The Changes in the Circulation After Birth

Their Importance in Congenital Heart Disease

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SUMMARY
Circulatory changes at birth have a profound influence on the physiology of the circulation in normal infants and those with congenital heart disease. Since the concept that cardiac defects are fixed entities is being superseded by an appreciation of the changing nature of physiologic disturbances and their clinical consequence, the course and distribution of the fetal circulation with the influences of the major changes at birth, including changes in pulmonary vascular resistance, and closure of the ductus arteriosus and foramen ovale, require study. This lecture traces these and other changes and discusses their influences on congenital heart disease.

Additional Indexing Words:
Atrial septal defect   Ductus arteriosus   Hypoxemia   Oxygen tension
Pulmonary circulation   Pulmonary vascular resistance   Types of shunting
Regression of smooth muscle

The concept that congenital cardiac defects are fixed anatomic entities, each of which results in a specific disturbance in the course of the circulation, is being superseded by an appreciation of the changing nature of the physiologic disturbances, and thus the clinical consequences, of congenital heart lesions throughout life. The most dramatic changes which occur in the circulation during the life of an individual are those associated with the transference of the function of gas exchange from the placenta to the lungs at the time of birth. I propose to discuss these adjustments and how they may be important in the adaptation and survival of normal infants and those with congenital heart disease. As a basis for this discussion, the course and distribution of the fetal circulation are first described and the influences of the major transitions, including the decline in pulmonary vascular resistance, the closure of the ductus arteriosus, and the closure of the foramen ovale, on the physiology of the circulation are reviewed.

The Course and Distribution of the Fetal Circulation

The pattern of venous return and the course of blood flow in the fetal heart have been graphically demonstrated by the angiographic studies of Barclay et al.,1 and Lind and Wegelius.2 More recently, we have used radioactive microspheres for quantitative studies of the amounts of blood flow in the major veins, and the distribution of blood from each major vein to the fetal body.3, 4 Most of our current knowledge of the fetal circulation (fig. 1) derives from studies in lambs, and the quantitative data presented here applies to the lamb. However, preliminary observations in pre-viable human fetuses indicate that pat-
FETAL CIRCULATION

Figure 1

In the fetal circulation the ductus venosus (DV) serves as a bypass for umbilical venous blood to enter the inferior vena cava directly. The foramen ovale (FO) carries well oxygenated blood from the inferior vena cava into the left atrium and left ventricle. The ductus arteriosus (DA) carries the major portion of blood ejected from the right ventricle to the descending aorta and mainly to the placenta. SVC = superior vena cava; IVC = inferior vena cava; RA = right atrium; LA = left atrium; RV = right ventricle; LV = left ventricle; PA = pulmonary artery; Ao = aorta.

Patterns of flow are similar. Umbilical venous blood, returning from the placenta, is relatively well oxygenated with a \( P_{O_2} \) of about 30 mm Hg. About 40 to 60% of umbilical venous blood passes through the liver; the remainder bypasses the hepatic capillary circulation through the ductus venosus which connects the umbilical veins directly with the inferior vena cava. The inferior vena caval blood, as it enters the heart, is largely deflected by the crista dividens through the foramen ovale to the left atrium, but some of the inferior vena caval return enters the right atrium and flows through the tricuspid valve. Almost all the superior vena caval blood passes into the right atrium and through the tricuspid valve, only 2 to 3% crossing the foramen ovale. Since the inferior vena cava receives the total umbilical venous return, blood entering the left atrium and left ventricle has a considerably higher \( P_{O_2} \) than that entering the right ventricle. Right ventricular blood is ejected into the main pulmonary artery, but only 10 to 15% of right ventricular stroke volume reaches the pulmonary circulation, the remainder being diverted away from the lungs through the ductus arteriosus to the descending aorta. Blood ejected by the left ventricle is distributed to the coronary circulation, brain, head, and upper extremities, and the remainder passes into the descending aorta. This design of the fetal circulation provides blood of a higher \( P_{O_2} \) to the coronary and cerebral circulations than to the lower body organs; it also helps divert venous blood to the placental circulation where oxygenation occurs. The \( P_{O_2} \) in the ascending aorta is 25 to 28 mm Hg, whereas that in the descending aorta is 19 to 22 mm Hg. The ductus arteriosus in the fetus is a large channel, as large as the aorta itself, and it therefore allows for an equalization of pressures in the aorta and pulmonary artery.

FETAL HEART

Figure 2

Pressures (mm Hg) in the heart and great vessels before and after birth. Fetal pressures are shown within chambers and vessels and postnatal pressures alongside. The pulmonary arterial pressure drops when the ductus arteriosus closes and pulmonary vascular resistance falls. Systemic arterial pressure increases when placental circulation is removed. Left atrial pressure rises and right atrial pressure falls after birth, reversing the pressure difference.

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(fig. 2). Under these circumstances, the blood flow to the lungs as well as to the fetal organs deriving their blood supply from the aorta is dependent on local vascular resistances. The placenta, which has a very low vascular resistance, receives 40 to 50% of the total fetal left and right ventricular output. The lungs, however, receive only about 5 to 10% of the total cardiac output in the lamb at near term gestation.3

The Fetal Pulmonary Circulation

The low pulmonary blood flow and diversion of right ventricular output away from the lungs through the ductus arteriosus are due to the very high pulmonary vascular resistance in the fetus. From histologic examination of the fetal and neonatal lungs of guinea pigs, Reynolds5 suggested that the high pulmonary vascular resistance in the fetal lung was due to the fact that the small blood vessels in the unexpanded lung were tortuous and kinked and this retarded flow. More recent evidence suggests, however, that the alveoli of the fetal lung are not collapsed, but filled with fluid6; the appearance of the vessels described by Reynolds may be related to the manner of preparation of the sections. A great deal of evidence has now been accumulated demonstrating the importance of hydrogen-ion concentration and P O2 of blood perfusing the fetal lung in regulating pulmonary vascular resistance. Several studies have shown that the pulmonary vessels of the fetal lamb constrict markedly when P O2 is reduced or when P CO2 is raised, thus increasing H+ ion concentration.7, 8 Blood perfusing the lungs in the fetus has a relatively low P O2, as right ventricular blood consists of the total venous return from the superior vena cava and a relatively smaller proportion of the inferior vena cava return. The low P O2, to which the fetal pulmonary arterioles are constantly exposed, is probably primarily responsible for the high pulmonary vascular resistance.

Changes in the pulmonary circulation in the fetus are diagrammatically presented in figure 3. The fetal pulmonary vessels, in response to the hypoxic constriction and high pulmonary arterial pressure, develop an increase of the medial muscular layer. The actual thickness of

Figure 3

Schematic representation of fetal and postnatal changes in pulmonary vascular resistance, pulmonary blood flow, pulmonary arterial systolic pressure, and thickness of smooth muscle in medial layer of pulmonary arterioles. There is no known difference in the pulmonary vascular development in the fetus in women at high altitudes or when a ventricular septal defect is present in the fetus. Postnatally, the pulmonary vascular resistance falls more slowly in infants born at high altitude or with a ventricular septal defect of large size. Pulmonary blood flow increases rapidly at birth in the normal infant and probably at the same rate at altitude. In the presence of a ventricular septal defect, pulmonary blood flow increases as pulmonary vascular resistance falls. Pulmonary arterial pressure normally falls rapidly after birth; the fall is delayed at altitude and pressure remains slightly elevated. Pulmonary arterial pressure does not fall when a large ventricular septal defect is present, and it increases as systemic arterial pressure rises. The muscle in the pulmonary arterioles does not regress as rapidly as normal in infants at high altitudes. In infants with ventricular septal defect, the muscle does not regress normally and soon after birth increases in amount.
the smooth muscle layer progressively increases during the second half of gestation; so presumably the vessels are capable of a greater degree of constriction in later gestation. In fetal lambs, measurements of pulmonary vascular resistance, reflecting total cross-sectional area of the pulmonary vascular bed, have shown a progressive decrease in resistance during the latter half of gestation with an increase not only of actual pulmonary blood flow, but of pulmonary flow in relation to body weight (Rudolph and Heymann, unpublished data). However, pulmonary vascular resistance related to body weight remains fairly stable throughout the latter half of gestation. The development of the pulmonary vascular musculature may be crucial in determining the onset of symptoms in patients with congenital heart lesions, but effects of these lesions on the pulmonary circulation prenatally are poorly understood. Naeye and Blanc have noted that the pulmonary vascular smooth muscle is excessively thick in infants with premature closure of the foramen ovale. They have suggested that this is due to the fact that the total venous return to the fetal heart is now ejected by the right ventricle, with an unusually high pulmonary arterial pressure which stimulates undue muscle hypertrophy in the medial muscular layer.

It is interesting to speculate whether in fetuses in whom the pulmonary circulation is perfused by blood with higher $P_{O_2}$, such as in transposition of the great arteries or in mitral atresia, the pulmonary vascular smooth muscle is less fully developed, and whether this may influence the postnatal adjustments.

**Postnatal Changes in the Pulmonary Circulation**

Ventilation of the lungs after birth is associated with a dramatic increase in pulmonary blood flow (fig. 3). Although it has not been fully resolved, it appears that simple mechanical expansion of the lung alone does not produce any major reduction of pulmonary vascular resistance. However, the introduction of air into the alveoli produces a gas-fluid interface, and the surface forces tending to collapse the alveoli may exert some distending force on the small vessels in the interalveolar spaces, tending to hold them open. The most important factor in reducing pulmonary vascular resistance after birth is the rise in $P_{O_2}$ to which the pulmonary vessels are subjected. The increase in alveolar $P_{O_2}$ would hardly be expected to dilate the precapillary pulmonary arterioles, which are the major resistance vessels in the lung. Staub has shown, however, that oxygen diffuses into the precapillary vessels from surrounding alveoli, and in this manner could influence arterioles. The dilator effect of oxygen on pulmonary vascular smooth muscle is the opposite of that on most other vascular smooth muscle, but in spite of extensive investigative efforts, the reasons for this difference in the response of the vessels are unresolved. Lloyd has recently done a most intriguing experiment which suggests that the effect of oxygen and hypoxia on the pulmonary vessels is dependent on the release or inhibition of some substance from the lung parenchyma. He showed that a strip of pulmonary or carotid artery, when suspended in a bath, failed to constrict with hypoxia but that both arteries constricted in response to hypoxia when surrounded by a cuff of lung tissue.

The possible mediation of the oxygen effect on the pulmonary circulation after birth through release of bradykinin has received much attention recently. Campbell et al. showed that bradykinin is a potent vasodilator of fetal pulmonary blood vessels. Heymann et al. have demonstrated that expansion of fetal lamb lungs with oxygen, but not with nitrogen, results in a reduction in levels of kininogen, a bradykinin precursor, in left atrial blood, suggesting that bradykinin is formed in the lung. It was also shown that when the $P_{O_2}$ in the lamb fetus was raised by placing the ewe in a hyperbaric chamber in which she was ventilated with oxygen, there was measurable bradykinin formation.

In the normal infant, the ductus arteriosus constricts after birth, thus separating the pulmonary and systemic circulations, and the decrease in pulmonary vascular resistance
Effects of Changes of Placental Circulation and Pulmonary Vascular Resistance in Congenital Heart Lesions

The elimination of the placental circulation after birth results in a marked increase in overall systemic vascular resistance. This, associated with the fall in pulmonary vascular resistance, produces a reorientation of flow patterns in the circulation. While the ductus arteriosus remains widely patent, the pressures in the systemic and pulmonary circulations will remain the same, but there will be preferential flow of blood through the lungs with reversal of fetal right-to-left flow through the ductus to a neonatal left-to-right shunt. Normally, the ductus arteriosus is functionally closed within 10 to 15 hours after birth and pulmonary arterial pressure drops, while systemic arterial pressure increases further.18

When a congenital heart lesion exists in which there is equalization of systemic and pulmonary pressures, the hemodynamic disturbance and clinical features are largely dependent on the relationship between systemic and pulmonary vascular resistance. This applies to lesions such as large ventricular septal defects, large patent ductus arteriosus, truncus arteriosus communis, aortopulmonary fenestration, double outlet right ventricle, and single ventricle. The decrease in pulmonary vascular resistance after birth will favor flow through the lungs versus the systemic circulation. An increase in pulmonary venous return to left atrium and ventricle will result, with an increased diastolic volume in the ventricle, and on the basis of the Frank-Starling mechanism, in an increase in left ventricular stroke volume. The magnitude of the pulmonary blood flow and thus the degree of increase in left ventricular output would be directly determined by the ratio of pulmonary to systemic vascular resistance.

The importance of the pulmonary vascular resistance in regulating the hemodynamic changes with large systemic-pulmonary communications has been demonstrated experimentally with artificially controlled aortopulmonary shunts.19,20 When a large aortopulmonary shunt was opened in newly born

Figure 4
Decline in right ventricular systolic pressure after birth in the puppy, calf, piglet, and human infant. Difference in rate of decline of pressure is shown.

The initial dramatic fall of pulmonary vascular resistance at birth is associated with expansion of the lungs with air and is due to the release of pulmonary arteriolar vasoconstriction and possibly active vasodilatation. The subsequent fall is related to a decrease in the amount of pulmonary vascular smooth muscle. There is a rapid thinning of the medial muscle layer in the first few days after birth,9,16 and these histologic changes in the pulmonary vessels parallel the fall in pulmonary arterial pressure.17

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ventricular stroke volume which is shunted; and thus, to maintain systemic blood flow, left ventricular output will be increased accordingly. Left ventricular diastolic volume is markedly increased, and to maintain adequate filling, left ventricular end-diastolic and left atrial pressures are elevated. If left atrial and pulmonary venous pressures exceed plasma oncotic pressures, excess fluid accumulation will develop in the lung, producing pulmonary edema which, in the infant, is first manifested clinically by tachypnea and later dyspnea. Subsequently, right ventricular end-diastolic pressure rises, and evidence of right ventricular failure supervenes (fig. 6).

Factors Influencing Pulmonary Vascular Changes after Birth (Fig. 3)

On the basis of the relationship between the decline of pulmonary vascular resistance and the development of left-to-right shunt, it may be expected that symptoms of systemic-
Pulmonary communications would be evident within the first week after birth. It is, however, most unusual for the features of left ventricular failure to occur before 4 to 12 weeks have passed.\textsuperscript{21} The explanation for this occurrence can be found in the slower rate of fall of pulmonary vascular resistance in these infants. Whereas the pulmonary vessels appear to be normal histologically in fetuses with ventricular septal defect, there is persistence of the amount of smooth muscle in the media after birth.\textsuperscript{22} Physiologic studies have shown that pulmonary vascular resistance has not dropped normally in these infants with large ventricular septal defects. The resistance is in the same range as in normal infants in the immediate neonatal period; whereas it drops to levels of 1 to 3 mm Hg/L/min/m\textsuperscript{2} of body surface area within the first week in normal infants, it falls more gradually to levels of 2 to 6 mm Hg/L/min over a 4 to 12-week period in infants with large ventricular septal defects.\textsuperscript{21} This slower and less marked fall in pulmonary vascular resistance in infants with large systemic-pulmonary communications is most important in the adaptation of the circulation to the defect. The mechanism for this delay in pulmonary vascular change after birth has not been definitely elucidated. Since the large communication results in persistence of a pulmonary pressure equal to systemic pressure, it is possible that the retention of fetal smooth muscle is due to a response to the high pressure.

Hypoxia, due to alveolar hypoventilation or to exposure of subjects to low oxygen in the environment after birth, may markedly influence maturational changes in the pulmonary circulation. Arias-Stella and Saldaña\textsuperscript{23} have shown that the pulmonary vessels of individuals born and living at high altitudes in the mountains in Peru have a greater amount of pulmonary vascular smooth muscle after birth than those at sea level. Similar findings were reported by Naeye and Letts\textsuperscript{24} in a group of infants who had been hypoxic due to lung disease or hypoventilation from cerebral causes, for a considerable period after birth.

The persistence of a thick muscular media in the pulmonary vessels is associated with a delayed fall in pulmonary vascular resistance. Sime et al.\textsuperscript{25} and Peñaloza et al.\textsuperscript{26} have shown that pulmonary arterial pressure and pulmonary vascular resistance are considerably higher in young as well as older individuals living at altitude, suggesting that the pulmonary vessels retain a greater degree of smooth muscle into adult life if the stimulus for constriction remains. Studies in animals by Grover et al.\textsuperscript{27} have shown considerable species differences in the pulmonary vascular response to altitude. Whereas calves develop a markedly increased pulmonary vascular resistance when taken to altitude after birth and often develop right heart failure, lambs do not demonstrate much pulmonary vascular response. Grover and associates have suggested that humans have a variable response, some hyperreacting to hypoxia like calves and others showing little reaction. Pulmonary vessels in which the smooth muscle layer persists retain a much greater degree of responsiveness to vasoactive stimuli. In calves after birth, hypoxia and acidemia cause an extreme rise in pulmonary vascular resistance in the first 24 hours but a much smaller response after 4 days.\textsuperscript{28}

The persistent high pulmonary vascular resistance after birth resulting from hypoxia has a profound influence on hemodynamic effects and clinical features of systemic-pulmonary communications. Vogel et al.\textsuperscript{29} have compared infants with ventricular septal defect at the moderate altitude of Denver (5,280 feet) with those at sea level. A higher pulmonary blood flow and a much greater incidence of cardiac failure was found in those at sea level. Similar findings have been observed in infants with lung disease. We have frequently noted either a decrease in left-to-right shunt or an actual right-to-left shunt in infants with cardiac defects in association with lung disease; the clinical features of shunt murmur and mitral flow murmurs may also disappear. With improvement of the lung disease, typical features of the defect reappear (table 1).
Table 1

Infant with a Patent Ductus Arteriosus Had Atelectasis of the Right Lung at the Time of the First Catheterization Study

<table>
<thead>
<tr>
<th>Catheterization studies</th>
<th>First</th>
<th>After recovery</th>
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</thead>
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<tr>
<td>O₂ saturations (%)</td>
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<td></td>
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<tr>
<td>Superior vena cava</td>
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<td>70</td>
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<tr>
<td>Right atrium</td>
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<td>69</td>
</tr>
<tr>
<td>Right ventricle</td>
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</tr>
<tr>
<td>Pulmonary artery</td>
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<tr>
<td>Left atrium</td>
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<td>96</td>
</tr>
<tr>
<td>Right pulmonary vein</td>
<td>64</td>
<td>98</td>
</tr>
<tr>
<td>Descending aorta</td>
<td>58</td>
<td>98</td>
</tr>
<tr>
<td>Pressures (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Right atrium</td>
<td>m 5</td>
<td>m 2</td>
</tr>
<tr>
<td>Left atrium</td>
<td>m 3</td>
<td>m 3</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>62 m 74</td>
<td>22 m 30</td>
</tr>
<tr>
<td>Descending aorta</td>
<td>95</td>
<td>108</td>
</tr>
</tbody>
</table>

NOTE: At the time of the first study, the oxygen saturation in the right pulmonary vein was decreased, and there was a lower saturation in the descending aorta compared to the left atrium suggesting a right-to-left shunt through the ductus arteriosus. No left-to-right shunt was detected. Pulmonary arterial pressure was markedly elevated to systemic levels and right atrial pressure was higher than that in the left atrium. After recovery, the infant had a large left-to-right shunt through the ductus arteriosus with no right-to-left shunt. The pulmonary arterial pressure was considerably reduced, as was right atrial pressure.

In certain unusual instances, the pulmonary vascular resistance may fall very rapidly after birth. This could be related to an abnormally rapid regression of smooth muscle, as suggested by Heath et al.⁵⁰ in two infants who died on the second day after birth as a result of left ventricular failure resulting from patent ductus arteriosus. It is also possible that there may be a great difference in the behavior of the pulmonary vasculature after birth in premature as compared with mature infants. It is evident that the onset of cardiac failure in premature infants often occurs within the first month after birth, whereas in mature infants, although failure may be observed this early, it is usually delayed to the second or third month (Hoffman and Rudolph, unpublished observations). Also, a high incidence of cardiac failure is associated with persistent patent ductus arteriosus in premature infants within the first 4 weeks after birth, particularly in those weighing under 1,500 g. The greater susceptibility of premature infants with cardiac defects to early cardiac failure could be related to a difference in pulmonary vasculature. The actual pulmonary vascular resistance decreases in the latter part of gestation, but pulmonary vascular resistance in relation to fetal body weight does not change significantly.¹⁰ This change could be related to an increase in diameter of the vessels or to growth of new vessels but is almost certainly not due to a progressive decrease in vascular tone, as the amount of smooth muscle in the pulmonary arterioles increases with advancing gestation⁶ (fig. 3). Thus, a prematurely born infant may have a pulmonary vascular resistance at birth equivalent to that of a full-term infant in relation to body weight, but since there is less smooth muscle in the pulmonary arterioles, a more rapid drop in pulmonary vascular resistance, with early onset of symptoms of failure, may be expected in the presence of the applicable cardiac lesions.

Atrial Septal Defect and the Pulmonary Circulation

Although it has generally been supposed that the foramen ovale is functionally closed after birth, studies in newborn infants on the first day of life have revealed some left-to-right shunt across the atrial septum.¹⁹ Subsequent observations have demonstrated that several infants in the first few months after birth may have an atrial left-to-right shunt which later disappears; this is probably related to an incompetence of the foramen ovale flap, which later closes (Hoffman, Danilowicz and Rudolph, unpublished data). The development of an atrial left-to-right shunt after birth was at one time explained on the basis of an increase in right ventricular muscle compliance, associated with a decreased thickness of right ventricular muscle after birth. This thesis cannot, however, explain atrial left-to-right shunt in the immediate postnatal period.

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Shunting in atrial septal defect is probably also directly related to the fall in pulmonary vascular resistance after birth. A decrease in the impedance against which a ventricle is ejecting will result in an increased stroke volume. Thus, as pulmonary vascular resistance falls and systemic vascular resistance rises after birth, the stroke volume of the right ventricle will be higher than that of the left. If there is a large atrial septal defect which allows for an equalization of atrial pressures, the right ventricle, which has undergone a greater systolic emptying, will fill preferentially. If there is no communication between the left and right ventricles, or aorta and pulmonary artery, the fall in pulmonary vascular resistance will result in a drop of pulmonary arterial pressure, and the left-to-right shunt will be greater. The importance of the relationship between systemic and pulmonary vascular resistances in influencing shunting has been recently demonstrated in experimental atrial septal defects in adult dogs.

Dependent and Obligatory Shunting (Fig. 7)

To explain some of the phenomena observed in patients with congenital heart lesions, I would like to introduce the concept of dependent and obligatory (or independent) shunting. As I have already discussed, the development of left-to-right shunts in patients with large communications between the aorta and pulmonary artery, between the two ventricles, and between the left and right atria, is dependent on the decrease in pulmonary, relative to the systemic, vascular resistance. In certain other lesions, however, there may be an arteriovenous shunt in which the magnitude of the shunt is unrelated to the changes in pulmonary vascular resistance. When there is a direct communication between systemic arteries and systemic veins, or between the left ventricle and the venous atrium, an obligatory shunt, which is independent of changes in pulmonary vascular resistance, will occur. Lesions which fall into this category are large congenital arteriovenous fistulae, such as cerebral arteriovenous fistulae or aneurysms of the great vein of Galen (fig. 8), congenital sinus of Valsalva

![Figure 7](image_url)

**Figure 7**

Dependent and obligatory shunts. With dependent shunts the change in pulmonary vascular resistance is followed by changes in pulmonary blood flow. The postnatal fall in pulmonary vascular resistance is associated with an increase in pulmonary blood flow. Later, when secondary pulmonary vascular disease occurs and resistance rises, pulmonary blood flow falls. In obligatory shunts, the high pulmonary blood flow prevents the normal drop in pulmonary vascular resistance and subsequently pulmonary vascular resistance rises but does not significantly affect the increase in flow.

![Figure 8](image_url)

**Figure 8**

Diagram of circulation in large cerebral arteriovenous fistula with an obligatory shunt. The large pulmonary blood flow prevents the normal fall of pulmonary arterial pressure and resistance. Right-to-left shunt through the foramen ovale and ductus arteriosus (if patent) occurs. Pressures shown in cardiac chambers and great vessels. RA (right atrium) mean pressure elevated. LA (left atrium) mean pressure elevated. RV (right ventricle) systolic pressure at systemic levels and PA (pulmonary artery) pressure is equal to that in aorta. CA = carotid arteries. Pressures in mm Hg.
communications with the right atrium, left ventricular-right atrial shunts, and certain types of atrioventricularis communis. The importance of the appreciation of this concept is well demonstrated in patients with atrioventricularis communis. Although these patients have an atrial and a ventricular communication with deformed mitral and tricuspid valves, it is not usually possible from an examination of the anatomy of the defects to reconstruct the physiologic disturbance. Careful examination of cineangiograms in a group of infants with atrioventricularis communis defects has revealed great differences in the type of shunting that occurs after injection of contrast medium into the left ventricle and left atrium (fig. 9). In some cases, a predominant shunt from left-to-right ventricle, or left-to-right atrium occurs, with negligible mitral regurgitation or shunting from the left ventricle to the right atrium. These may be classified as dependent shunts. In others, an enormous shunt occurs from the left ventricle, either directly into the right atrium or through a deformed mitral valve into the left atrium and then across the atrial defect into the right atrium, resulting in an effective left ventricular to right atrial shunt. These infants have obligatory shunts. The importance of this concept in regard to pulmonary vascular changes after birth is discussed later, but it is also of great importance in considerations regarding treatment of patients with atrioventricularis communis by pulmonary artery banding to control cardiac failure. In those individuals who have a dependent shunt, pulmonary vascular resistance influences the size of the shunt and thus pulmonary artery banding, which increases outflow impedance from the right ventricle, would decrease the shunt and lessen the failure. In the presence of an obligatory shunt, however, banding would not materially influence the left ventricular to right atrial shunt; a pressure load would be added to the volume load on the right ventricle, with the probability that right ventricular failure would result.

**Pulmonary Arterial Pressure, Pulmonary Blood Flow, and Pulmonary Vascular Resistance**

The persistence of a high pulmonary vascular resistance after birth in the presence of large aortopulmonary communications is probably related to a maintained high pulmonary arterial pressure; changes in pulmonary blood flow are secondary to changes in pulmonary vascular resistance. A good deal of evidence has now been accumulated indicating that a persistent elevation of pulmonary blood flow after birth may also prevent the normal decrease in pulmonary vascular resistance. Pneumonectomy or ligation of the left pulmonary artery in young puppies resulted in the development of an elevated pulmonary arterial pressure; this did not occur in adult dogs. Vogel et al. have performed an interesting series of experiments in which the effects of mild hypoxia and of an increased pulmonary blood flow produced by ligation of one pulmonary artery were shown to be additive in stimulating pulmonary vasoconstriction in newborn calves. Newborn calves born in Denver showed similar pulmonary arterial pressures to those born at sea level; left pulmonary artery ligation at sea level did not result in any significant difference in pulmonary arterial pressures. However, ligation of the left pulmonary artery in calves in Denver resulted in marked progressive pulmonary hypertension.

Pulmonary hypertension and a delayed fall of pulmonary vascular resistance are also

**Figure 9**

Diagrams of dependent and obligatory shunt in atrioventricularis communis: Dependent shunt is a left-to-right atrial and left-to-right ventricular shunt. Obligatory shunt is a direct shunt from left ventricle to left atrium and right atrium.
observed in infants with high pulmonary blood flow due to obligatory shunts. Walker et al., commented on the persistence of increased pulmonary vascular resistance in an infant with a large arteriovenous fistula between the subclavian artery and the superior vena cava.

In four infants with cerebral arteriovenous fistulae whom we studied by cardiac catheterization, pulmonary arterial pressures were maintained at or near systemic levels. In three of these patients, pulmonary vascular resistance was maintained at levels high enough to result in right-to-left shunting through a patent ductus arteriosus, or patent foramen ovale or both (fig. 8). This represents the interesting situation in which an obligatory left-to-right shunt may maintain the pulmonary vascular resistance at a level high enough to result in right-to-left shunting through a systemic-pulmonary communication.

In patients with atrioventricular communis, a similar situation may exist. We have frequently encountered infants who have large left ventricular to right atrial shunts, who have high pulmonary vascular resistances and shunt right to left through a patent ductus arteriosus. This hypothesis also helps to explain the fact that many infants with atrioventricularis communis have considerably higher pulmonary vascular resistance than infants of similar age with a huge ventricular septal defect or patent ductus.

Increased pulmonary blood flow is probably important, not only in preventing the normal maturational changes in the pulmonary blood vessels, but also in causing the secondary intimal proliferative and obstructive changes. Patients with atrial septal defect frequently develop these changes in the second or third decades, whereas intimal damage occurs much earlier in children with ventricular septal defects. Fry has recently demonstrated that intimal damage results from the shearing forces attendant on an elevation of pulmonary blood flow to about three times normal levels. In normal or dilated pulmonary vessels seen with atrial septal defect, the changes develop slowly and only become evident after many years. When pulmonary vessels are constricted by muscular hypertrophy, as occurs in ventricular septal defect or patent ductus arteriosus, the shearing force on the endothelium with increased pulmonary blood flow is much greater, and thus early intimal damage may result. This effect of blood flow on the endothelium of constricted vessels may also explain the intimal damage occurring in the pulmonary circulation of individuals living at high altitude.

**Postnatal Changes in the Main and Branch Pulmonary Arteries**

Although the decrease in pulmonary vascular resistance after birth is largely associated with changes in the precapillary pulmonary vessels, alterations in the configuration of the pulmonary artery trunk and its main branches may play some part in postnatal adjustments (Danilowicz, Hoffman, Heymann, and Rudolph, unpublished data). The main pulmonary artery continues as a major trunk into the ductus arteriosus in the fetus, and the left and right pulmonary arteries arise as branches from this trunk (fig. 10). We have also observed that there is frequently a pressure drop between the main pulmonary artery and its right and left branch in newborn infants as well as in newborn animals. This pressure difference may be associated with a systolic murmur in the periphery of the chest, suggesting peripheral pulmonary stenosis. With growth of the infant, the discrepancy in size between the main pulmonary artery and its branches disappears, the pressure difference is no longer detectable, and the murmurs disappear.

**The Ductus Arteriosus**

**Closure of the Ductus Arteriosus**

The ductus arteriosus in the fetus is a large communication between the main pulmonary artery and the aorta, and it conducts the major portion of right ventricular output into the descending aorta. Several investigations have demonstrated that the ductus constricts when the oxygenation of the arterial blood is increased. The actual level to which \( P_o \) must be elevated before ductal closure occurs
is not known. Although Assali and associates\textsuperscript{37} have reported a linear relationship between $P_{O_2}$ and ductal resistance in the lamb, this study is open to some question since ductal constriction continued to increase when $P_{O_2}$ was elevated to 600 mm Hg. Yet in lambs born normally, complete ductal closure may be observed although $P_{O_2}$ levels are only raised to about 80 mm Hg. It is possible, however, that there are factors other than the increase in $P_{O_2}$ after birth, which are responsible for ductal closure. The role of bradykinin in closure of the ductus arteriosus has not been delineated. Bradykinin produces constriction of the ductus arteriosus\textsuperscript{39} and is present in arterial blood after birth.\textsuperscript{40} However, it is not known whether it is important in normal physiologic closure.

In the normal full-term human infant, the ductus arteriosus is functionally closed within 10 to 15 hours after birth.\textsuperscript{19} If it remains open, a small left-to-right shunt will be present, since pulmonary vascular resistance falls and systemic resistance rises. The initial closure is due to muscular contraction, and the ductus may reopen if there is a decrease in arterial $P_{O_2}$. Moss and associates\textsuperscript{41} showed that hypoxemia produced by ventilation with low oxygen gas mixtures could reopen the ductus up to the third day after birth. Subsequent closure is due to thrombosis in the subintimal region with fibrosis. In normal mature infants, the ductus is permanently closed within 2 to 3 weeks after birth.\textsuperscript{42}

We have previously reported delayed closure of the ductus arteriosus in several premature infants.\textsuperscript{43} More recently a review of all premature infants born in the University of California Medical Center has revealed an incidence of patent ductus arteriosus of 13%. All were diagnosed by clinical features of a typical murmur and bounding peripheral
pulses, and in many the lesion was confirmed by cardiac catheterization. Although many of these infants required no therapy, or responded to medical management, and then the ductus subsequently closed spontaneously, some required surgical closure because of uncontrollable failure (Kitterman, Stanger, Phibbs and Rudolph, unpublished observations). Cardiac failure was frequently manifest in these infants within the first month after birth; this early onset of failure was probably related to a rapid decrease in pulmonary vascular resistance in the premature infant, as discussed above. The reason for this delayed closure of the ductus arteriosus in the premature infant is not known. The possibility that it is due to a lower $P_{O_2}$ in arterial blood of premature infants associated with ventilatory difficulties has been considered, but a definite relationship has not been confirmed. Patent ductus arteriosus has been frequently observed after recovery from an episode of neonatal respiratory distress, and in several of our patients this was also noted. Another possibility is that the ductal smooth muscle is poorly developed in early gestation and is unable to effect immediate postnatal closure.

**Hypoxemia, Congenital Heart Disease, and the Ductus Arteriosus**

An interference in adequate oxygenation of arterial blood after birth may prolong or prevent ductal closure. The incidence of patent ductus arteriosus in individuals who are born, and continue to live, at high altitude is much greater than those born at sea level. Marticorena et al. reported an incidence of 0.74% in children living in Cerro de Pasco at 14,200 feet as compared to 0.05% in Lima at sea level. It is also well recognized that the ductus arteriosus is frequently patent for a longer period than usual in infants with congenital heart lesions associated with severe hypoxemia. In patients with pulmonary atresia or tricuspid atresia with intact ventricular septum, the ductus arteriosus is usually the only means by which blood may reach the lungs for oxygenation. The other mechanism for providing a pulmonary blood flow is through a large bronchial collateral circulation, but this is rarely adequately developed in early infancy. An interesting balance between the size of the ductus arteriosus and the arterial $P_{O_2}$ exists in these infants. If the ductus remains widely patent, a large pulmonary blood flow may be maintained. This would allow the arterial $P_{O_2}$ to increase, thus tending to close the ductus arteriosus, thereby reducing pulmonary blood flow. The persistence of a decreased arterial $P_{O_2}$ does not, however, always prevent ductal closure in later infancy and as this occurs, increasing hypoxemia and metabolic acidemia develops. The reason that the ductus closes in spite of continued hypoxemia is not at all clear. It is possible that intimal thrombosis occurs in spite of continued reduction of arterial $P_{O_2}$. No information is available regarding the size of the ductus arteriosus in fetuses or in infants at the time of birth in whom pulmonary or tricuspid atresia is present. Since pulmonary blood flow is small in the fetus, it is possible that the ductus is underdeveloped. The presence of an abnormally small ductus arteriosus in the fetus may account for the fact that the ductus may not be able to provide adequate pulmonary flow after birth in these infants. Whatever the cause of ductal closure in spite of persistent hypoxia in these infants with cyanotic congenital heart disease, the event may occur suddenly and result in the rapid demise of the infant.

**Systemic Blood Flow and the Ductus Arteriosus**

The ductus arteriosus is extremely important in providing adequate systemic blood flow in several congenital cardiac anomalies. In aortic atresia or mitral atresia with intact ventricular septum, the ductus arteriosus is the only means by which blood may enter the systemic arterial system. Inability to maintain an adequate systemic blood flow is the major difficulty in these infants. Immediately after birth, while the ductus arteriosus is wide open, the infant may have normal peripheral pulses, but as ventilation is established and $P_{O_2}$ increases in the blood perfusing the ductus from the pulmonary artery, there is a tendency for ductal constriction to occur. This results
in a fall of systemic arterial pressure below
that in the pulmonary artery, with poor pulses
and pallor due to peripheral vasoconstriction.
It is common practice to administer oxygen
to infants in cardiorespiratory difficulties after
birth. Although there is at present no evidence
to support it, the possibility that this practice
may be disadvantageous to these infants by
stimulating ductal constriction should be
seriously considered. The ductus arteriosus
may also be important in determining the
clinical features of infants with coarctation
of the aorta. When severe preductal coarctation
is present, the ductus arteriosus may provide
the major blood flow to the descending aorta.
Should ductal closure occur before the estab-
lishment of an adequate collateral circulation,
a marked increase in pressure in the proximal
aorta and left ventricle would have to be
developed in order to sustain flow across the
obstruction. I have had personal experience
with two infants in whom femoral pulses were
well palpable and blood pressures (by flush
method) were equal in the legs and arm in
early infancy, who developed severe cardiac
failure 1 and 3 weeks later and were
demonstrated to have severe coarctation of
the aorta of the adult type. This rapid onset of
cardiac failure several weeks after birth could
be related to ductal closure.

The Foramen Ovale

The foramen ovale permits passage of blood
from the inferior vena cava to the left atrium
in the fetus. It has been suggested that
premature closure of the foramen in utero
may cause hypoplasia of the left side of the
heart because only a minimal amount of blood
would reach the left atrium.47 After birth, the
foramen ovale closes by apposition of the left
and right atrial flaps bordering the opening.
The closure is effected by the reversal of the
fetal right-to-left atrial pressure difference. In
a number of infants with no evidence of heart
disease, the closure is not absolute, and an
atrial left-to-right shunt may be detected for
several months after birth (Hoffman, Danilo-
wicz and Rudolph, unpublished observa-
tions). In infants with lesions causing an
elevation of the left atrial pressure, such as
left-sided obstructive lesions, patent ductus
arteriosus, or ventricular septal defect, the
left-to-right shunt through the foramen may
be very large but disappears if the cause of
the left atrial pressure elevation can be
removed.48 It is possible that by decreasing
left atrial pressure the severity of the pulmo-
nary edema may be diminished.

Conditions which elevate right atrial pres-
sure will cause blood to shunt right to left
through the foramen particularly during in-
fanty. Infants with pulmonary disease with
increased pulmonary vascular resistance may
have enormous right-to-left shunts through the
foramen, which contribute to the arterial
cyphoxemia. Right-to-left shunt through the
foramen may, however, be the only means of
survival in infants with pulmonary atresia and
intact ventricular septum or tricuspid atresia.
It allows the total systemic venous return to
enter the left atrium, where admixture with
pulmonary venous blood occurs. The foramen
ovale also provides the total systemic arterial
supply in most patients with total pulmonary
venous drainage anomaly.

In infants with left-sided obstructive lesions
such as mitral atresia, the foramen ovale may
be the only means by which pulmonary
venous blood may enter the right heart, then
to be distributed with systemic venous blood
to pulmonary and systemic circulations.

Persistent patency of the foramen ovale is
very important in postnatal survival of infants
with transposition of the great arteries and an
intact ventricular septum. These infants re-
quire both shunting of systemic venous blood
to the pulmonary circulation for oxygenation
and shunting of pulmonary venous blood to
the systemic circulation to provide oxygen to
the tissues. Usually in the immediate postnatal
period, the drop in pulmonary vascular
resistance permits a shunt from the aorta to
the pulmonary artery through the ductus
arteriosus. The foramen ovale provides an
opening for passage of blood from the left to
the right atrium. If left atrial pressure exceeds
right atrial pressure, the foramen will close,
thus interfering with the shunt, which is
essential for survival. Enlargement of the

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foramen ovale or creation of an atrial septal defect to permit bidirectional shunting has effectively prolonged the life of these infants.49, 50

The Ductus Venosus

Although the ductus venosus is an abdominal structure, it is important in determining the clinical features of a congenital cardiac anomaly in which all the pulmonary veins enter the portal vein (fig. 11). The clinical course of infants with total pulmonary venous drainage connection is largely determined by the degree of obstruction to pulmonary venous return into the systemic circulation (Tarnoff, Rudolph and Hoffman, unpublished observations). When there is obstruction, the infants manifest severe pulmonary edema and cyanosis due to the markedly elevated pulmonary venous pressure. When the pulmonary veins all drain to the portal vein, closure of the ductus venosus would necessitate passage of the total pulmonary venous return through the hepatic circulation, which imposes considerable impedance with an effective obstruction. While the ductus venosus remains open, the infant may not have severe symptoms for several weeks, but pulmonary edema rapidly develops as the vessel closes.

Conclusion

I have attempted to convey to you the profound influence that circulatory changes at the time of birth may have on the physiology of the circulation in congenital heart disease. Many questions are left unanswered; among the most provocative are: Why does oxygen dilate the pulmonary vessels and constrict the ductus arteriosus? Is there a chemical mediator for the effects of oxygen? What is the relationship between ductal oxygen and P02? How does the presence of various congenital cardiac defects influence the development of the pulmonary circulation and the ductus arteriosus during fetal life; and how do fetal developmental disturbances influence postnatal adaptation? I hope that my presentation will stimulate you to seek the answers since they have great bearing on our management of infants with congenital heart disease.

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