After the postnatal mammalian circulation has been established, blood flows serially from the systemic veins through the right side of the heart to the lungs, then to the left atrium and ventricle, which ejects the blood into the aorta to be distributed to the body, after which it returns to the systemic venous system. Apart from a small amount of coronary venous blood which enters the left ventricular cavity through thebesian veins, there is essentially no admixture of oxygenated pulmonary venous blood and venous blood from the systemic circulation. The tissues therefore are supplied by blood that is fully oxygenated. During fetal life, the placenta serves as the site for gas exchange, and blood that is almost fully oxygenated returns to the fetal body through the umbilical veins. The common umbilical vein enters the porta hepatis, where it is joined by the portal vein. From the portal sinus, branches are provided to the left and right lobes of the liver, and the ductus venosus connects the sinus to the inferior vena cava; the ductus venosus thus permits umbilical venous blood to bypass the hepatic microcirculation. The connections between umbilical and portal veins and ductus venosus and inferior vena cava provide sites for admixture of well-oxygenated umbilical venous and poorly oxygenated systemic venous blood in the fetus. In addition to the ductus venosus shunt, the fetal circulation is characterized by the presence of two other shunts, the foramen ovale and the ductus arteriosus, which serve to direct blood returning to the heart away from the pulmonary circulation.

In this review, I have considered two important aspects of the circulation during fetal and neonatal life. First, I have described the patterns of blood flow in the fetal liver and heart, and the preferential streaming of blood flow, which favors distribution of oxygen to the brain and myocardium. Second, I have discussed the factors determining cardiac output in the fetus and the changes in cardiac output after birth. Although considerable work has been done largely in acute studies in exteriorized fetal lambs and in anesthetized newborn lambs, these maneuvers may profoundly affect circulatory responses. Therefore, this review is largely concerned with studies in chronically instrumented fetal and neonatal lambs.

Patterns of Blood Flow in the Fetal Circulation

Patterns of blood flow in the fetal heart had been examined previously by Pohlman (1907) who injected starch granules into superior and inferior vena caval tributaries, and by Barclay et al. (1944) who used cineradiography in exteriorized fetal lambs. These studies demonstrated that almost all superior vena caval blood passed through the tricuspid valve, with only small amounts entering the left atrium through the foramen ovale. Also, inferior vena caval blood largely passed through the foramen ovale into the left atrium. Blood ejected by the right ventricle was observed to pass to the lungs, but largely through the ductus arteriosus to the descending aorta, whereas blood ejected by the left ventricle entered the ascending aorta and vessels to the head and forequarters. Because the inferior vena caval blood that crossed the foramen ovale contained oxygenated umbilical venous blood passing through the ductus venosus, as well as distal inferior vena caval systemic venous blood, oxygen saturation of left atrial and left ventricular blood would be higher than that in the right ventricle. This information could thus explain the observation of Barcroft (1946) that, in fetal lambs, carotid arterial blood had a higher oxygen saturation than femoral arterial blood. These early studies defined directions of blood flow, but could not provide quantitative in-
Hepatic and Ductus Venosus Blood Flows

The ductus venosus has been considered to have the function in the fetal circulation of providing a bypass of the hepatic microcirculation. Barron (1942) described a sphincter in the lamb ductus venosus and could identify vagal fibers distributed to the vessel. Brinkman et al. (1970) proposed that the ductus venosus is important in regulating blood flow to the liver. However, by reducing the proportion of umbilical venous return that would flow through the liver, the ductus venosus is more likely to be important in providing adequate venous return to the heart.

The vascular morphology in the hepatic sinus to some extent determines the patterns of blood flow (Fig. 2). The umbilical vein provides branches to the left lobe of the liver; the ductus venosus then arises, after which the umbilical vein arches horizontally to the right to connect with the portal vein. The portal branches to the right liver lobe arise beyond the junction of the umbilical and portal veins. Using the microsphere method, we showed that about 55% of umbilical venous blood passes through the ductus venosus, while 45% is distributed to both right and left lobes of the liver. The left lobe of the liver is supplied almost exclusively by umbilical venous blood, with a very small contribution from the hepatic artery. At least 90–95% of portal venous blood is distributed to the right lobe of the liver. A small amount may pass through the ductus venosus, but none passes across to the left lobe. The blood supply to each lobe of the liver, and the distribution of portal and umbilical venous blood, are shown in Figure 3.

In the adult, the liver is a highly compliant organ; about 25% of liver volume is provided by blood, and this constitutes about 10% of total blood volume (Greenway and Stark, 1971). The fetal liver is also highly vascular and has been shown to be very compliant (Gilbert et al., 1981). The large blood flow through the liver and its compliance could make it an important organ in regulating venous return to the heart. Almost 25% of venous return to the fetal heart is derived from liver blood flow; this is comprised of portal venous flow (5% of venous return), a small amount of blood from hepatic arteries (1–2% of venous return), and 45% of umbilical venous blood flow, which provides 40% of venous return (18% of total venous return to the heart).

The relative roles of the hepatic vasculature and the ductus venosus in determining the distribution of umbilical venous blood have not been clearly defined. Apparently, during conditions of fetal stress, there is an attempt to maintain ductus venosus flow and reduce hepatic blood flow. When we reduced umbilical blood flow by inflating a balloon in the fetal descending aorta just above the origin of the umbilical arteries, the proportion of umbilical blood passing through the ductus venosus increased...
FIGURE 2. Silicone rubber cast of major venous channels in fetal liver, as seen from the left (left panel) and right (right panel) sides. The umbilical vein (UV) provides branches to the left lobe (LP) and then divides into the ductus venosus (DV) and the arch which joins the portal vein (PV). Branches then are given to the right lobe (RP). The left hepatic vein (LHV) is seen to join the ductus venosus before connecting with the inferior vena cava (IVC). The right hepatic vein (RHV) joins the inferior vena cava separately. A small caudate lobe vein (CV) enters the inferior vena cava directly. The diaphragmatic vein (DiV) is noted, joining the inferior vena cava above the hepatic veins. A constriction, suggesting a sphincter, is noted at the junction of the ductus venosus with the major umbilical vein [from Rudolph AM (1983) Hepatic and ductus venosus blood flows during fetal life. Hepatology 3:254].

Dramatically, whereas hepatic blood flow fell (Edelstone et al., 1980). Similarly, when umbilical venous return was progressively reduced by compressing the umbilical cord, the percentage of umbilical venous blood passing through the ductus venosus increased progressively; with reduction at 50%, the ductus venosus proportion of umbilical venous return increased to 65–70% (Itskovitz et al., 1983). Reducing fetal blood volume by hemorrhage decreased umbilical blood flow and increases the percentage of umbilical blood passing through the ductus venosus (Itskovitz et al., 1982a). The mechanisms responsible for the changes in distribution have not been delineated. In a review of the ductus venosus, Edelstone (1980) concluded that the vessel probably responds passively to intraluminal pressure, and that distribution of blood flow from the portal sinus between the liver circulation and ductus venosus is regulated primarily by changes in hepatic vascular resistance. Redistribution could result from dilation of the ductus or its sphincter; this would have to be an active process because reduction of venous return would reduce intraluminal volume. The ductus venosus has shown variable responses to norepinephrine in vivo and in vitro. Ehinger et al. (1968) found that topical application of norepinephrine to the ductus venosus caused constriction. Zink and Van Petten (1980), using an intact fetal lamb model, suggested that norepinephrine dilates the ductus venosus. Cociani et al. (1984) found that in the isolated ductus venosus, norepinephrine produced α-adrenergic-induced constriction, but β-ad-

FIGURE 3. Blood flow to the left and right lobes of the liver, in relation to organ weight, is shown in the left panel. The left lobe is seen to receive almost all its flow from the umbilical vein (UV), whereas the right lobe receives portal venous (PV) as well as umbilical venous blood. The right panel shows the distribution of umbilical and portal venous blood. Note that somewhat more than half of umbilical venous blood passes through the ductus venosus (DV), whereas almost all the portal venous blood passes to the liver [from Rudolph AM (1983) Hepatic and ductus venosus blood flows during fetal life. Hepatology 3:254]. HA = hepatic artery.
renergic-induced dilation. As suggested by Edelstone (1980), differences in in vitro and in vivo responses may be related to changes in blood flow and vascular pressures resulting from drugs administered to the intact fetus. Another mechanism that could explain the changes in distribution of umbilical venous blood between the liver and ductus venosus is active vasoconstriction in the hepatic circulation. In the adult liver, sphincters have been described at the entrance of portal venules into the central sinusoids (Elias and Sherrick, 1969), as well as at the junction of the sinusoids with the hepatic veins (Knisely et al., 1957).

When fetal hypoxemia is produced by reducing the fraction of oxygen in maternal inspired air, umbilical blood flow is maintained, although blood flow to the fetal body is reduced (Cohn et al., 1974). However, the proportion of umbilical venous blood that passes through the ductus venosus increases from 55% to about 65%, whereas the percentage to the liver falls to 35% (Reuss and Rudolph, 1980; Bristow et al., 1983). This alteration in distribution can be accounted for only by active relaxation of the ductus venosus or by vasoconstriction in the hepatic circulation. Either or both of these mechanisms could result from neural or hormonal responses to fetal hypoxemia. Possibly, the response could result from a direct local vascular effect of the reduction in oxygen content of umbilical venous blood.

Reduction of umbilical venous return results in a marked fall in liver blood flow; a 50% fall in umbilical blood flow is associated with a 75% fall in liver blood flow (Itskovitz et al., 1983). Although total blood flow to each lobe of the liver is similar in relation to tissue weight, the contribution of umbilical venous blood to the right lobe is drastically reduced, so that a much greater proportion of right lobe blood flow is derived from the portal vein than the umbilical vein. Because oxygen saturation of portal venous blood is low (about 30%), this could seriously influence oxygen delivery to the right lobe of the liver.

**Distribution of Ductus Venosus, Hepatic Venous, and Inferior Vena Caval Blood**

The different blood supplies to the left and right lobes of the liver stimulated an examination of the composition of left and right hepatic venous blood by selective catheterization of the left and right veins in chronically instrumented fetal sheep (Bristow et al., 1981b, 1983). Oxygen saturation in the umbilical veins of the lamb is about 85%, and in the portal vein about 30%. Left hepatic venous blood has an oxygen saturation of about 70–75%, whereas the saturation of right hepatic venous blood is about 50–55%.

In the region just distal to the diaphragm, the inferior vena cava thus receives blood from four different sources, all with different oxygen saturations; ductus venosus blood is almost exclusively derived from the umbilical vein and has an oxygen saturation of about 85%, whereas distal inferior vena caval blood has a saturation of about 35%. Although it had generally been assumed that blood from these sources has reasonably good admixture in the inferior vena cava, Behrman et al. (1970) suggested that blood derived from the ductus venosus and the distal inferior vena caval streams selectively, so that ductus venosus blood preferentially passes across the foramen ovale. Their results were open to some question, because the studies were performed acutely in exteriorized anesthetized primates. However, we have confirmed this observation in the chronically instrumented sheep fetus. When radionuclide-labeled microspheres were injected simultaneously into the inferior vena cava and umbilical venous streams, both ductus venosus and distal inferior vena caval blood were distributed across the foramen ovale and through the right atrium across the tricuspid valve. However, ductus venosus blood was preferentially directed across the foramen ovale, while distal inferior vena caval blood preferentially passed through the tricuspid valve (Edelstone and Rudolph, 1979; Reuss et al., 1981). We also injected microspheres into the left or right hepatic vein and observed an interesting pattern of flows; the right hepatic venous blood followed the pattern of distribution of distal inferior vena caval blood, whereas left hepatic venous blood was preferentially directed across the foramen ovale with ductus venosus blood (Bristow and Rudolph, unpublished observations).

Not all of the factors which contribute to this preferential streaming have been determined. We have described the presence of valve-like structures in the inferior vena cava of the fetal lamb that may direct blood from the various vessels to facilitate streamlining of flow (Bristow et al., 1981a). A thin membrane partly covers the lower margin of the orifice of the right hepatic vein. The left hepatic vein joins the ductus venosus just before the entry into the inferior vena cava (see Fig. 2). A membrane valve partly covers the distal margin of the joint orifices of these vessels into the vena cava (Fig. 4). Well-oxygenated blood from the ductus venosus and left hepatic vein appears to be deflected to the posterior left portion of the thoracic inferior vena cava, and thus toward the foramen ovale. Right hepatic venous blood is directed anteriorly and to the right by the membranous valve so that, with distal inferior vena caval blood, it is preferentially directed to the tricuspid orifice. This streaming can be clearly observed in the living lamb fetus when the thoracic portion of the inferior vena cava is exposed by right thoracotomy.

It is not known whether other factors contribute to the streamlining of flows in the inferior vena cava. The magnitude and velocity of blood flows in the various vessels may influence preferential streaming. During fetal hypoxemia induced by maternal hypoxia, ductus venosus flow is increased and distal inferior vena caval flow falls; the preferential streaming of distal inferior vena caval and ductus
Valves partly covering the orifices of the joint orifices of the left hepatic vein and ductus venosus (left) and the right hepatic vein, with the inferior vena cava, are shown [from Rudolph AM (1983) Hepatic and ductus venosus blood flows during fetal life. Hepatology 3:254].

venous blood is maintained (Edelstone and Rudolph, 1979; Reuss et al., 1981), but the pattern of flow of hepatic venous blood has not been described. When umbilical venous return is reduced by cord compression, a greater percentage of upper body blood flow is derived from the distal inferior vena cava, suggesting that there may be some interference with the streamlining of flow (Itskovitz, LaGamma, and Rudolph, unpublished observations).

Distribution of Superior Vena Caval Flow

Superior vena caval blood flow contributes about 20% of venous return to the fetal lamb heart. Almost all superior vena caval blood is directed across the tricuspid valve into the right ventricle. In the normal fetus in utero, only about 2% of superior vena caval blood crosses the foramen ovale to be distributed to the upper body (Rudolph and Heymann, 1967). Dawes (1968) suggested that fetal hypoxia is associated with a considerable increase in supraventricular venous blood flow across the foramen ovale, but this could not be corroborated in studies in fetal lambs in utero in which the percentage of supraventricular venous blood crossing the foramen ovale increased to only 4-5% of total flow (Cohn et al., 1974). Similarly, in association with umbilical cord compression, the proportion of superior vena caval blood crossing the foramen ovale increases from about 2% to only 4-5%.

The patterns of blood flow in the fetal liver and heart can clearly account for the higher oxygen saturation of blood in the ascending aorta and its branches, as compared with that in the descending aorta. These blood flow patterns are depicted in Figure 5. The preferential streaming of ductus venosus and left hepatic venous blood across the foramen ovale, and the small proportion of superior vena caval blood, with an oxygen saturation of about 35% that crosses the foramen ovale, account for the relatively high saturation (about 65%) of left ventricular blood. The preferential distribution of right hepatic venous and distal inferior vena caval blood, as well as passage of all superior vena caval blood through the tricuspid valve, results in a lower oxygen saturation (about 50-52%) in right ventricular blood. Almost all the blood ejected by the right ventricle is directed through the ductus arteriosus to the descending aorta, and only about 30% of blood from the ascending aorta passes across the aortic valve.
Isthmus to the descending aorta. The oxygen saturation in descending aortic blood is therefore only 2–3% higher than that in the pulmonary artery. Because pulmonary blood flow is low during fetal life, the oxygen saturation of blood entering the left atrium across the foramen ovale is lowered only slightly by pulmonary venous blood, which has a saturation of about 45–48% (Rudolph, unpublished observations).

The venous and arterial flow patterns facilitate the delivery of blood with relatively high oxygen content to upper body organs, including the brain and the heart, and blood of lower oxygen content to the lower body, as well as to the placenta, the site of oxygen uptake.

In addition to facilitating oxygen delivery, the distribution of flow results in higher concentrations in the ascending aortic blood of any substance that enters the umbilical venous blood. Thus glucose concentrations are higher in ascending aortic blood, compared with descending aortic blood (Charlton and Johengen, 1984). Also, concentrations of drugs administered to the mother, which cross the placenta, will also be delivered in higher concentrations to the fetal brain and heart.

**Cardiac Output and Its Distribution**

In the adult, cardiac output represents the volume of blood that flows serially through the pulmonary and systemic circulations; apart from minor temporary differences, each ventricle ejects this similar volume. In the fetus, this concept of cardiac output cannot be applied because of the presence of shunts, admixture of oxygenated and venous blood, and the supply of certain parts of the body from both ventricles. The term "combined ventricular output (CVO)" has been applied to the output of the two ventricles, and it also represents total venous return to the fetal heart. In chronically instrumented fetal lambs, CVO is about 450 ml/min per kg fetal body weight, as measured by the microsphere method or by electromagnetic flow transducers applied around the pulmonary trunk and ascending aorta (Rudolph and Heymann, 1967); this output is similar at all ages in the latter half of gestation (Rudolph and Heymann, 1970). The right ventricle ejects about 60–65%, and the left only 35–40% of CVO. The lung receives 7–8% of CVO, and the remaining 55% of CVO ejected by the right ventricle passes through the ductus arteriosus. The left ventricle provides 3% CVO to the myocardium, 20% to the head, neck, upper trunk, and forequarters, and only about 10–15% of CVO passes across the aortic isthmus to the descending aorta. The placenta receives 40% of CVO, or about 200 ml/min per kg fetal body weight.

The difference in output of the left and right ventricles in the fetus is of considerable interest. The left and right ventricles are subjected to the same filling pressures because atrial pressures are almost identical, as a result of the presence of the foramen ovale. Also, the thickness of the free walls of the two ventricles is similar. The aortic and pulmonary trunk systolic and diastolic pressures are almost identical in fetal lambs up to about 0.9 (135 days) gestation, after which pulmonary arterial pressure may be slightly higher, reflecting a minor degree of ductus arteriosus constriction. However, although the pressures are equal, the resistances against which the ventricles eject are apparently different. The aortic isthmus is narrower than the ascending or descending aorta. In the fetal lamb, the diameter is about 0.7 that of the remainder of the aorta. Thus, its cross-sectional area is only about half that of the descending aorta. Although the pressures in the ascending and descending aorta are almost identical, there is evidence that the aortic isthmus presents a site of functional separation. We have observed that a small amount of acetylcholine, a potent vasodilator, injected into the descending aorta results in a greater fall in pressure in the descending as compared with the ascending aorta over several beats (Rudolph and Heymann, unpublished observations). Similarly, acetylcholine injected into the ascending aorta causes the pressure at this site to fall more than it does in the descending aorta. Small amounts of norepinephrine, a vasoconstrictor injected into the ascending or descending aorta, also separates the pressures for several beats with a greater increase in the site of the circulation in which it is administered. We also noted that stroke volume of the right ventricle, but not of the left, increased when acetylcholine was injected into the descending aorta.

The difference in outflow resistance of the two ventricles is also evident in comparing the velocity contours, as recorded simultaneously by electromagnetic flow transducers around the ascending aorta and pulmonary trunk (Fig. 6). The velocity profile of the pulmonary trunk shows a much steeper ascent than that of the aorta; there is also a pronounced backflow at the end of systole in the aortic tracing with no backflow in that of the pulmonary trunk. Although part of the backflow could be related to flow into the coronary arteries (caused by the flow transducer's position above their origin), this is unlikely, since the backflow occurred in only a short phase at the end of systole. The descending limb of the pulmonary trunk tracing characteristically shows a sharp incisura. The cause of this is not known, but may be related to a change in velocity associated with the aortic wave reaching the ductus arteriosus and modifying right ventricular ejection.

These observations indicate that, in spite of similar filling pressures and equal systolic and diastolic pressures in the ventricles and great arteries in the fetus, the aortic isthmus acts as a site of functional separation. The right ventricle is presented with the high resistance of the pulmonary circulation and, through the widely patent ductus arteriosus, with the resistance of the lower body, including the placenta, the resistance of the umbilical-placental circulation is relatively quite low. The left ventricle is
poxemia (Cohn et al., 1974). This was probably
levels, but decreasing heart rate by vagal stimulation
in part be related to an increase in afterload associ-
ministration abolished the bradycardia and the fall
caused a marked fall in output of each ventricle.
Combined ventricular output also fell in association
ventricles, resistance against which the ventricles
eject, or afterload, and myocardial contractility.

Heart Rate

Spontaneous changes in fetal heart rate occur in
association with alterations in electrocortical activity
and sleep state, and fetal activity (Dawes, 1973).
During continuous measurement of left and right
ventricular output with electromagnetic flowmeters
in chronically instrumented fetal lambs, we ob-
served that spontaneous increases in heart rate were
associated with increases of output, whereas de-
creases in heart rate resulted in a considerable fall
in both left and right ventricular outputs (Rudolph
and Heymann, 1976). Electrical pacing of the right
atrium above the resting rate of 160–180/min re-
sulted in a progressive increase in left ventricular
output to a maximum of about 15% above resting
levels, but decreasing heart rate by vagal stimulation
caused a marked fall in output of each ventricle.
Combined ventricular output also fell in association
with the bradycardia that occurred during fetal hy-
poxemia (Cohn et al., 1974). This was probably
secondary to the bradycardia, because atropine ad-
ministration abolished the bradycardia and the fall
in output (Itskovitz et al., 1982b), but could at least
in part be related to an increase in afterload associ-
ated with vasoconstriction in some organs and in
the peripheral circulation. The stroke volume of each
ventricle increased only slightly when heart rate was
reduced (Rudolph and Heymann, 1973). In these
studies, it was not possible to separate the individual
influences of heart rate and preload and afterload
on ventricular output. Thus, associated with vagal
stimulation, arterial pressure increased, and an in-
crease in afterload could have contributed to the fall
in ventricular output, as well as the bradycardia.
Also, the studies with atrial pacing demonstrated
that the site of pacing profoundly influences fetal
ventricular output. Thus, although in these studies
left ventricular output consistently increased with
right atrial pacing, left atrial pacing at the same rate
resulted in a variable decrease in left ventricular
output, up to as much as a 50% fall. This was
ascribed to alteration of the atrial pressure pulse
contours, which disrupted the small positive pres-
sure difference between the inferior vena cava and
left atrium normally observed consistently through-
out the cardiac cycle. Depending on the pacing rate
and the site of pacing, left atrial pressure exceeded
inferior vena caval pressure in some phases of the
cycle; it was suggested that flow across the foramen
ovale was reduced, thus interfering with filling of
the left ventricle.

These observations of changes in ventricular out-
put with spontaneous alterations in heart rate could
not be confirmed in chronically instrumented fetal
lambs by Kirkpatrick et al. (1976). They measured
left ventricular output in four fetal lambs by an
indicator-dilution technique, injecting dye into the
left atrium and sampling from the carotid artery. In
two animals, however, single measurements were
made with heart rate differences of only about 10
beats/min. Also, the reliability of the technique in
measuring left ventricular output is open to question
because of the short distance and small volume
between the injection and sampling sites. The actual
values of left ventricular output they recorded are
considerably greater than those reported by other
investigators. Anderson et al. (1983a, 1983b) did not
observe significant increases in right ventricular out-
put with atrial pacing, but did confirm a marked
reduction in left ventricular output with left atrial
pacing. This was associated with a fall in end-
diastolic dimension of the left ventricle, suggesting
that the foramen ovale flow may be reduced by left
atrial pacing, as mentioned above. This limited abil-
ity to increase stroke volume with bradycardia sug-
gested that the fetal heart is functioning at or near
its maximum performance.

Ventricular Filling Pressure and Compliance

The end-diastolic pressure of both left and right
ventricles in our studies in the fetal lamb in utero is
about 3–5 mm Hg above intraamniotic pressure. We
examined the effect of increasing filling pressure of
the right ventricle by rapidly infusing normal saline,
while continuously measuring right ventricular out-
put (Heymann and Rudolph, 1973). Responses varied with gestational age; in the fetus at about 0.75 gestation, even with increases of end-diastolic pressure to 20 mm Hg, right ventricular output barely increased. At about 0.95 gestation, right ventricular output increased slightly, by 10–15%. Gilbert (1980, 1982) and Thornburg and Morton (1983) examined, in fetal lambs, the effects on cardiac output of varying filling pressure by hemorrhage to decrease it, and by rapid volume infusion to increase it. Reducing ventricular filling pressure below its resting level resulted in a dramatic fall in cardiac output. They confirmed our observation that increasing end-diastolic pressure to levels as high as 20 mm Hg produced only small increases in ventricular output. These findings all suggest that the fetal ventricle normally functions near the top of its function curve and has little reserve to increase its output further. The lack of response to increasing filling pressure could indicate that the fetal myocardium does not have the ability to increase its force of contraction, but it could possibly be related to poor compliance of the ventricles. Friedman (1973) found that resting tension was much greater in fetal myocardial strips than in adult myocardium at similar lengths. Romero et al. (1972) showed that intact fetal lamb hearts were much less compliant than those of adult sheep. Thus, the apparent poor performance of the fetal myocardium could at least in part be accounted for by poor distensibility of the ventricles, so that high filling pressures have a limited effect on individual sarcomere length.

Kirkpatrick et al. (1976) and Anderson et al. (1982, 1984) have conducted studies in fetal lambs in utero to assess the interrelationships between ventricular distension and filling pressure and their influence on ventricular output. Ultrasonic crystals were inserted on the endocardial surface of the left and right ventricles to measure the lesser dimension of the ventricles as an index of ventricular volume, and a catheter-tip pressure transducer was used to record high-fidelity pressure tracings. Ventricular end-diastolic pressures were altered by superior vena caval occlusion or by infusion of blood to produce a range between 0 and 13 mm Hg. A linear relationship was observed between the extent of left ventricular shortening, as reflected by changing lumen diameter, and end-diastolic pressure over the range from 0–6 mm Hg. Above pressures of 7 mm Hg, no further increase in the extent of shortening occurred. There was a linear relationship between the extent of left ventricular shortening and end-diastolic diameter over the range of 9–13 mm. In these studies, end-diastolic diameter varied with fetal respiratory movements and with spontaneous changes in heart rate. Based on these observations, and on those of Thornburg and Morton (1983) and Gilbert (1980, 1982), it is evident that the Frank-Starling mechanism is operative in the fetal heart. If overall circulatory responses are considered, however, it is evident that the combined ventricular output is near its maximum level in the fetus at resting atrial filling pressures, and volume loading further increases output to a limited extent, possibly because the heart is very sensitive to the increased afterload created by the rise in arterial pressure, or because ventricular compliance is relatively low, or because ability to increase myocardial contractility is limited, or a combination of these factors.

Afterload

Inflation of a balloon in the fetal descending aorta produces a dramatic fall in right ventricular output, indicating that the fetal heart is very sensitive to increases in afterload (Rudolph and Heymann, 1973). Gilbert (1982) studied how changing afterload affects ventricular function curves of the fetal sheep heart; he infused methoxamine to produce peripheral vasoconstriction, which resulted in a marked depression of cardiac output as compared with control values at similar right atrial mean pressures. Also, Thornburg and Morton (1983) noted that, at the same end-diastolic pressures, right ventricular output fell when arterial pressure was increased by vasoconstriction with phenylephrine infusion, but increased when pressure was reduced by vasodilation with nitroprusside. The relative influence of afterload change on ventricular output at different gestational ages and different postnatal ages is yet to be assessed.

Myocardial Contractility

Morphological studies of the fetal myocardium have demonstrated considerable differences from adult heart muscle. The myofibrillar content is less relative to tissue volume, so that the fetal myocardium has less contractile tissue. Friedman (1973) demonstrated that active tension developed by fetal myocardial strips obtained from lambs in the last trimester of gestation was considerably lower than that developed by adult tissue. He suggested that this difference could be related to relative differences in myofibrillar content. A low concentration of myofilaments has also been described in neonatal cat myocytes (Maylie, 1982). Ultrastructural studies of fetal myocardium have shown a paucity of sarcoplasmic reticulum and, strikingly, a poorly developed or absent T-tubule system as compared with adult myocardium (Hoerter et al., 1982). The possibility has been considered that, after birth, the relationship between sarcoplasmic reticulum and sarcotubular system in regulating excitation-contraction coupling may change, with a resultant modification of intracellular calcium cycling (Boucek et al., 1984). In the fetal heart, the increase in cytosolic calcium following excitation may be provided largely by transsarcomemmal movement of calcium. Studies have been reported on the effects of blockers of slow inward calcium movement in newborn and adult rabbit hearts; the results have been conflicting. George et al. (1981) found that verapamil, a calcium...
channel blocker, had a greater effect on developed tension of adult than neonatal myocardium. Boucek et al. (1984), however, found that perfused newborn rabbit hearts showed much greater depression of myocardial function with blockade of slow inward calcium current by verapamil, nifedipine, or diltiazem, than did adult rabbit hearts. The latter investigators explained the absence of specific effect of verapamil in immature hearts in the George et al. (1981) study on the basis of the slow stimulation frequencies that were used.

As mentioned above, ventricular function curves in chronically instrumented fetal lambs are relatively flat above filling pressures of 3–4 mm Hg (Heymann and Rudolph, 1973; Gilbert et al., 1981; Gilbert, 1982; Thornburg and Morton, 1983). After birth, left ventricular output increases considerably in the lamb, from fetal levels of about 150 ml/min per kg body weight to 250–400 ml/min per kg (Klopfenstein and Rudolph, 1978). The variability in newborn lambs is primarily related to measurements at different environmental temperatures (Sidi et al., 1983). Postnatally, resting cardiac output decreases progressively in relation to body weight, reaching levels of 160 ml/min per kg within 6–8 weeks. The response of cardiac output to rapid infusion of 0.9% NaCl solution shows a much steeper function curve than in the fetal lamb. The maximum cardiac output achieved with infusion was about 35% above resting levels during the first week, and about 65% by the 6th week (Klopfenstein and Rudolph, 1978) as compared with 10–15% in the fetal lamb. These findings suggested that the newborn heart is capable of achieving high cardiac outputs, but that there is a reduced reserve for increasing output in response to volume loading. The studies of Romero and Friedman (1979) in newborn lambs suggest that this may in part be related to lesser compliance of the left ventricle during the neonatal period.

Using an index based on postectopic potentiation, both in isolated muscle strips and in a chronically instrumented fetal lamb preparation, Anderson et al. (1982) reported an increase in myocardial contractility immediately after birth and then a slow decrease over several weeks. Teitel et al. (1985) assessed myocardial contractility at various periods after birth in lambs by applying an in vivo analog of the end-systolic pressure-volume relationship described by Suga and Sagawa (1974) in isolated canine hearts. They found that resting inotropic state was high in the first week and progressively decreased over 3–4 weeks.

It is of interest that, although the fetal lamb heart does not increase ventricular output more than 10–15% in response to volume loading, within a few days after birth the left ventricle is able to sustain an output twice the fetal level. This did not appear to be related to sympathethico-adrenal stimulation because β-adrenergic receptor blockade produced only a 10–12% reduction in resting cardiac output (Klopfenstein and Rudolph, 1978). We examined the possible role of the rise in plasma triiodothyronine (T3) concentrations that occurs shortly after birth (Fisher et al., 1977). Cardiac output was measured after birth in three groups of lambs that were prepared with intravascular catheters at 130 days gestation, so that measurements of cardiac output could be made immediately after birth (Breall et al., 1984). The first group served as control; in the second group, thyroidectomy was performed at the time of fetal surgery; in the third group, the thyroid gland was removed immediately before birth. The changes in plasma T3 concentrations and left ventricular output are shown in Figure 7. The control group showed a rise of T3 concentrations with a high cardiac output. In the group thyroidectomized at 129 days, T3 was undetectable in fetal plasma, and

![Figure 7](https://example.com/figure7.png)

**FIGURE 7.** Top panel: post-delivery changes in plasma T3 concentrations (mean ± sem) are shown in the first 6 hours after birth for three groups of lambs. ○ control, □ group of lambs that were thyroidectomized at time of delivery, ■ lambs that were thyroidectomized in utero at 130 days of gestation. Bottom panel: changes in left ventricular output (mean ± sem in the same groups of lambs. Note that left ventricular output in the animals thyroidectomized at time of delivery was similar to the control animals, whereas in the animals thyroidectomized in utero, it was considerably lower. [From Breall JA, Rudolph AM, Heymann MA (1984) Role of thyroid hormone in postnatal circulatory and metabolic adjustments. J Clin Invest 73:1418.]
left ventricular output did not rise normally but remained at fetal levels for the 6 hours of observation. In the group in which thyroidectomy was performed just before birth, T\textsubscript{3} concentrations did not rise above fetal levels, yet cardiac output rose normally. Based on these observations, T\textsubscript{3} appears to be important during late gestation rather than after birth in maturation of the fetal myocardium. The mechanisms by which T\textsubscript{3} produces this change have not been determined but one or more of several could be involved. In adult myocardium, it has been suggested that the inotropic effect of T\textsubscript{3} was dependent on altered cardiac myosin adenosine triphosphatase (ATPase) activity (Morkin, 1979). Fink and Morkin (1977) suggested that increased contractility caused by thyroid could be accounted for by appearance of a new species of myosin with greater actin-activated ATPase activity. Other possible mechanisms include T\textsubscript{3} effects on Na\textsuperscript{+}-K\textsuperscript{+}-ATPase activity (Philipson and Edelman, 1977), or an increase in the number of myocardial \(\beta\)-adrenergic receptors (Williams et al., 1977; Whitsett et al., 1982).

Thyroid hormones also have been shown to influence the relationship between the \(\alpha\) and \(\beta\)-heavy chain myosin in ventricular myocardium. Adult myocardium contains largely HC\(\beta\), but during the neonatal period HC\(\alpha\) constitutes about 50% of the heavy chain myosin. The change in \(\alpha\) and \(\beta\)-myosin relationships is associated with changes in plasma thyroid hormone concentrations. Also, administration of thyroid hormone to rabbits resulted in a 3-fold increase in the synthesis rate of HCa and a corresponding fall in synthesis of HC\(\beta\) (Zak et al., 1979; Everett et al., 1983).

Conclusions

The transfer of the function of oxygen uptake, from the placenta during fetal life to the lung after birth, is associated with dramatic alterations in the course and distribution of blood flow, as well as in myocardial demands and function. In the fetus, oxygenated blood returns to the body through the umbilical veins and about half of this blood bypasses the hepatic microcirculation through the ductus venosus to enter the central circulation. Preferential streaming of blood in the thoracic inferior vena cava enhances the flow of well-oxygenated blood from the ductus venosus and left hepatic vein across the foramen ovale. This facilitates oxygen delivery to the fetal brain and myocardium. Current evidence indicates that the fetal myocardium is structurally and functionally immature as compared with that of the adult. The fetal heart appears to be functioning near the top of the ventricular function curve, and increases in filling pressure produce little increase in ventricular output. This could be related to low myocardial compliance or to reduced intrinsic myocardial contractility. Because of the limitation of myocardial performance, circulatory responses are largely related to adjustments in afterload and local vascular resistances. After birth, cardiac output as well as its response to increased filling pressure is enhanced. This ability to increase cardiac output appears to be related to the effects of thyroid hormone in late prenatal life. Postnatally, cardiac output requirements are high relative to body weight, and there is limited reserve for further increases in output with volume loading. During postnatal development, resting cardiac output decreases in relation to body weight, and there is greater reserve, so that the percentage increase in response to volume loading increases greatly.

This work was supported by grants from the U.S. Public Health Service, Program Project Grant HL24056, and HL23681.

Address for reprints: Abraham M. Rudolph, M.D., 1403-HSE, University of California, San Francisco, California 94143.

References


Anderson PAW, Mainwarine R, Glick KL (1983b) Fetal right ventricular output modulation: A new model to study ventricular interaction (abstr). Circulation 68 (suppl III): 122


Circulation Research 67: 120-130


Dawes GS (1968) Foetal and Neonatal Physiology. Chicago, Year Book Medical Publishers


Pohlman AG (1907) The fetal circulation through the heart. Bull Johns Hopkins Hosp 18: 409


INDEX TERMS: Fetal hepatic blood flow • Ductus venosus flow • Fetal vascular shunts • Fetal cardiac output • Thyroid hormone
Distribution and regulation of blood flow in the fetal and neonatal lamb.
A M Rudolph

Circ Res. 1985;57:811-821
doi: 10.1161/01.RES.57.6.811

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1985 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/57/6/811.citation