1 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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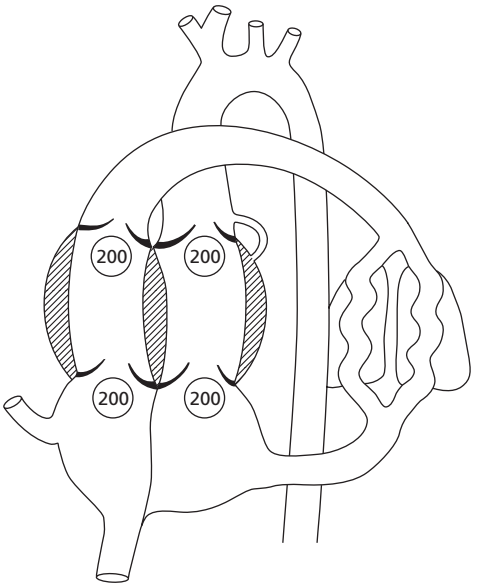

Figure 1.1 Course of blood flow in the adult circulation. The volumes of blood ejected by each ventricle and returning to each atrium are similar postnatally.

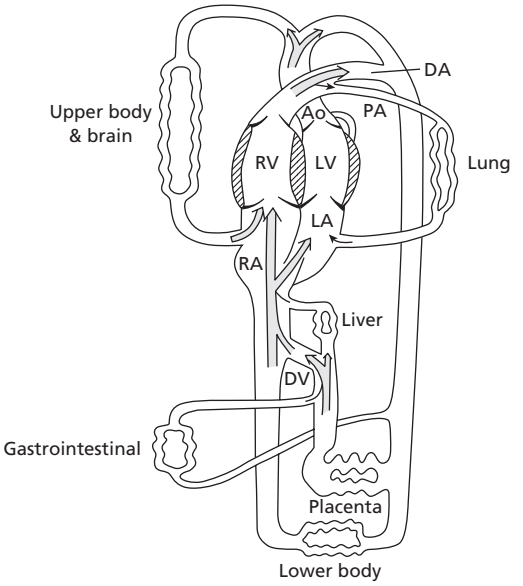

Figure 1.2 The general course of the mammalian fetal circulation. Ao, aorta; DA, ductus arteriosus; DV, ductus venosus; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

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

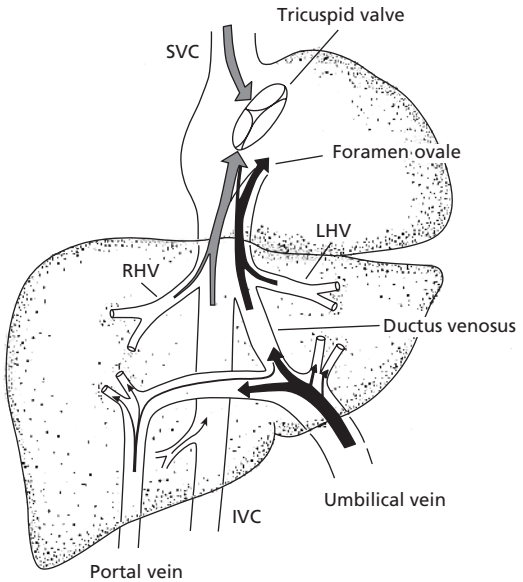

Figure 1.3 Course of blood flow in the region of the porta hepatis. Umbilical venous blood is distributed to the left lobe of the liver. The ductus venosus arises from the umbilical vein, which then arches to the right to join the portal vein. Portal venous blood is largely distributed to the right liver 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).

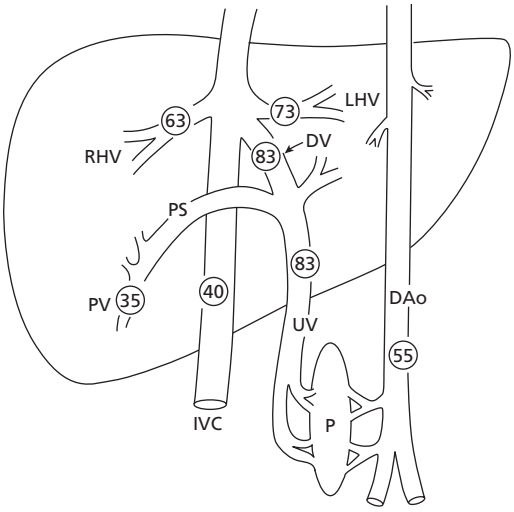

Figure 1.4 Blood oxygen saturations are shown in vessels in the region of the liver in the fetal lamb. DAo, descending aorta; DV, ductus venosus; IVC, inferior vena cava; LHV, left hepatic vein; P, placenta; PS, portal sinus; PV, portal vein; RHV, right hepatic vein; UV, umbilical vein.

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

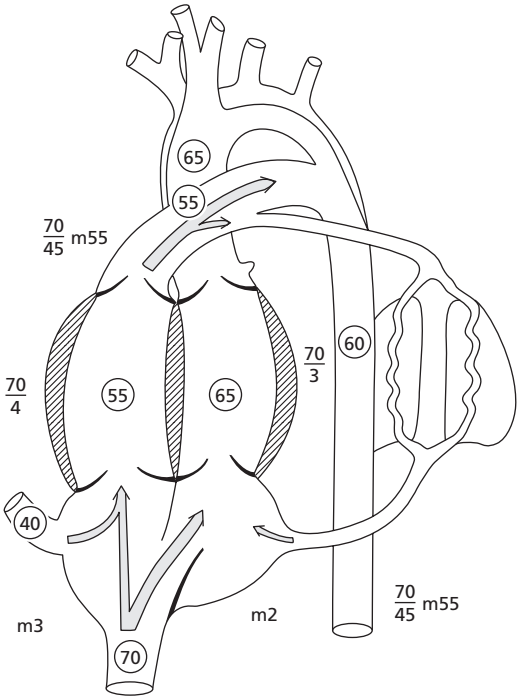

Figure 1.5 Course of the circulation in the heart and great vessels in the late-gestation fetus. The figures in circles within the chambers and vessels represent percent oxygen saturation levels. The figures alongside the chambers and vessels are pressures in mmHg related to amniotic pressure level as 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

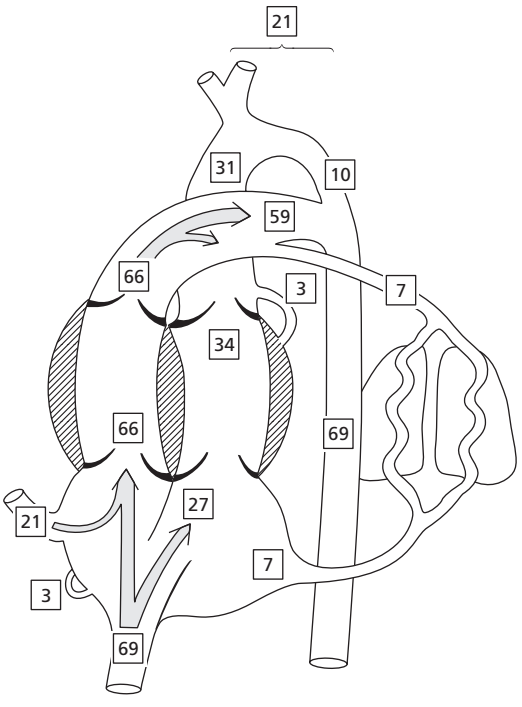

Figure 1.6 Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels. Figures represent values for late-gestation lambs.

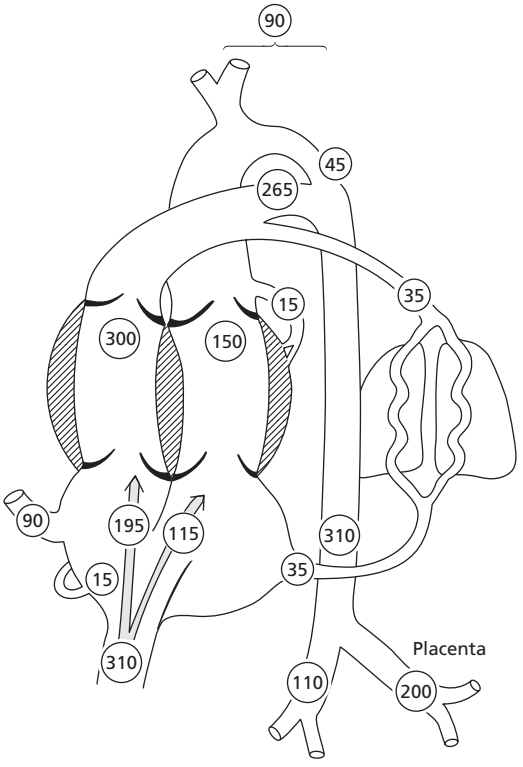

Figure 1.7 Volumes of blood (mL/min per kg body weight) flowing through cardiac chambers and great vessels in the late-gestation fetal lamb.

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

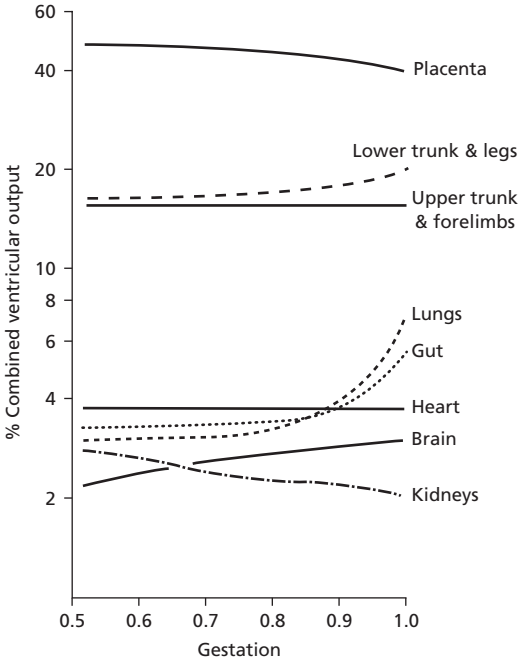

Figure 1.8 Changes in the percentage of fetal combined ventricular output distributed to various organs, body and limbs and the placenta at different gestational ages in the fetal lamb.

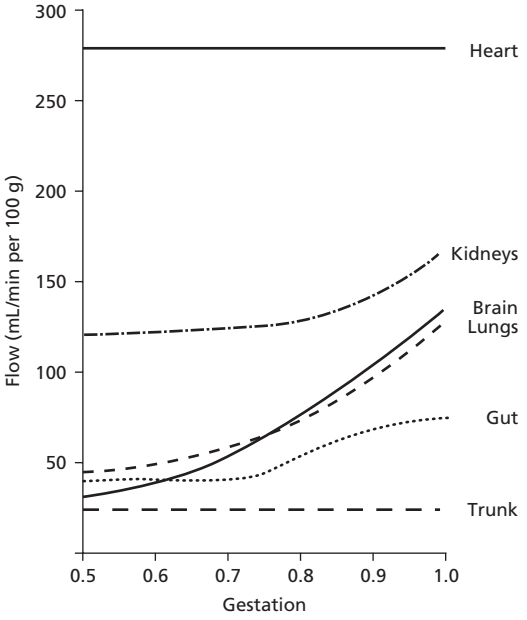

Figure 1.9 Changes in actual blood flow to various organs in the lamb during the latter half of gestation.

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

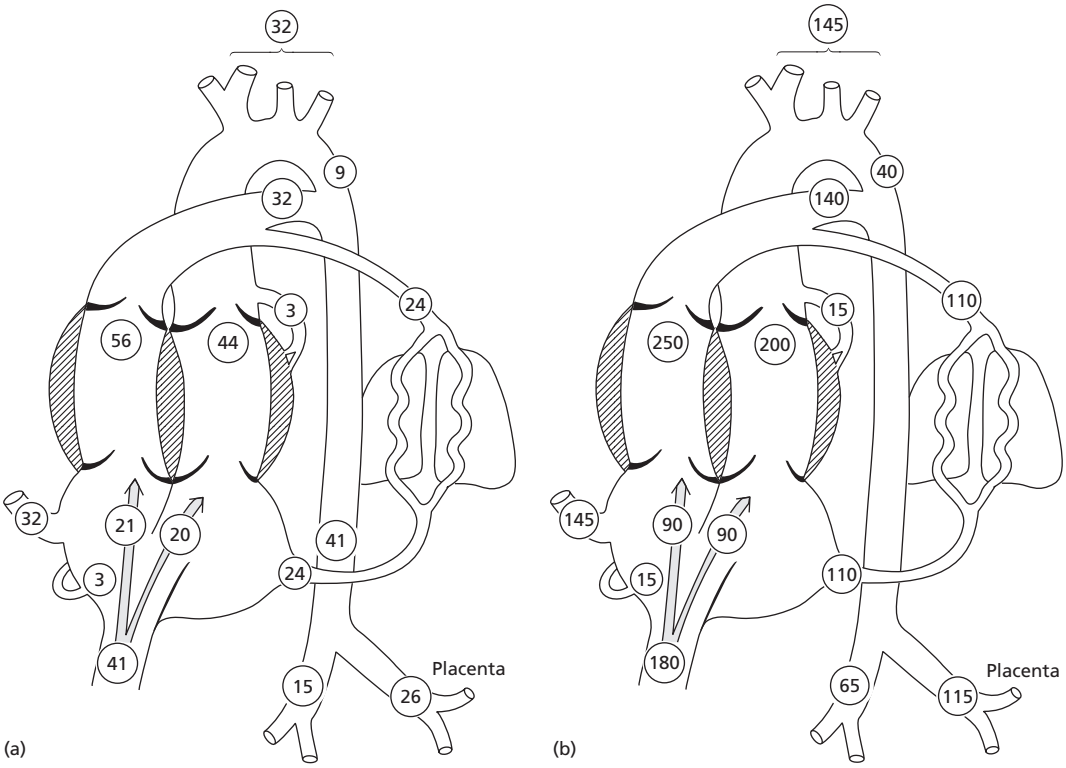

Figure 1.10 (a) Percentages of combined ventricular output that return to the fetal heart, that are ejected by each ventricle, and that flow through the main vascular channels for the late-gestation human fetus. (b) Volumes of blood flowing through cardiac chambers and great vessels for the late-gestation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

Pulmonary blood flow

In fetal lambs less than 0.8 gestation (120 days), only 3.5–4.0% of CVO is distributed to the lungs; after this there is a gradual increase to 7–9% at term (~145 days). Actual flow to the lungs is about 18–20 mL/min per kg fetal weight below 0.8 gestation and about 35–40 mL/min per kg at term. Reported values for pulmonary blood flow in human fetuses vary considerably. As mentioned above, in most reports pulmonary flow has been estimated as the difference between RVO and ductus arteriosus flow. Therefore possible errors in measurement of RVO or ductus arteriosus flow would tend to create variability in pulmonary flow. In those studies in which both left and right branch pulmonary artery flow was measured, errors in measurement in the two arteries could result in variability in estimation of total flow. It is thus not surprising that the magnitude of pulmonary blood flow in the human fetus has been reported to range from about 11% [15] to as much as 22–25% [12,14] of CVO. An increase in the proportion of CVO distributed to the lungs with advancing gestation has been reported [14]. In human fetuses less than 20 weeks' gestation, only about 13% entered the lungs, but after 32 weeks the lungs received 25% of CVO. Reported actual blood flow values would thus vary between 45 and about 120 mL/min per kg fetal weight.

Foramen ovale blood flow

Because of the complex velocity flow contour and the inability to define diameter of the foramen ovale, blood flow cannot be measured accurately by ultrasound in the human fetus. Foramen ovale flow, estimated from LVO minus pulmonary blood flow, constitutes about 30% of CVO in the fetal lamb [23]; it is slightly lower in younger fetuses and slightly higher in older fetuses. Reports in human fetuses vary considerably. In one study foramen ovale flow was about 30–33% of CVO in fetuses at all gestational ages [16]. However, in other reports it was about 18% of combined output before 20 weeks, but about 34% of combined output after 32 weeks' gestation [15].

Ductus arteriosus blood flow

In the lamb fetus about 90% of blood ejected by the right ventricle is directed through the pulmonary trunk and ductus arteriosus to the descending aorta. Thus more than half of CVO passes through the ductus. In the human, only about 55% of RVO passes through the ductus. RVO is also relatively lower than in the lamb so the proportion of CVO traversing the ductus is only about 30%.

Thus the major differences between the sheep and human fetus are more evident in the latter period of gestation and are characterized by the much greater cerebral and pulmonary blood flows and much lower umbilical–placental blood flow relative to fetal weight. The high cerebral flow accounts for the greater LVO in the human; because umbilical blood flow is derived largely from blood passing across the ductus arteriosus to the descending aorta, the low umbilical flow in the human accounts for the smaller flow across the ductus arteriosus and the lower RVO compared with the lamb.

Hepatic and ductus venosus blood flows

The pattern of flow in the liver region appears to be similar in the human and lamb fetus. Ultrasound examination of fetal lambs showed a blood flow velocity of 55–60 cm/s in the ductus venosus, whereas abdominal inferior vena cava velocity was only about 16 cm/s [6]. The ductus venosus stream was directed preferentially through the foramen ovale (see above). In the human fetus, blood flow velocity in the ductus venosus has been reported to be 65–75 cm/s, and the ductus venosus stream also flows preferentially through the foramen ovale [24].

Factors affecting perinatal cardiac output

Cardiac ventricular output is the product of heart rate and stroke volume. Stroke volume is determined by preload, afterload, and myocardial contractility. In isolated myocardial strips, the initial length of the myocyte, which determines sarcomere length, influences the force of muscle contraction. In the intact heart, ventricular volume at end diastole determines sarcomere length and the force of contraction and is the basis of the Frank–Starling mechanism. An increase in initial length or increase in end-diastolic ventricular volume increases the force of contraction of the muscle and, in the intact heart, increases stroke volume if other factors are

unchanged. Afterload, or load on the muscle during development of active force, determines the degree of shortening. In the intact circulation, afterload is influenced by several factors (e.g., arterial pressure, compliance of the arterial system, and peripheral vascular resistance). In isolated myocardial strips, the greater the load on the muscle, the less the degree of muscle shortening. In the intact heart, an increase in afterload results in a reduction in stroke volume. Contractility is the intrinsic force of contraction of the muscle; with isolated muscle, increased contractility increases force developed and, in the intact heart, increases stroke volume, or developed pressure. In the cardiovascular system, a change in one factor influencing ventricular output may affect other parameters. It is therefore important to consider possible changes in these other parameters when assessing the effects of alteration of one regulatory factor.

Effects of heart rate

In the adult, cardiac output is relatively constant over a wide range of heart rates. Increasing heart rate to 150/min or decreasing it to 50/min from a resting rate of about 70/min does not alter output. Greater increases in heart rate may decrease cardiac output because the reduction in diastolic filling time does not permit adequate filling to maintain stroke volume. With very slow heart rates, stroke volume is increased to maintain cardiac output, but when maximal diastolic filling has been achieved, further slowing results in a decrease of ventricular output.

In studies in fetal sheep, spontaneous increases in heart rate above the resting level of about 160/min are associated with increases of ventricular output of up to 15–20%, and spontaneous decreases in heart rate results in a fall in output [25]. Because the cause of the spontaneous heart rate change was not known, it cannot be assumed that heart rate variation alone was responsible for the changes in ventricular output. For example, an increase in heart rate may be related to fetal activity or the onset of fetal respiratory movement. This may induce changes in sympathetic nervous activity that may affect myocardial contractility as well as heart rate. The effects of electrical pacing of the right or left atrium to increase rates to 240–300/min were studied in fetal lambs [25]. Pacing the atrium resulted in an increase in LVO of up to 15%, with only a small increase or no change in RVO. At rates above 300–320/min, ventricular output fell progressively with increasing rate, presumably because diastolic filling time is markedly reduced. RVO increased when the left atrium was paced, but LVO fell, often dramatically, by 50% or more. Normally the pressure pulses of the right and left atria are similar in the fetus, with a dominant *a* wave in both chambers; right atrial is slightly higher than left atrial pressure in all phases of the cardiac cycle. During pacing the left atrial pressure pulse is altered so left atrial pressure exceeds that in the right atrium during some phases of the cycle and interferes with flow through the foramen ovale into the left atrium, reducing left ventricular filling and output.

Vagal stimulation decreases both RVO and LVO; when heart rate falls from a resting level of 160/min to about 120/min, output decreases by 15–20%. Stroke volume increases slightly, but not adequately to maintain output as rate falls. Vagal stimulation results in an increase in systemic arterial pressure and a rise in intrapleural pressure in the fetus. The increase in arterial pressure causes an elevation of afterload and the increase in intrapleural pressure could reduce venous return to the heart. Thus the fall in ventricular output may not be the result of the bradycardia but of the associated changes.

Effect of preload and afterload

Preload and afterload are discussed together because there is usually an interaction between them in the intact circulation. If afterload is increased, the volume ejected by the ventricle during systole is reduced and residual ventricular volume increases. If ventricular filling is maintained, preload is greater with the next beat. *In utero* studies of fetal lambs have been performed to assess the role of preload on cardiac output. In most of these studies, ventricular end-diastolic or atrial pressures have been used as an index of preload. However, pressure measurements may not be a reliable indicator of volume, because ventricular compliance determines the volume at any particular pressure. Studies in isolated myocardium and intact hearts have shown that fetal myocardium is less compliant than that of the adult.

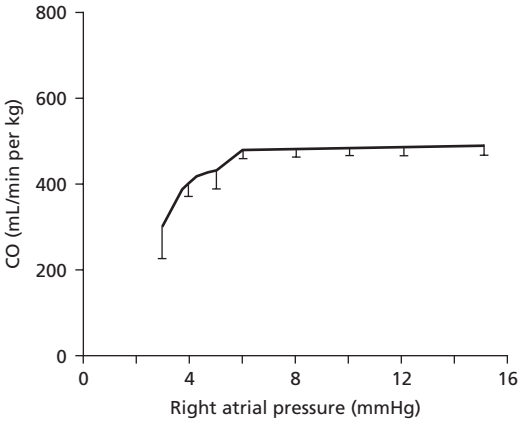

Figure 1.11 Changes in cardiac output (CO) associated with acute reduction of atrial pressure by blood removal and increase in atrial pressure by infusion of electrolyte solution in fetal lambs [26].

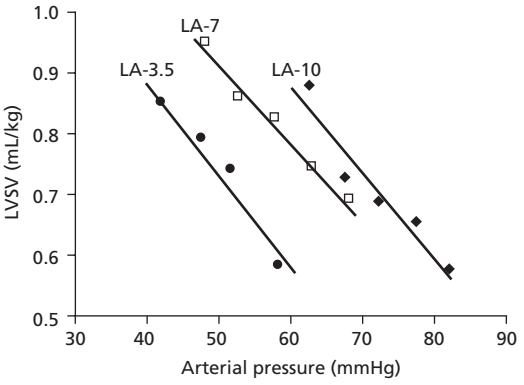

Figure 1.12 When systemic arterial pressure is regulated, an increase in pressure results in a decrease in left ventricular stroke volume (LVSV) at fixed left atrial pressure. At any level of arterial pressure, an increase in left atrial pressure increases left ventricular stroke volume.

Several investigators have studied the effects of decreasing or increasing preload in fetal lambs *in utero*. The preload was decreased by reducing fetal blood volume by removal of blood and increased by rapid intravenous infusion of electrolyte solution. A fall in right atrial and right ventricular end-diastolic pressure resulted in a marked decrease in ventricular output. Output rose when ventricular end-diastolic or atrial pressure increased by 2–4 mmHg above resting levels, but further increases in filling pressure did not result in greater output by the ventricle [26] (Figure 1.11).

This response is distinctly different from that of the adult heart, in which increases in atrial pressure to 15–20 mmHg are associated with a progressive increase in ventricular output. Based on these studies, it was proposed that the fetal heart is normally operating near the top of its ventricular function curve, so that a fall in preload results in a decrease in output. However, the rise in output associated with an increase in preload is limited because myocardial performance, or contractility, is relatively poor in the fetus.

In these studies, the effects of rapid infusion of electrolytes on arterial pressure were not considered. Associated with the infusion, fetal arterial pressure also increased and thus affected afterload. We examined the effects of changing preload at various constant levels of arterial pressure. Arterial pressure elevation dramatically reduced left ventricular stroke volume at all levels of mean atrial pressure [27] (Figure 1.12). At constant arterial pressure levels, progressive elevation of left atrial pressure increased left ventricular stroke volume even with atrial pressures as high as 10–15 mmHg. This study demonstrated that the fetal heart does respond to increases in preload by increasing its output. It did not, however, resolve whether performance of the fetal and adult myocardium are comparable.

Myocardial contractility

Studies of isolated myocardium from fetal and adult sheep have demonstrated that fetal myocardium develops less active tension than adult myocardium at similar muscle lengths. The maximal force that can be generated is considerably lower for fetal than for adult myocardium. Several differences in morphological and biochemical parameters of myocardium have been described that could account for the lesser contractility of fetal myocardium. Friedman [28] suggested that fetal myocardium contains fewer sarcomeres, or contractile units, in each myocyte. Also, as mentioned above, the parallel orientation of the myofibrils has not developed during early gestation.

Another factor that may be important is the development of the sarcoplasmic reticulum, which regulates movement of calcium ions essential for myocardial contraction. The fetal myocardial

sarcoplasmic reticulum is well developed, but the T-tubular system, representing the extension of the sarcoplasmic reticulum to provide closer relations with the contractile elements, is either poorly developed or absent in immature myocardium. Not only are there structural differences in sarcoplasmic reticulum, but in studies with isolated sarcoplasmic reticulum vesicles calcium uptake was found to be impaired in fetal myocardium [29].

Local release of norepinephrine at sympathetic nerve endings is an important mechanism for increasing myocardial contractility. Morphological studies of fetal hearts using monoamine oxidase fluorescence have demonstrated absent or poor sympathetic innervation of the immature myocardium. The abundance of sympathetic nerve endings varies greatly at different periods of gestational and postnatal development among species. In the guinea pig, myocardial sympathetic innervation is almost fully developed at birth, whereas in the rabbit and rat there is almost no innervation at birth (it develops within 14–21 postnatal days). The sheep fetus has no detectable sympathetic innervation at 75 days (mid-gestation), but innervation begins to appear at 90–100 days and is abundant but not yet fully developed just before birth.

In addition to the difference in sympathetic innervation, possible differences in β-adrenergic receptor concentration in fetal and adult myocardium have been postulated. Although these differences in sympathetic innervation and β-adrenoceptor concentration may not be important in the resting fetal heart, they could influence the ability to respond to stress.

Circulatory regulation in the fetus

In the adult the systemic and pulmonary circulations are separate. Each ventricle is subjected to potentially different preload and afterload, and the stroke volume of each ventricle could vary greatly. The Frank–Starling mechanism is useful for adjusting the outputs of the two ventricles so that over a short period the ventricles eject similar volumes. A reduction in venous return to the right atrium reduces filling pressure and end-diastolic volume of the right ventricle, resulting in a decrease in stroke volume. Pulmonary blood flow and venous return to the left atrium and ventricle is reduced and stroke volume falls. An increase in systemic arterial pressure will restrict left ventricular stroke volume; end-diastolic volume will increase so that, with the next beat, greater force is generated to increase stroke volume.

In the fetus the presence of the foramen ovale tends to make right and left atrial pressures equal throughout the cardiac cycle. The ductus arteriosus provides a large communication between the aorta and pulmonary artery, which causes the pressures to be almost identical. In view of the similar atrial pressures and similar aortic and pulmonary arterial pressures, the differences in stroke volumes of the left and right ventricles in the fetal lamb are difficult to explain. Differences in afterload of the two ventricles could explain this. The aortic isthmus, which in the fetus is narrower than the ascending and descending aorta, might functionally separate the upper and lower body circulation to some extent. The left ventricle ejects into the ascending aorta and the vessels of the head and neck, a circulation that would be poorly compliant and have a relatively high vascular resistance. The right ventricle ejects into the pulmonary trunk and directly through the large ductus arteriosus into the descending aorta and its branches. This circulation would have a higher compliance and a lower resistance because it includes the umbilical–placental vasculature. This functional separation of the aorta at the isthmus has been demonstrated in fetal lambs. Rapid reduction in peripheral vascular resistance in the lower body circulation induced by a vasodilator causes a decrease in descending aortic pressure and an increase in right ventricular stroke volume for several beats, whereas ascending aortic pressure and LVO do not change. Similarly, injection of a vasodilator into the ascending aorta causes an evanescent decrease of ascending aortic pressure and increase in left ventricular stroke volume.

Baroreflex regulation

In the adult the arterial baroreflex modulates arterial pressure over a fairly narrow range. When arterial pressure is increased, the aortic and carotid baroreceptors respond, inducing reflex bradycardia, depression of myocardial contractility, and peripheral vasodilatation, all of which tend to decrease arterial pressure. When the aortic and carotid baroreflexes are abolished by bilateral

section of the aortic and carotid afferent nerves, there is initially an increase in resting heart rate and arterial pressure, but within 1–2 days these parameters return to average levels present during the pre-denervation period. Wide swings of arterial pressure and heart rate occur around the average pressure and rate, in association with stimuli that produce small changes in the normal animal [30]. Arterial baroreceptors are functional in the fetus relatively early in gestation. In the fetal lamb, baroreflex sensitivity increases with gestational age from about 80 days' gestation; near term, it is as sensitive as in the neonate and adult in terms of the bradycardia induced by arterial pressure increase [31]. In fetal lambs, sinoaortic denervation results in the same wide variation in heart rate and blood pressure observed in adult animals. The variability is similar in fetal lambs and adult sheep, indicating that the baroreflex is fully operative in regulating arterial pressure in the late-gestation fetal lamb.

Chemoreflex regulation

Based on studies in acutely exteriorized lambs, it was proposed that the aortic and carotid chemoreceptors are relatively inactive in the fetus. However, more recent studies in fetal lambs have shown that they are active, at least in the latter third of gestation [32]. Responses to carotid chemoreceptor stimulation are much greater than to aortic receptor stimulation. The chemoreceptors are stimulated by hypoxemia and can be activated experimentally by intravascular injection of small doses of sodium cyanide. The cardiovascular response dominates, with bradycardia and immediate hypotension, but respiratory gasps are noted. The bradycardia can be abolished if the lambs are pretreated with atropine, indicating that the bradycardia is induced by vagus nerve stimulation. Confirmation that the cyanide response is the result of chemoreceptor stimulation was obtained by demonstrating the loss of the cardiovascular and respiratory responses in fetal lambs in which sinoaortic denervation had been accomplished [32].

In the adult, chemoreceptor stimulation may be associated with reflex peripheral vasoconstriction. This response has not been studied adequately in the fetus, but it can be inferred that the marked vasoconstriction induced in the peripheral circulation during hypoxia in fetal lambs (see below) is partly the result of chemoreceptor stimulation. It is apparent from studies in the fetal lamb that chemoreflex responses are different from those in the adult. The respiratory response in the adult animal dominates, whereas only minor and unsustained respiratory response results in the fetus. Whether it is due to a difference in chemoreceptor response or a difference in central response has not been resolved.

Fetal circulatory response to reduced oxygen delivery

The mechanisms responsible for decreased oxygen supply to the fetus and the effects on oxygen uptake and delivery are discussed in Chapter 3.

Heart rate and blood pressure response

In fetal lambs beyond about 110 days' gestation (term about 145 days), acute hypoxemia results in bradycardia and arterial hypertension. In one study a change of 4–5 mmHg in carotid arterial blood was necessary to produce bradycardia. Boekkooi *et al.* [33] have shown that the magnitude of the bradycardia is directly related to the degree of fall in oxygen saturation of carotid arterial blood. The bradycardia induced by hypoxemia can be abolished by atropine administration, indicating that it is induced reflexly through vagal stimulation. With extreme changes in Po_2 to levels below about 12 mmHg, the bradycardia cannot be completely prevented by atropine. It has been proposed that severe hypoxemia has a direct depressant effect on the heart that causes bradycardia. The hypothesis had been proposed that hypertension was the primary change, related to catecholamine-induced vasoconstriction, and that the bradycardia was a baroreflex response. However, as has been mentioned above, the bradycardia is the result of chemoreceptor stimulation. In chronic sinoaortic denervated fetal lambs, hypoxemia does not induce bradycardia even though it results in progressive hypertension.

With prolonged fetal hypoxemia, heart rate gradually increases although it does not usually achieve control values. The mechanism for this recovery is not defined, but it could be due to resetting of chemoreceptor sensitivity.

Cardiac failure in the fetus

Prior to the examination of fetuses *in utero* by ultrasound, it was thought that some stillborn fetuses with gross edema had cardiac malformations. With the advent of ultrasound it is now recognized that hydrops fetalis is frequently due to cardiovascular disturbances. Although decreased ventricular ejection, suggesting impaired cardiac function, can be recognized by ultrasound examination, the diagnosis of cardiac failure is usually made when the fetus is seen to have hydrops. Many conditions other than cardiovascular disturbances are associated with hydrops fetalis, including erythroblastosis fetalis due to Rh or other incompatibilities, severe anemia, hepatic dysfunction, and genetic conditions such as Turner syndrome. Cardiovascular factors associated with hydrops fetalis are listed in Table 1.5.

The hemodynamic feature common to all these causes of fetal hydrops is an increase in systemic venous pressure. We have shown experimentally in fetal lambs that acute constriction of the ductus arteriosus elevates right atrial and vena cava pressures. Increases in ventricular output associated with volume loading are also associated with an increase in right atrial pressure. Electrical pacing of the left or right atrium in fetal lambs alters the pressure contour and also raises right atrial and venous pressures. Bradycardia induced by stimulation of the vagus nerve is also associated with raised venous pressure.

It is of interest that, postnatally, the usual manifestation of cardiac failure is respiratory distress resulting from elevated pulmonary venous pressure and increased fluid transudation into the lungs. However, in the fetus, pulmonary edema is an unusual manifestation of cardiac failure. This can be accounted for by several factors.

- Pulmonary arterioles are markedly constricted and limit pulmonary blood flow as well as transmission of arterial pressure into the capillaries.
- A rise in left atrial pressure is limited by the presence of the foramen ovale. If left atrial pressure should tend to increase, flow through the foramen ovale would be reduced, thus preventing significant elevation of left atrial pressure.
- The intrathoracic pressure is positive in the fetus because intraamniotic pressure is transmitted to the fluid-filled lung. Postnatally, intrapleural pressure becomes negative, thus increasing the pressure differences across capillaries and favoring fluid transudation.

Increased fluid accumulation in the lung of the fetus is manifested as pulmonary lymphangiectasia. This occurs only in those conditions in which pulmonary venous pressure can be raised to high levels, such as total pulmonary venous drainage with obstruction and aortic or mitral atresia with a small or closed foramen ovale.

Table 1.5 Cardiovascular disturbances associated with the development of fetal hydrops.

Obstructive lesions
Small or closed foramen ovale
Constricted ductus arteriosus
Atrioventricular valve insufficiency
High cardiac output states
Sacrococcygeal teratoma
Parasitic fetus
Twin-to-twin transfusion
Anemia
Decreased myocardial function
Arrhythmias

Factors contributing to hydrops in the fetus

The fetus is greatly affected by even small increases in venous pressure. This is due to several features that favor accumulation of fluid in fetal tissues, as compared with postnatally. Body water content is considerably greater in the fetus than in the adult. Furthermore, the proportion of extracellular fluid is much larger in the fetus. The lower the gestational age, the greater the relative amount of body water, as well as the proportion of extracellular fluid (Figure 1.13). The extracellular space in the fetus is capable of accommodating a much greater volume as compared with postnatally, with a lower tissue pressure, because tissue turgor is less.

The factors regulating movement of fluid between the circulation and the extravascular or extracellular space are expressed in the Starling law of the capillary:

$$Q_s = K_f[(P_c - P_i) - \sigma(\pi_c - \pi_i)]$$

where Q_s represents fluid movement across the capillary, K_f fluid filtration coefficient (mL/min per

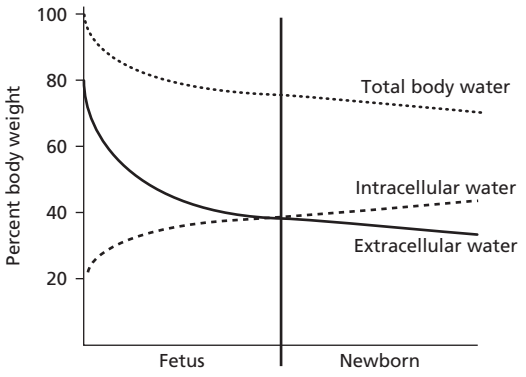

Figure 1.13 Changes in total body water, extracellular fluid and intracellular fluid during prenatal and postnatal development.

mmHg), P_c capillary hydrostatic pressure, P_i interstitial hydrostatic pressure, σ reflection coefficient, π_c capillary osmotic pressure, and π_i interstitial osmotic pressure.

In the adult, pressure at the arterial end of the capillary is about 45 mmHg and at the venous end about 15 mmHg. No measurements are available for the fetus, but based on arterial and venous pressures, they can be estimated to be about 30 mmHg at the arterial end and about 5 mmHg at the venous end of the capillary (Figure 1.14). Colloid osmotic pressure is largely related to plasma albumin concentration, which is considerably lower in the fetus than postnatally. The albumin concentration increases with gestational age so that the younger the fetus, the lower the colloid osmotic pressure. In Figure 1.14 the osmotic pressure in the fetus is depicted as being considerably lower in the fetal than the adult capillary.

Tissue turgor in the fetus is not known, but it is considerably lower than postnatally; it has been assumed to be 2 mmHg in Figure 1.14. In the adult capillary, there is a balance of hydrostatic and osmotic pressures so that most fluid transferred to the tissue space at the arterial end returns to the intravascular space at the venous end (Figure 1.14). Only a small volume is removed from the extracellular fluid by the lymphatic system. However, in the fetus, based on information regarding the volume of lymph flow (see below), a relatively large amount is removed by this means. It is therefore likely that there is a net movement of fluid out of the capillary into the extracellular space.

The filtration coefficient (see Chapter 1) is determined by the capillary membrane; in the fetus, the capillary is more permeable not only to fluid but also to protein. An elevation of venous pressure will increase the force driving fluid into the tissue space, which has a very large capacity in the fetus. In addition, the low colloid osmotic pressure may be further reduced by movement of albumin across the capillary membrane into the tissue space. Compared with the adult, where the difference in hydrostatic and colloid osmotic pressure is about 15 mmHg, the difference in the fetus is less. Therefore, elevation of venous pressure by only 2–3 mmHg, which does not appear to be very significant, may have a profound influence in increasing extracellular fluid volume.

An additional mechanism by which increased venous pressure may exaggerate the amount of extracellular fluid is by reducing lymphatic flow. In the adult sheep, left thoracic duct lymph flow is about 50 mL/kg per 24 hours; in the fetal lamb, it is

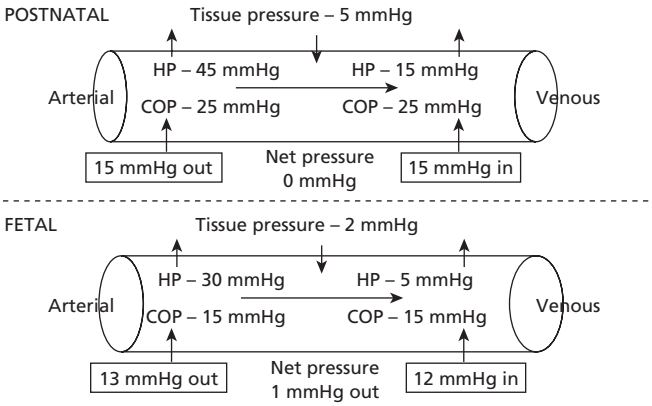

Figure 1.14 Factors affecting fluid transfer across capillary membranes during the postnatal and prenatal periods. COP, colloid osmotic pressure; HP, hydrostatic pressure.

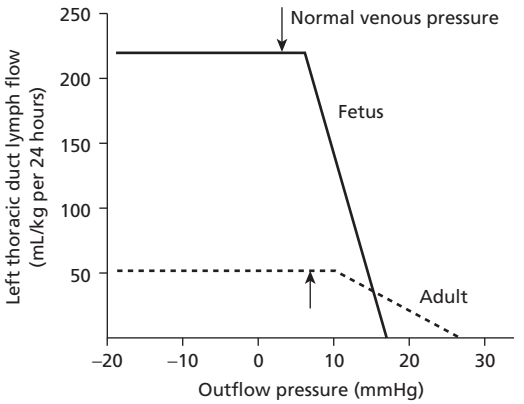

Figure 1.15 Effects of increasing venous pressure on left thoracic lymph flow in the fetal and adult sheep.

about 250 mL/kg per 24 hours. Elevation of venous pressure has a much greater effect in reducing lymph flow in the fetus than in the adult. This has been well demonstrated by Brace and is depicted in Figure 1.15. Not only does a similar increase in venous pressure have a more dramatic effect in reducing lymph flow in the fetus, but flow ceases at venous pressures of about 15 mmHg, whereas in the adult flow stops at pressures of 25–30 mmHg [34,35].

Thus any cardiovascular disturbance that increases fetal systemic venous pressure is likely to induce fetal edema. The factors that contribute to the development of hydrops as a manifestation of fetal cardiac failure are shown in Table 1.6.

Hormonal factors may also play a role in the increase in extracellular fluid volume. An increase in fetal venous pressure induces elevation of plasma arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) concentrations. The reduction in arterial pressure that may occur if fetal cardiac output falls results in elevation of plasma AVP and angiotensin II concentrations. AVP decreases urinary output and, in the late-gestation fetus, reduces lung fluid production. ANP increases urinary output, but increases capillary permeability. Angiotensin II increases fetal fluid accumulation.

Table 1.6 Factors contributing to edema formation in the fetus.

High compliance of interstitial space: allows accommodation of large volume at low tissue pressure
High capillary filtration coefficient: allows large water flux at low vascular pressure
Low colloid osmotic pressure: reduces fluid movement from interstitium to capillary
High capillary permeability to protein: reduces fluid movement from interstitium to capillary
Sensitivity of lymphatic drainage to increased venous pressure: decreases removal of fluid from interstitium via lymphatic channels

Congenital cardiovascular malformations and the fetal circulation

It has long been recognized that congenital cardiovascular malformations may influence the development of the fetal circulation. In recent years ultrasound examination has provided the opportunity to assess the changes in circulatory development associated with advancing gestation. It has also become apparent that gestational changes in development and responses of the fetal circulation may affect the influence of various cardiovascular anomalies. The principal mechanisms by which congenital cardiovascular anomalies may affect fetal circulatory development are discussed in this section. Detailed considerations of these effects are presented in the chapters dedicated to individual lesions.

Cardiovascular malformations may:

- cause hydrops fetalis by increasing venous pressure (discussed above);
- change the volume or direction of blood flow;
- cause obstruction to blood flow;
- alter the oxygen saturation of blood delivered to various organs.

Changes in blood flow

Ventricular development

Interference with blood flow into or out of the left or right ventricle has for some time been thought to interfere with its development. Restriction of the foramen ovale or mitral orifice reduces blood flow into the left ventricle and results in hypoplasia as a result of the decreased volume in the chamber.

Experimental reduction of inflow of blood into the left ventricle of the fetal lamb for at least several days interferes with growth of the chamber [36].

Obstruction of outflow from a ventricle postnatally restricts ejection and induces enlargement as a result of the increased end-systolic volume. Atrial filling pressure increases and this helps to maintain stroke volume of the ventricle. Hypertrophy then ensues but ventricular volume is not significantly different from normal. In the fetus, the foramen ovale provides a large communication between the right and left atria. Aortic or pulmonary stenosis interferes with outflow of the left or right ventricle respectively and restricts the stroke volume of the affected chamber. Ventricular muscle mass increases in response to the increased systolic pressure. However, unlike postnatally, left or right atrial pressure does not increase significantly because of the presence of the foramen ovale. Venous return is diverted away from the ventricle with obstructed outflow and preferentially enters the ventricle with the greater diastolic compliance.

The total CVO can be maintained at normal levels, but ejection is increased from the normal ventricle and reduced from the obstructed chamber. We induced outflow obstruction of the left ventricle in fetal lambs by placing a constriction around the ascending aorta; this resulted in increased left ventricular muscle mass but a substantial reduction in the size of the left ventricle within just a few days [36]. These studies are discussed in Chapter 10. We induced pulmonary stenosis in fetal lambs at about 60 days' gestation by placing a band around the pulmonary trunk. The lambs were allowed to develop *in utero* and studied at about 120 days' gestation. Right ventricular muscle mass was greatly increased but, in the majority of fetuses, the size of the cavity of the ventricle, as well as the diameter of the tricuspid valve, were markedly reduced. The findings are reviewed in detail in Chapter 15.

Ascending aorta and aortic arch development

In fetal lambs, the left ventricle ejects about one-third of CVO, and about two-thirds of blood entering the ascending aorta is distributed to the brain and upper body. Thus only about 10% of CVO passes through the aortic isthmus. The relatively low blood flow through this segment is reflected by the fact that the diameter of the isthmus is only about half that of the ascending aorta.

In the human fetus, the left ventricle ejects about 45% of CVO. The volume passing through the aortic isthmus is not known, but it appears to be similar to that in the lamb and thus accounts for the fact that the diameter of the isthmus is also about 75% of that of the ascending aorta.

The diameter of the ascending aorta is affected by the magnitude of blood flow. Thus in the fetus with aortic atresia, no blood enters the aorta from the left ventricle, but flow occurs retrograde from the ductus arteriosus across the arch to the ascending aorta. The flow conducted by the ascending aorta is only that passing to the coronary circulation and the vessel is quite hypoplastic (see Chapter 11).

In the fetus with pulmonary atresia, no blood can be ejected by the right ventricle. All blood returning to the right side is directed through the foramen ovale and joins pulmonary venous return to the left atrium. Thus the total CVO is ejected into the ascending aorta. In the lamb, this would represent a flow about three times normal and in the human fetus a flow somewhat higher than twice normal. This high flow is associated with an aortic diameter considerably greater than normal (see Chapter 15).

Ductus arteriosus size and orientation

Normally, almost 60% of CVO traverses the ductus arteriosus from the pulmonary trunk to the descending aorta in the fetal lamb. In the late-gestation human fetus, flow is also exclusively from the pulmonary trunk to the descending aorta, although only about 30% of CVO passes through the ductus. Because a large volume is ejected by the right ventricle, the pulmonary trunk is large and, as a result of the direction of flow through the ductus, the inferior angle between the ductus and the descending aorta is oblique.

When RVO is markedly reduced, or completely obstructed, as with pulmonary atresia, flow into the pulmonary trunk is relatively low and is supplied by retrograde flow from the descending aorta across the ductus arteriosus. This results in poor development of the main pulmonary artery, and possibly the ductus arteriosus and the direction of flow in the ductus results in an acute inferior angle of the ductus with the descending aorta.

Conversely, severe reduction or curtailment of LVO, as in the presence of aortic atresia, results in hypoplasia of the ascending aorta (see above). If LVO is completely obstructed, the right ventricle

ejects a much larger volume than normal, equivalent to the CVO. The blood flow through the ductus arteriosus is markedly increased, because the total cardiac output, excluding that distributed to the pulmonary circulation, passes through the ductus to provide both systemic and umbilical–placental flows. The ductus is large and connects with the descending aorta with a wide oblique inferior angle (see Chapter 6).

Effect of obstruction

The effect of obstruction of left or right ventricular output on blood flow into and out of the ventricle and on development of chamber size has been discussed above. Two other sites of obstruction that may affect fetal development are in the ductus arteriosus and in the aortic arch proximal to the ductus.

Ductus arteriosus obstruction and the pulmonary circulation

Pulmonary arterial and aortic pressures are similar in the fetus. Studies in fetal lambs have shown that constriction of the ductus arteriosus elevates pulmonary arterial pressure. This may result from constriction by mechanical means [37,38]. We have also shown that persistent compression of the ductus arteriosus in fetal lambs induces an increase in the medial smooth muscle layer of small pulmonary arteries, resulting in increased pulmonary vascular resistance [39]. The increased smooth muscle development may interfere with the normal fall in pulmonary vascular resistance after birth; studies in lambs have confirmed these observations [37,38].

Constriction of the ductus arteriosus *in utero* may result from administration of nonsteroidal antiinflammatory agents to the mother. One of the mechanisms that maintains patency of the ductus in the fetus is the relaxant effect of prostaglandin on ductus smooth muscle. Nonsteroidal antiinflammatory agents inhibit prostaglandin production and have been shown to constrict the ductus in both the sheep and human fetus (see Chapter 6). The resulting induction of an increase in the amount of pulmonary vascular smooth muscle could interfere with the postnatal fall in pulmonary vascular resistance and be responsible for the syndrome of persistent pulmonary hypertension of the newborn infant.

Constriction of the ductus reported in some fetuses with aortopulmonary transposition is discussed in Chapter 18.

Aortic arch obstruction and cerebral blood flow

In fetuses with aortic atresia, there is no blood ejected from the left ventricle into the ascending aorta. Blood flow to the head is derived from blood traversing the ductus arteriosus and then passing retrogradely across the aortic arch to the carotid arteries. Aortic atresia is frequently associated with coarctation of the aorta adjacent to the ductus arteriosus. As discussed in Chapter 12, it has been proposed that the coarctation is a result of the very high flow through the ductus; the junction between the aortic isthmus and the ductus arteriosus acts as a branch point and narrowing results at this site. Infants with aortic atresia have been reported to show a high incidence of neurodevelopmental problems as well as cerebral lesions on imaging and it has been suggested that reduced cerebral blood flow during fetal life may be responsible.

Effects of changes in blood oxygen content

Increased oxygen saturation of pulmonary arterial blood

Several congenital cardiovascular malformations alter the pattern of blood flow in the circulation in the fetus. These changes in the course of the circulation could potentially modify the oxygen saturation of blood delivered to various organs. In the normal fetus, well-oxygenated umbilical venous blood passing through the ductus venosus is preferentially directed through the foramen ovale to the left atrium and ventricle, which ejects it into the ascending aorta. However, in the fetus with aortopulmonary transposition, the pulmonary artery arises from the left ventricle. I previously speculated that the pulmonary circulation is exposed to blood with a higher oxygen content than normal and, because it is very reactive to small changes in oxygen, pulmonary vascular resistance and vascular development could be affected [40]. Jouannic *et al.* [41] reported that infants with transposition who had developed serious clinical deterioration soon after birth were identified to have had a

small foramen ovale and/or a constricted ductus arteriosus during fetal life.

I have proposed that the observations of the abnormal foramen ovale and ductus could be related to the high oxygen saturation of blood entering the pulmonary circulation. The increased oxygen saturation will induce pulmonary vasodilatation, increase pulmonary blood flow, and result in increased pulmonary venous return to the left atrium. This will elevate left atrial pressure and tend to shift the flap of the foramen ovale to the right, thus reducing the size of the foramen. With the increase in LVO passing through the pulmonary circulation, a smaller proportion would be available to traverse the ductus arteriosus; this could account for the smaller ductus observed in some fetuses with transposition. Also, because the ductus is exposed to blood passing from the pulmonary trunk to the descending aorta, in the fetus with transposition it is subjected to a higher Po_2, which may further contribute to the constriction. These changes in the circulation in the fetus with aortopulmonary transposition are discussed in detail in Chapter 18.

Decreased oxygen saturation of ascending aortic blood

In the normal fetus, ascending aortic blood is derived from the left ventricle and has an oxygen saturation of about 65%. However, with aortopulmonary transposition, the aorta arises from the right ventricle and ascending aortic blood oxygen saturation will be considerably lower, probably about 45–50%. Whether this lower oxygen saturation will affect the cerebral circulation is open to speculation. Ultrasound studies have indicated that cerebral vascular resistance is decreased [42], suggesting that cerebral blood flow is increased to compensate for the lower oxygen saturation and thus maintain oxygen delivery. It is possible, though, that if the fetus is subjected to intrauterine stress, oxygen supply to the brain would be more readily compromised than in the normal fetus (see Chapter 18).

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