. Blood flows have been estimated at various sites; left and right ventricular outputs have been calculated from flow measurements across the mitral or tricuspid valves [10,11], or in the pulmonary trunk or ascending aorta [12–16]. Flows have also been measured through the ductus arteriosus and the

Table 1.3 Comparison of the distribution of blood flows in the sheep and human fetus as percent combined ventricular output (%CVO) and as actual blood flows (mL/min per kg fetal weight).

	Sheep[1]		*Human*[2]	
	%CVO	*mL/min/kg*	*%CVO*	*mL/min/kg*
Combined ventricular output	100	450	100	450
Left ventricular output	34	150	45	202
Aortic isthmus	10	45	8	36
Brain	3.5	16	24	107
Upper trunk, forelimbs	20.5	90	13	59
Right ventricular output	66	300	55	248
Ductus arteriosus	58	260	30	135
Pulmonary circulation	8	36	25	113
Descending aorta	68	305	38	171
Umbilical–placental circulation	40	180	26	112
Hepatic circulation	18	80	14	68
Ductus venosus	22	100	11	44
Lower body organs, hindlimbs	28	125	12	60
Superior vena cava	24	108	37	165
Inferior vena cava + umbilical flow	68	305	38	172
Foramen ovale	25	115	20	90

1 The values for sheep represent those obtained in fetuses in the latter part of gestation [9].

2 The values for human fetuses in the third trimester were obtained by ultrasound [10–17]; in view of the considerable variation in reported measurements, I have selected those I considered most appropriate.

common umbilical vein [17]. From these measurements it has been possible to calculate various other flows. Thus CVO is the sum of right ventricular output (RVO) and left ventricular output (LVO). Pulmonary blood flow is represented by RVO minus ductus arteriosus flow. Pulmonary blood flow has also been calculated from direct measurement of right and left branch pulmonary arteries in some studies [14,16]. Flow through the foramen ovale has been estimated from LVO minus pulmonary blood flow, because blood entering the left ventricles is derived from blood entering the left atrium through the foramen ovale and from pulmonary venous return.

Volume of blood flow ($\dot{Q}$) is determined from the product of average flow velocity (V_m) and cross-sectional area (πD^2). Because diameter (D) of the vessel is measured by ultrasound, the flow is calculated as:

$$\dot{Q} = V_m \times \pi D^2/4$$

It is apparent that, because the diameter is squared, small errors in measuring diameter could create major errors in calculation of flow. This would be a particular problem if vessel diameter is small. Also, in making these calculations, it is assumed that the diameter is constant throughout the cardiac cycle. An additional potential error is that the velocity should be recorded from the center of the vessel at an appropriate angle of insonation; this may be difficult to accomplish because of the position of the fetus in the maternal abdomen. When expressing blood flows in relation to fetal weight, it is necessary to use various formulae, based on age or various fetal measurements to estimate fetal weight and considerable error could be introduced into these calculations.

Table 1.3 shows a comparison of CVO and blood flow per kilogram of fetal weight, in the sheep and human fetus at about 0.8 gestation.

Left and right ventricular output

Estimates of CVO in the human fetus are similar to values measured in sheep fetuses. In the latter third of gestation CVO is about 400–450 mL/kg per min, whereas in earlier gestation it is somewhat higher. This compares with the fetal sheep levels of about 450–500 mL/kg per min. However, the proportions

of combined output ejected by the left and right ventricles are quite different in the human. In the sheep, the ratio of right to left ventricular output is almost 2:1, whereas in the human, measurements vary from 1.2:1 to 1.5:1. The relatively higher proportion of blood ejected by the left ventricle appears to be related to the higher pulmonary blood flow in the human fetus and is important in providing the higher cerebral blood flow in the human fetus.

Cerebral blood flow

The relative weights of some organs are very different in the human compared with the lamb and thus the proportions of CVO distributed to body organs differ. Perhaps the most important factor is brain size; in the mature human fetus the brain constitutes 12% of body weight, as compared with 3% in the late-gestation lamb. It is reasonable to assume that the organ blood flow related to weight is similar in the two species. Near term, both human and sheep fetal body weights are about 3.5 kg, and brain weights are about 65 g in the sheep and 350 g in the human [18]. If it is assumed that blood flow to the brain is similar in relation to tissue weight (120 mL/min per 100 g), total brain flow would be about 80 mL/min in the sheep and about 420 mL/min in the human, or 22 and 120 mL/min per kg respectively in the term fetus (Table 1.4). Study of the proportions of CVO distributed to the brain in the primate versus the sheep show an enormous difference: 16% in the rhesus monkey versus 3–4% in the sheep fetus [19]. In the human fetus it is estimated that, in the third trimester, the brain receives about 24% of CVO. If LVO is 40–45% of CVO, about 25–30% of combined output is available for the peripheral circulation of the head and upper extremities and to traverse the ductus arteriosus to the descending aorta. Thus the proportion of combined output passing across the aortic isthmus is probably about 8%, similar to that in the lamb.

Table 1.4 Comparison of body weight, brain weight, and brain blood flow in the late-gestation lamb and human fetus.

	Lamb	*Human*
Body weight (g)	3500	3500
Brain weight (g)	65	350
Brain blood flow (mL/min per 100 g)	120	120
Total brain blood flow (mL/min)	78	420
Brain flow per kg body weight	22	120

Because cerebral blood flow is much higher in the human fetus, the volume of blood returning to the heart via the superior vena cava is proportionately considerably greater. In the lamb, about 24% of CVO returns via the superior vena cava, but in the human fetus superior vena cava flow probably represents about 37% of CVO ventricular output.

Umbilical–placental blood flow

In fetal lambs, umbilical–placental blood flow constitutes about 38–45% of CVO and is about 180–220 mL/min per kg fetal body weight The higher values are noted in younger fetuses at 0.5–0.75 gestation and the values decrease toward term [9]. A mean of about 55% of umbilical venous blood passes through the ductus venosus, but there is a wide range (20–90%) [3].

Umbilical–placental blood flow is much lower in the human than in the lamb fetus. In fetuses under 32 weeks' gestation it was reported to be about 32% of CVO, but after 32 weeks it fell to only about 21%. Flow was about 130–135 mL/min per kg estimated fetal weight before 32 weeks, but only about 90–100 mL/min per kg after 32 weeks [20]. In another report, umbilical blood flow was higher near term, about 117 mL/min per kg [21]. In the human fetus a mean of only 25–40% of umbilical venous blood passes through the ductus venosus, but there is also a wide range in the proportion [22].

Oxygen consumption in the human and lamb fetus is similar at about 7–9 mL/min per kg fetal weight. Umbilical venous oxygen saturations are about 80–85% in both the lamb and human fetus and umbilical arterial oxygen saturations are also similar at about 50%. The ability of the human fetus to maintain the same oxygen uptake per kilogram as the lamb when umbilical blood flow is about half as great is related to the much higher hemoglobin concentration and oxygen capacity in human fetal blood. Hemoglobin concentration in the human is about 16.5 g/dL with an oxygen capacity of 22.5 mL/dL near term compared with hemoglobin concentration of 8–9 g/dL and oxygen capacity of about 11–12 mL/dL in the sheep.