Persistence of Fetal Ductus Function after Birth
The Ductus Arteriosus as an Avenue of Escape

By HERBERT L. ABRAMS, M.D.

Within recent years there has been increasing interest in the presence of reversed flow through the ductus arteriosus. Most reported cases have been in older children and young adults. There is a group of cases in which the ductus serves as a site of a veno-arterial shunt in infancy, and thus continues to perform its fetal function. The conditions under which veno-arterial shunting persists after birth are illustrated and analyzed, and an effort is made to clarify the common features of these lesions.

The function of the ductus arteriosus in the fetal circulation as a carrier of blood from the pulmonary artery to the aorta has been carefully studied and well documented. It is generally accepted that the resistance to flow through the unexpanded lungs and fetal pulmonary arteries is sufficiently high to explain the passage of blood from the pulmonary artery into the descending aorta, which must constitute a receptacle of lower resistance. Some veno-arterial shunting through the ductus arteriosus may persist in a significant percentage of normal infants up to the age of 3 days, although an arteriovenous shunt develops in most normal infants shortly after birth. The pulmonary hypertension of the fetus is sustained for a variable time after birth. Anatomic closure of the ductus normally occurs in 4 to 8 weeks after birth.

If the ductus remains patent, it usually functions as an arteriovenous fistula, aortic blood entering the relatively low-resistance pulmonary circuit through the ductus. Within recent years, there has been increasing interest in the association of pulmonary hypertension with patent ductus arteriosus, and in particular in the so-called “reversal of flow” that is occasionally found.* In such cases, the ductus arteriosus may constitute an “avenue of escape,” which protects the right ventricle from having to force its entire output through a contracted pulmonary arterial bed, and thereby prevents it from failing.

The role of the ductus arteriosus as an escape valve may be discerned in a number of malformations. In all these conditions, the pulmonary vascular resistance must be higher than the resistance to blood flow in the descending aorta; but, in some, the fundamental difficulty almost certainly lies in the inability of pulmonary blood to reach the left heart and systemic circulation through normal channels (table 1). A description of the sites of obstruction to flow in these anomalies may clarify the role of the ductus when it retains its fetal function.

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*The term “reversal of flow” refers to a predominantly veno-arterial (pulmonary artery to aorta) shunt through the ductus arteriosus, in contrast to the arteriovenous (aorta to pulmonary artery) shunt that is usually present when the ductus arteriosus remains patent beyond the newborn period.

Table 1.—Conditions Associated with Veno-Arterial Shunting of Blood Through the Ductus Arteriosus in Infancy

| 1. Isolated patent ductus arteriosus with marked increase in pulmonary resistance |
| 2. Patent ductus arteriosus associated with congenital pulmonary disease |
| 3. Pulmonary vein atresia |
| 4. Mitral atresia |
| 5. Mitral stenosis |
| 6. Aortic atresia |
| 7. Interruption of the aortic arch |
| 8. Pseudovalvular coarctation |

Circulation, Volume XVIII, August 1958
Fig. 1. Case 1. Isolated patent ductus with reversal of flow. A. Posteroanterior film. There is gross cardiac enlargement, mainly right ventricular and right atrial as determined in the oblique projections. Peripheral vascularity is diminished, and the central vessels are poorly delineated. The diminished vascularity is a reflection of increased resistance in the pulmonary arterial bed. B. Retrograde brachial aortogram. The opaque medium has been injected into the brachial artery, and fills the left subclavian artery, the aortic arch and the descending thoracic aorta. Minimal reflux into the mouth of the ductus arteriosus is visible (arrow). C. and D. Angiocardiogram demonstrates the enormous size of the right ventricle (RV) and its outflow tract. The main pulmonary artery (PA) is also enlarged. There is an abrupt taper in the size of the pulmonary arteries beyond the main branch division. Synchronous with pulmonary artery opacification, the descending thoracic aorta opacified through the ductus arteriosus. At autopsy, the only congenital cardiac anomaly was a large patent ductus arteriosus. (RA = right atrium.)
Fig. 2. Case 2. Reversal of flow through the ductus arteriosus in the presence of congenital pulmonary disease. A. Posteroanterior projection. The cardiac outline cannot be clearly delineated, indicating the presence of disease anteriorly placed in the lungs. Hyperexpansion of the lungs is noted. B. Left lateral projection demonstrates the overexpanded lower lobes, *Continued on opposite page*
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SITES OF INCREASED RESISTANCE TO BLOOD FLOW WHEN THE DUCTUS ARTERIOSUS RETAINS ITS FETAL FUNCTION

1. In the Pulmonary Arterial Bed (Isolated Patent Ductus Arteriosus with Reversal of Flow)

Case 1. This infant was noted to have tachypnea shortly after birth, and clubbing of the toes, associated with lower limb cyanosis, by 9 months. He was underdeveloped, and gradually developed intractable right heart failure, with generalized cyanosis. On physical examination a right ventricular heave, a soft systolic murmur to the left of the sternum, and a loud pulmonic second sound were noted. The red blood cell count was 8.7 million mm$^3$ and the hemoglobin 16 Gm. per 100 ml. The electrocardiogram showed a pattern of right ventricular hypertrophy.

Roentgenologic studies showed cardiac enlargement, mainly right ventricular, with a striking diminution in peripheral vascularity (fig. 1A). The clarity of the peripheral lung fields indicated diminished blood flow through the pulmonary arterial bed, reflecting the increased pulmonary resistance. A retrograde aortogram (fig. 1B) demonstrated no evidence of coarctation, and angiocardiographic studies (fig. 1C) showed opacification of the descending aorta from the pulmonary artery through a patent ductus arteriosus. In spite of therapy, intractable right heart developed, and death followed. At autopsy, a patent ductus arteriosus was the only cardiovascular malformation found. Marked right ventricular hypertrophy was present.

Comment. A number of recent studies have clarified the clinical, radiologic, and physiologic criteria for diagnosis of patent ductus arteriosus with reversal of flow.\textsuperscript{10-17} There has been much speculation as to whether the increase in pulmonary resistance develops because of a sustained elevation of pulmonary blood flow, or is congenital in origin. Almost certainly, both explanations are correct. In case 1, as in other cases with cyanosis at birth and thereafter,\textsuperscript{16} the venoarterial shunt of the fetus was present during the postnatal period and hence pulmonary resistance must have been sustained at the fetal level. In those cases in which the reversal of shunt and development of cyanosis later in life has been verified, the pulmonary resistance must have increased over a period of years. This is in accord with experimental evidence indicating that marked pulmonary hypertension can be produced by creating an artificial "ductus arteriosus."\textsuperscript{12-20} When the ductus is the site of a large right-to-left shunt in older patients, it is again fulfilling the function of an escape valve. Surgical closure is usually accompanied by right heart failure and death.\textsuperscript{16, 18, 19}

2. In the Pulmonary Parenchyma (Reversal of Flow Through the Ductus Arteriosus in the Presence of Congenital Pulmonary Disease)

Case 2. A 5-week-old baby entered the hospital because of persistent respiratory distress. On physical examination tachypnea and tachycardia were apparent. There was a grade II systolic murmur heard best in the second left intercostal space, associated with a loud pulmonic second sound. Conventional roentgenologic studies demonstrated bilateral upper lobe collapse (or failure of expansion) with hyperexpansion of the lower lobes (fig. 2). On bronchography, no upper lobe bronchi could be delineated. The heart borders were difficult to define. Angiocardiography, performed in order to delineate the pulmonary arterial branches, demonstrated larger central pulmonary arteries with absence of both upper lobe pulmonary arteries and filling of the descending thoracic aorta from the pulmonary artery through a large ductus arteriosus (figs. 2C-2F). Retrograde thoracic aortography showed no evidence of coarctation of the aorta. The child is still alive but severely ill.

Comment. In the absence of necropsy and the areas of density anteriorly placed which represent the unexpanded or collapsed upper lobes. No upper lobe bronchi were delineated on bronchography. C. and D. Angiocardiogram, anteroposterior projection. A huge pulmonary artery (PA) is opacified from the right ventricle (RV), and immediately thereafter, the descending thoracic aorta is clearly filled with the opaque medium. No upper lobe pulmonary arteries are visible, and there is truncation of the remaining pulmonary arteries. E. and F. Lateral angiocardiogram demonstrates the opaque medium entering the right atrium (RA) from the superior vena cava (SVC). Right ventricular (RV) and pulmonary artery (PA) opacification follow. Synchronous with this, the descending thoracic aorta is opacified through a patent ductus arteriosus (PDA).
proof, it is impossible entirely to exclude other factors that might be responsible for reversal of flow. On the other hand, it is well known that extensive pulmonary disease—such as fibrosis and emphysema—may increase the resistance to blood flow through the lungs and provoke pulmonary hypertension and cor pulmonale.\textsuperscript{21} Agensis of the upper lobes, associated with marked hyperexpansion of the lower lobes, offers a reasonable explanation for increased resistance to flow through the lungs. Whether hypoxia, which is known to cause elevation of pulmonary artery pressure,\textsuperscript{22} is a major factor in the increased resistance, or whether compression of the pulmonary capillary bed and the smaller arterial branches is an important factor\textsuperscript{23} cannot be stated with assurance.

Cardiac enlargement has been noted to accompany pulmonary disease in newborn infants.\textsuperscript{23, 24} In these cases, the early cor pulmonale that is noted with neonatal atelectasis or extensive neonatal pneumonitis may be reversed with regression of the pulmonary disease.\textsuperscript{25} The cor pulmonale itself reflects the increased resistance to blood flow through the lungs.\textsuperscript{23} In this regard, it is of interest that a recent case has been reported in which agenesis of the left lung was associated with reversal of flow through the ductus arteriosus, although this patient was in a somewhat older age group.\textsuperscript{26}

3. In the Pulmonary Venous Bed (Atresia of the Pulmonary Veins)

Case 3. A 16-day-old infant entered the hospital because of tachypnea and tachycardia that had developed at about the age of 1 week. Grade I systolic and diastolic murmurs were heard in the first and second left interspaces. Rales were audible at both bases, the liver was down 5 cm. below the costal margin, and there was suggestive cyanosis of the nailbeds. The electrocardiogram showed a pattern of right ventricular hypertrophy. Chest films showed diffuse mottling of both lungs with poorly defined heart borders but obvious cardiac enlargement (fig. 3A). It was impossible to be certain whether the pulmonary densities were all on the basis of pulmonary edema, or whether there was significant pulmonary parenchymal dis-

Fig. 3. Case 3. Reverse ductus flow in the presence of pulmonary vein atresia. A. Posteroanterior projection 16 days of age. There are marked bilateral pulmonary congestion and cardiac enlargement. The right heart border is obscured by the overlying pulmonary densities. B. Posteroanterior projection, 23 days of age. Both lungs are now diffusely opaque except at the periphery. The degree of pulmonary congestion has increased markedly during the preceding week. (Compare with figure 5A.)
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ease. In spite of oxygen therapy and continued digitalization, the infant's course progressively worsened. At 23 days of age, the mottling of the lungs had increased significantly (Fig. 3B). Death occurred at 1 month of age. At autopsy, the right atrium and right ventricle were enormous, but the left atrium and left ventricle were diminutive (Fig. 3C). A common pulmonary vein with a completely occluded lumen was connected to the left atrium. The ductus arteriosus was patent, and there was a small patent foramen ovale. Marked pulmonary congestion and large bronchial and subpleural veins were noted.

Comment. Blood leaving the right ventricle entered the pulmonary arteries and veins, was unable to reach the left atrium through the occluded common pulmonary vein, and was forced to leave the pulmonary vascular bed through the ductus arteriosus or bronchial collateral veins. Because of the obstruction to venous return from the lungs, marked pulmonary congestion developed (clearly explaining the roentgen findings).

The fetal circulation was not sufficiently embarrassed to cause death in utero because right heart blood could reach the left heart through the patent foramen ovale, and could reach the aorta through the ductus arteriosus. The fact that survival to 30 days was possible is unusual, since blood exposed to alveolar oxygen could only leave the lungs through the bronchial veins, flowing into the azygos system, and returning to the heart through the superior vena cava. This permitted only a limited amount of mixing of systemic venous blood and oxygenated pulmonary venous blood in the right cardiac chambers. Blood from the right heart reached the systemic circulation through the ductus arteriosus or possibly through the small patent foramen ovale. The marked hypoplasia of the left atrium and left ventricle reflects the insignificant role that they played in the circulation.

Edwards et al.27 have described a case of atresia of a common pulmonary vein, but the presence of a communication between the proximal portion of the vein and the superior vena cava enabled pulmonary venous blood to leave the lungs without excessive pulmonary engorgement. Their case, then, is essentially one of total anomalous pulmonary venous return into the superior vena cava. In such cases, one might expect the ductus arteriosus to remain open; but the tremendous dilatation of the right atrium is usually accompanied by a large patent foramen ovale, allowing right-to-left shunt. Nonetheless, in a few such cases, patency of the ductus has persisted.28, 29 Similarly, in the rare cor triatriatum, patency of the ductus arteriosus might be expected, but has not yet been reported.30

4. At the Mitral Valve

Mitral Atresia with Patent Foramen Ovale

Case 4. A Negro infant was noted to be cyanotic on the second day of life. Respiration became labored on the following day. On physical examination, a systolic murmur was heard over the precordium and a large liver was felt. The electrocardiogram showed a pattern of right ventricular hypertrophy. Chest films demonstrated gross cardiac enlargement, mainly involving the right cardiac chambers, and moderate pulmonary engorgement (fig. 4A). In spite of digitalization, the child died 4 days later. Autopsy demonstrated mitral atresia, a huge pulmonary artery, and a patent ductus arteriosus larger than the proximal
tion no murmurs were heard. Respirations were rapid and shallow, and in spite of oxygen therapy cyanosis persisted and episodes of apnea were noted. Chest x-rays showed diffuse densities throughout both lung fields (fig. 5A). The child died 11 hours after birth, when she failed to be revived from an episode of apnea. At autopsy, mitral atresia with an imperforate foramen ovale, a single ventricle, a large ductus that supplied the entire systemic circulation, moderate coarctation, and aortic atresia were noted. (fig. 5B).

Multiple collateral pleural vessels were present, and there was a good deal of fluid in the alveoli.

Comment. In the presence of mitral atresia, normal left atrial emptying into the left ventricle is obviously impossible. Blood can leave the left atrium only through a patent foramen ovale or an atrial septal defect.31 If the foramen ovale is imperforate, the left atrium represents a blind alley, and right ventricular blood can only reach the systemic arterial circulation through a patent ductus arteriosus or by entering the left ventricle and aorta through a ventricular septal defect. Pulmonary venous blood returns to the right heart through bronchial collateral veins.

During fetal life, the major channel of blood flow to the systemic circulation in these cases is the ductus arteriosus. It is thus not surprising that the ductus persists after birth as a vessel of large size—frequently larger than the aorta—in many cases of mitral atresia. In virtually all cases in which the foramen ovale has been closed, the ductus arteriosus has been open.32 But the difficulties confronting the cardiovascular system when mitral atresia is accompanied by an imperforate foramen ovale are too profound to support life for a significant period of time.

In case 4, it is interesting to speculate as to what the consequences of surgically producing a mitral valve orifice might have been. If this were feasible, all of the other lesions would have been readily amenable to open heart surgery, and the infant might then have ended up with isolated mitral insufficiency. As more of these cases are seen, the need to create experimental mitral insufficiency and to evaluate the critical degree of insufficiency becomes more important.

Mitral Stenosis

Although congenital mitral stenosis is a
relatively rare lesion, a number of cases have been reported in which reversal of flow through the ductus arteriosus has been a complicating factor. In one case reported recently, the angiocardiogram showed clearly the continuity of the ductus arteriosus and the descending aorta. When a retrograde aortogram performed by injection into the right brachial artery failed to show the aortic arch, the 11-month-old infant was explored on the assumption that he had coarctation of the aorta. Ligation of the ductus arteriosus was followed immediately by cardiac arrest and death. At autopsy, significant stenosis of the mitral valve and dilatation of the left atrium were found. The left ventricle and aorta were hypoplastic.

Because of the increased resistance to flow at the mitral valve, even during fetal life the ductus was probably utilized as a more important channel of flow into the systemic circulation than the foramen ovale. At birth, the increased left atrial and pulmonary venous pressure presumably helped to sustain the fetal pulmonary hypertension, or to produce pulmonary hypertension as may occur in adults with acquired mitral stenosis. The pulmonary vascular resistance must have been high to sustain the ductal right-to-left shunt that was present in fetal life.

5. At the Aortic Valve (Aortic Atresia)

Case 6. A female infant developed tachypnea, poor feeding, and cyanosis during the first week of life. A murmur was heard at 1 month of age. Admitted at the age of 6 months, she showed general cyanosis. Blood pressure by the flush method was 70 in the right arm and 100 in the right leg. The heart was enlarged, with rapid rate, a gallop at the apex, and a grade III systolic murmur maximal at the apex. The pulmonic second sound was loud. The liver was felt 2 fingerbreadths below the costal margin. The red blood cell count was 6.5 million per mm. and the hematocrit 51 per cent. The electrocardiogram showed a pattern of right ventricular hypertrophy. Fluoroscopy and chest films demonstrated enlargement of the right atrium, right ventricle, and left atrium (figs. 6A and 6B). Peripheral pulmonary vascular was diminished, and the central vessels were poorly seen. Arterial oxygen saturation in the right upper extremity was 47 per cent, and in the right lower extremity 46 per cent. Angiocardiography demonstrated opacification of the aorta from the pulmo-

![Diagram of the heart and ductus arteriosus](image)

Fig. 5. Case 5. Reversed ductal flow associated with mitral atresia, imperforate foramen ovale and aortic atresia. Top. Posteroanterior projection. There are marked cardiac enlargement and gross pulmonary congestion. The lung fields resemble those in case 3 in which pulmonary vein atresia was present. Bottom. Diagrammatic representation of the autopsy findings. A large right atrium (RA) emptied into a common ventricle (CV), from which blood entered the pulmonary artery and through a large ductus arteriosus reached the aorta. Mitral atresia, an imperforate foramen ovale and aortic atresia were present, and there was a moderate degree of coarctation proximal to the ductus arteriosus. An aberrant right subclavian artery (RSA) was also noted.

nary artery through a patent ductus arteriosus, with a site of coarctation proximal to the insertion of the ductus (fig. 6C–6H). The right atrium was enlarged, as was the left atrium, but the left ventricle was hypoplastic. Persistent opaci-
Fig. 6. Case 6. Reversal of ductus flow associated with aortic atresia. A. Posteroanterior roentgenogram. The heart is enlarged, with a prominent right atrial silhouette. Although the central vessels are moderately full, the peripheral vessels appear small. B. Right anterior oblique projection. There is definite left atrial enlargement as well as right ventricular enlargement. C. and D. Angiocardiogram, anteroposterior projection, 2 seconds. The descending thoracic aorta has filled from the pulmonary artery through the ductus arteriosus. The arch of the aorta is also opacified, but the ascending aorta is not visible.

fication of the right atrium suggested the presence of an atrial septal defect. The diagnosis of a large patent ductus arteriosus with reverse flow, hypoplasia of the left ventricle, mitral stenosis, coarctation of the aorta, and an atrial septal defect was made, and the child was considered inoperable, was digitalized, and sent home. She returned in serious condition at the age of 9 months and died 4 days after admission.

Autopsy showed aortic atresia, a hypoplastic left ventricle communicating only with the left atrium, a dilated left atrium, a large patent foramen ovale with an incompetent valve, and a huge right atrium and right ventricle. The main pulmonary artery was dilated and communicated with the descending aorta by way of a large ductus arteriosus (fig. 6I). Moderate stenosis of the mitral valve was apparent. Just proximal to the entrance of the ductus was a localized zone of coarctation. Marked intimal and medial thickening of the small and medium-sized pulmonary arteries was noted, and the pulmonary veins were dilated.

Comment. It seems apparent that the aortic atresia was the primary lesion in this case. During fetal life, the left cardiac chambers played no significant role and the heart functioned as a 2-chambered pump. All blood
Fig. 6E. and F. The left atrium (LA) is now opacified and the pulmonary veins (PV) visible. A round sac is seen within the center of the cardiac silhouette, which represents the left ventricle (LV). There is persistent opacification of the right atrium, indicating a left to right interatrial shunt. G. and H. Steep right posterior oblique angiocardogram, 2 seconds. The right atrium (RA), right ventricle (RV), and pulmonary artery (PA) are opacified, and the aorta has been filled through the ductus arteriosus (PDA). A site of narrowing adjacent to the ductus is visible in the aorta (arrow). Some coronary sinus reflux is also noted.

returning from the venae cavae must have left the right atrium and right ventricle through the pulmonary artery and traversed the ductus arteriosus, the foramen ovale being incapable of serving as a channel of right-to-left flow because of the aortic atresia. In the absence of a ventricular septal defect, the left ventricle became a functionless diverticulum. After birth, blood entering the left atrium from the lungs could only escape by way
ventricle, and the ductus must remain patent if the systemic circulation is to receive any blood.\textsuperscript{35-38} In congenital aortic stenosis, however, the left ventricle, which has an enormous reserve, is rarely faced with the kind of resistance that prevents the expulsion during ventricular systole of an adequate quantity of blood. The cardiac output in congenital aortic stenosis is usually normal at rest, unless or until heart failure ensues.\textsuperscript{39} It is of interest in this regard that we have not observed or noted in the literature any cases of congenital aortic stenosis complicated only by persistence of a right-to-left shunt through the ductus arteriosus.

6. Beyond the Aortic Valve

Although a number of anatomic variations in the site, length, and caliber of stenosis of the aortic arch or isthmus may be observed, cases of coarctation or interruption of the isthmus with reverse ductal flow should probably be considered as a group whose common denominator is the predual location of the narrowed zone. If the narrowing is severe enough, and hence the obstruction to flow high grade, persistence of the fetal function of the ductus may occur. A number of such cases have been reported in the literature.\textsuperscript{40-44} Because of the therapeutic implications of this lesion, it deserves careful study, and a few illustrative cases may serve to emphasize the dynamic aberrations, the importance of early diagnosis, and the possibilities of cure.

Case 7. This premature baby girl born at 7½ months cried only when stimulated vigorously. The respirations were shallow, and slight peripheral cyanosis was visible. The heart sounds were of good quality but the rate was somewhat slow. At 3 days of age there were cardiac enlargement, a gallop rhythm, and an apical systolic murmur. The radial pulses were readily felt, but no femoral pulsations were palpable. The liver was markedly enlarged. Electrocardiograms showed a pattern of right ventricular hypertrophy. Chest roentgenogram demonstrated cardiac enlargement, with pulmonary vascular engorgement (fig. 7A). On the ninth day of life, a loud systolic murmur was heard throughout systole, transmitted in all directions. On the following day the infant developed Cheyne-Stokes breathing and died. Autopsy demonstrated absence of the aortic arch with complete

of the foramen ovale and the right atrium. It then mixed with systemic venous blood in the right atrium and right ventricle, and entered the pulmonary artery either to reach the systemic circulation through the ductus or to be carried back through the pulmonary vascular bed. The remarkable aspect of this case is that survival to 9 months of age could occur with a functionally 3-chambered heart, aortic atresia, and moderate coarctation of the aorta that prevented even the mixed pulmonary artery blood from reaching the brain easily. Of further interest is the fact that the blood pressure of the upper extremity was lower than that of the lower extremity. This paradoxical finding was an effect of the coarctation, which, in the absence of aortic blood flow from the left ventricle, had precisely the opposite blood pressure effect from that usually observed in uncomplicated coarctation of the aorta.

Obstruction at the aortic valve must be of a high order if the fetal right-to-left shunt is to be sustained. In aortic atresia no blood can reach the ascending aorta from the left
interruption of the isthmus of the aorta and a persistent large ductus (fig. 7B). The right ventricle was markedly hypertrophied. A ventricular septal defect was present.

Comment. In this case, the combination of interrupition of the aortic arch and reversal of flow through the ductus arteriosus was incompatible with life for more than a few days. That this is not always true is illustrated by the following case.

Case 8. An infant first seen at 4 months of age because of respiratory difficulty had been noted to have dyspnea first at 1 month of age, and cyanosis of the feet was observed at 2 months of age. Shortly before admission he had an episode of respiratory arrest. On physical examination blood pressure was 150/80 in the right arm and 90/70 in the legs. The heart was enlarged with a snapping second pulmonic sound and a faint systolic murmur along the left upper sternal border. The liver was felt 2 1/2 fingers below the costal margin, and the femoral pulses were faintly palpable. The fingers were pink, the toes cyanotic. Red blood cell count was 6.1 million per mm.³; hemoglobin 17 Gm. per 100 ml. Arterial oxygen saturation was 90 per cent in the right upper extremity, and 46 per cent in the right lower extremity. Electrocardiogram showed a pattern of right ventricular hypertrophy. Conventional radiologic studies showed moderate cardiac enlargement, mainly right atrial and right ventricular, and prominent central pulmonary arteries. Angiocardiogram showed a right-to-left flow through the ductus arteriosus, with opacification of the descending aorta from the pulmonary artery (fig. 8A). Retrograde thoracic aortogram showed complete interrupition of the aortic arch (fig. 8B). This child is still alive at the age of 4 1/2 years. His activity is limited and his physical signs are unchanged. Surgery has not been permitted.

Comment. In this patient, the right ventricle continues to supply all of the blood for the lower portion of the body through the ductus arteriosus, yet he has apparently reached a state of balance consistent with life. A final example of a somewhat more complicated case, which nonetheless fits in this category, deserves description.

Case 9. This 5-month-old girl entered the hospital because of heart failure, beginning at the age of 2 months and necessitating digitalization. She had had episodes of coughing and respiratory distress. On physical examination, tachypnea and irritability were noted. The heart was slightly enlarged and there was a systolic murmur over the right second interspace. The second pulmonic sound was louder than the second sound at the aortic arch. The blood pressure was recorded as 90/60 in the arms and 115/70 in the legs by the cuff method. A right ventricular heave was noted. The lungs were clear. Hemoglobin was 12.2 Gm. per cent. The electrocardiogram was suggestive of biventricular hypertrophy. Radiologic studies demonstrated marked increase in cardiac size, with combined ventricular enlargement and increased pulmonary vascularity. Cardiac catheterization demonstrated a large left-to-right shunt.

![Diagram](http://circ.ahajournals.org/)

**Fig. 7.** Case 7. Reversed ductal flow associated with interruption of the aortic arch. Top. Posteroanterior film. The heart is grossly enlarged, and there is pulmonary congestion. The aorta cannot be delineated. Bottom. Diagrammatic representation of autopsy findings. There is complete interrupition of the aortic arch. The pulmonary artery is continuous with the descending aorta through a patent ductus arteriosus. A small membranous ventricular septal defect (VSD) is present. (RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle.)
through a ventricular septal defect, and a right-to-left shunt through a patent ductus arteriosus. Arterial oxygen saturation was 93 per cent in the right upper extremity, and 80 per cent in the descending aorta. The pulmonary artery pressure was higher than the pressure in the descending aorta (table 2). Angiocardiogram demonstrated a right-to-left shunt through a patent ductus arteriosus with opacification of the descending aorta following pulmonary artery opacification, and a retrograde aortogram demonstrated complete stenosis of the aortic arch just beyond the origin of the left subclavian artery. Repair of the coarctation and surgical interruption of the ductus arteriosus were recommended.

At surgery the narrowed segment of the aortic arch extended beyond the subclavian artery for about 2 cm., at which point a large ductus joined the distal aorta. The ductus was divided and the distal thoracic aorta mobilized and anastomosed to the proximal portion of the aortic arch. After a somewhat stormy postoperative course, the child on discharge, 2 weeks after surgery, was in relatively good shape. Closure of the ventricular septal defect is contemplated after a period of stabilization.

Comment. Although there was a right-to-left shunt through the ductus arteriosus in this child, surgical closure of the ductus and excision of the coarcted segment were possible and helpful. It must be stressed, however, that the pulmonary resistance need not have

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TABLE 2.—Catheterization Data on Case 9

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Fig. 8. Case 8. Reversed ductal flow associated with interruption of the aortic arch. A. Angiocardiogram in steep right posterior oblique projection. The opaque medium enters the right atrium (RA) through the superior vena cava, fills the right ventricle (RV) and the pulmonary artery (PA) and then opacifies the descending aorta (A) through the patent ductus arteriosus (arrow). B. Retrograde thoracic aortogram in steep right posterior oblique projection. Following injection of opaque medium into the right brachial artery, the innominate artery and ascending aorta are visualized, and there is obvious interruption of the aortic arch (arrow).
been significantly elevated in the presence of a large left-to-right shunt through the ven- tricular septal defect, in spite of the marked pulmonary hypertension.

**DISCUSSION**

1. **Anatomic Basis of Persistent Fetal Ductus Function**

The common denominator of the malforma- tions in which right-to-left flow through the ductus arteriosus persists after birth is the presence of a site of obstruction to blood flow in the pulmonary vessels, left heart, or aorta at some point beyond the pulmonary origin of the ductus arteriosus but proximal to its aortic insertion (fig. 9). In isolated patent ductus arteriosus with reversal of flow in infancy, the obstruction appears to be primary in the pulmonary arteriolar bed; in the presence of congenital lung disease and reversal of ductal flow, the pulmonary capillary bed may also be implicated in the production of increased resistance; the other sites of obstruction—the pulmonary veins, the mitral valve, the aortic valve, and the preductal portion of the aortic arch—are all more sharply defined.

A distinction must be made between the primary and the secondary site of increased resistance; for, no matter where the obstruction is, the pressure on the arterial side of the pulmonary vascular bed must be markedly elevated to support right-to-left ductal flow. If the pulmonary arterial change is primary in isolated right-to-left ductal flow in infancy, it seems reasonable to consider it secondary in such lesions as mitral or aortic atresia.

It has been pointed out that the thickened muscular pulmonary arteries of the fetus may persist in infancy and because of the small size of their lumens, produce a high resistance to blood flow through the lungs. Such vessels have been described in detail in patent ductus arteriosus with reversal of flow in the presence of preductal aortic coarctation. What the precise stimulus is that prevents the thick muscular arteries from developing in the direction of the thin-walled adult type vessels is as yet unknown. But the analogy between those cases with anatomic obstruction between the pulmonary venous bed and the aortic valve—with consequent increase in the left atrial and pulmonary venous pressure—and the sequence of changes in mitral stenosis deserves emphasis. At least it
may be conjectured in these cases that the increased pulmonary arterial resistance of the fetus is sustained after birth because of the elevated pulmonary venous pressure. That medial thickening of the muscular pulmonary arteries is a relatively constant finding in congenital lesions of the left side of the heart, causing obstruction of pulmonary venous return, has been adequately demonstrated.\textsuperscript{47}

By contrast, in preductal coarctation of the aorta, so long as the left ventricle remains competent, the left ventricular diastolic pressure and left atrial pressure may be expected to be normal. Thus a factor other than elevated pulmonary venous pressure must be looked for. The concept of the right ventricle as a common ejective force for systemic (descending aortic) and pulmonary circulation is useful in this respect;\textsuperscript{46} yet it sheds no light on why the pulmonary resistance remains elevated. That left ventricular failure is present at birth in some of these cases has been apparent from the clinical course; and in these cases at least, a mechanical stimulus to sustained elevation of pulmonary artery pressure may be delineated, and a parallel drawn to the development of pulmonary hypertension in adults in chronic left ventricular failure.

In isolated patent ductus arteriosus with reversed flow in infancy, the ductus apparently provides an avenue of escape for blood which could not successfully be expelled from the right ventricle through a narrowed pulmonary arterial bed without right heart failure; in coarctation, reverse ductal flow may protect the left ventricle from failure by diverting a large portion of the cardiac output to the lower portion of the body. Perhaps the only common design in the conditions in which right-to-left ductal flow persists is this: in no other way could blood leaving the right ventricle reach all or part of the systemic circulation without precipitating or increasing right or left heart failure.

That the ductus is not an effective method of sustaining life indefinitely in these circumstances is clear from the fact that the average duration of life of the 9 patients reviewed above was 13 months, and 3 died before the age of 1 month. But its usefulness as an "avenue of escape" may be discerned in older patients with patent ductus arteriosus and reversed flow: their clinical course may be relatively benign. By contrast, patients with primary pulmonary hypertension and pulmonary vascular resistance equivalent to that noted in patients with reversed ductal flow develop right heart failure rapidly and have a poor prognosis. This observation prompted an attempt to create a pulmonary artery-subclavian artery anastomosis in at least 1 patient with primary pulmonary hypertension, in an effort to provide a safety valve.\textsuperscript{48}

2. Persistence of the Veno-arterial Ductal Flow: Primary or Secondary?

The concept outlined above of persistent fetal flow through the ductus in infancy as a result of distorted anatomy and physiology, rather than as a cause or a participating primary element in the malformation, deserves examination. It may be argued that, in coarctation of the aorta associated with the reversal of ductus flow, the failure of normal development of the left fourth branchial arch, which is relatively functionless in fetal life, and which gives rise to the isthmus of the aortic arch—the usual site of coarctation—is the result of persistent right-to-left flow through the ductus rather than the cause. Perhaps similarly the persistence of increased pulmonary resistance in isolated patent ductus arteriosus with reversal of flow is the result rather than the cause of the reversed shunt. This same approach cannot easily be held in the case of pulmonary venous or mitral and aortic valvular obstruction. In these cases, however, it can be said that the same disturbance in the development of the fetus that produced these anomalies causes the ductus to remain open.\textsuperscript{*}

These points are not susceptible to ready answer. But it must be stressed that most

\textsuperscript{*}It is of interest in this regard that a background of maternal rubella is more common when patent ductus arteriosus co-exists with additional cardiac lesions than when patent ductus arteriosus is found as an isolated anomaly.\textsuperscript{49}
cases in which the ductus remains patent in the absence of other anomalies are accompanied by left-to-right, rather than right-to-left shunts. In a minute fraction of cases, the right-to-left flow persists, and in virtually all of these, severe accompanying anomalies with a site of obstruction between the pulmonary origin of the ductus and the aortic insertion of the ductus are present. The inference seems proper that these additional anomalies influence the direction of flow.

In the fetal circulation, the ductus serves as a means of carrying pulmonary artery blood to the descending aorta, presumably because of the high resistance in the collapsed lungs. In most of the anomalies under discussion, a partial duplication of the fetal circulatory dynamics exists, in that resistance to the passage of blood through the pulmonary vessels and back to the left cardiac chambers is heightened. The ductus then would seem to be operating under the same general conditions that produce the fetal right-to-left shunt, and might be expected to sustain its fetal role.

A number of experimental avenues are open to investigation of the factors underlying persistence of the fetal ductus functions: (a) the artificial creation in the newborn animal of a zone of aortic stenosis proximal to the entrance of ductus arteriosus; (b) production of bilateral main pulmonary artery stenosis beyond the ductus; (c) production of pulmonary venous obstruction; (d) production of experimental mitral stenosis. The approach to all these procedures in the newborn dog suffers from the difficulty of sustaining life following this kind of surgery; in the attempt to create preductal coarctation, no dogs have yet survived. Efforts are underway, however, to explore this approach further. Another useful field of exploration involves the exposure of newborn dogs to chronic hypoxia in an effort to sustain fetal pulmonary hypertension and the right-to-left fetal ductus flow.

3. Increased Pulmonary Vascular Resistance

Why does the pulmonary vascular resistance, high during fetal life, remain elevated after birth in this group of cases? The primary factor associated with most cases in which increased pulmonary resistance is found in man is probably a diminution in the cross-sectional area of the arterial bed (other factors such as increased length of arteries or increased viscosity of blood are certainly of less significance). Such a diminution may follow massive thrombosis or multiple emboli with a consequent decrease in the total number of functioning arteries, or it may be associated with decreased size of the vessels. Decreased vessel size may be related to vasoconstriction, or to organic alterations in the arterial wall. The latter include both medial muscular thickening—which is found in the cases under discussion—and intimal thickening, usually found in the older age groups. That functional narrowing or vasoconstriction may play a role in pulmonary hypertension is now supported by a considerable body of evidence.\textsuperscript{10, 22, 50-62}

An analysis of the general factors associated with increased pulmonary arterial resistance must include:

1. Obstruction to pulmonary venous outflow. The analogy to mitral stenosis and chronic left ventricular heart failure in adults with the associated development of pulmonary hypertension, has already been alluded to.

2. Elevated pulmonary blood flow. The association of increased resistance is inconstant in human subjects and need not depend on the size of the shunt.\textsuperscript{85} Experimentally, it is possible to produce pulmonary hypertension and organic changes in the pulmonary arterial bed by creating large pulmonary artery aortic anastomoses in dogs and thus increasing pulmonary blood flow.\textsuperscript{29} In the presence of persistent reversal of ductal flow in infancy, there is no good evidence that the pulmonary blood flow need be elevated.

3. Pulmonary parenchymal disease. This factor, operative in adults with severe chronic pulmonary disease,\textsuperscript{21} might also apply to cases with congenital pulmonary disease and reversal of shunt.
4. Organic narrowing or occlusion of the pulmonary arteries, whether congenital or due to thrombosis, multiple emboli, or atheromatous change.67–69

5. Hypoxia.52, 50–55

None of the foregoing factors is common to all conditions with reverse flow through the ductus in infancy. On the other hand, hypoxemia is present in all such anomalies. In two of these, isolated patent ductus arteriosus with reversal of flow and preductal coarctation with reversal of flow, the hypoxemia involves mainly the descending aorta and the lower portion of the body. Thus, both the thoracic sympathetic chain, which may be involved in nervous regulation of the pulmonary arteries,68 and the bronchial arteries might be expected to be exposed to hypoxemia in virtually all of these lesions. Yet hypoxemia per se, as contrasted to alveolar hypoxia, clearly need not be associated with increased pulmonary resistance: in pulmonary arterio-venous fistulae, the tetralogy of Fallot and Ebstein’s anomaly, the pulmonary artery pressure is usually normal.

Among those cases in which reversal of ductus flow persists in infancy, at least 1 type—congenital pulmonary disease associated with reversal of ductus flow—presents a possible cause of hypoxia. A striking aspect of cases with right-to-left ductal flow is that evidence of congestive heart failure appeared shortly after birth in most instances, as might be expected from the nature of the anomalies. Certainly in those cases with marked increase in pulmonary venous pressure, consequent engorgement of the lungs, and associated with a moderate degree of bronchospasm, a certain amount of hypoxia may be presupposed. If it is assumed that hypoxia may occur in these children at birth, associated with congestive heart failure, then perhaps this is a partial explanation of the stimulus for persistence of the high fetal pulmonary resistance. The suggestion has been made that an inborn difference in reactivity on the part of some individuals underlies their development of marked pulmonary hypertension as a response to stimuli that provoke no such profound change in others.48

4. Therapeutic Implications

Five cases of coarctation of the aorta or complete interruption of the isthmus with a large distal ductus serving as the site of a right-to-left shunt have been operated on at this institution, with 1 death. The other 4 have either been significantly improved or cured. This is in marked contrast to the poor surgical experience in older patients with reversal of flow through a ductus arteriosus in the absence of coarctation.

Case 9 is an example of this lesion, complicated by a ventricular septal defect, in which surgical closure of the ductus and excision of the coarcted segment were followed by improvement. The very high pulmonary artery pressure (113/35 mm. Hg) may well have been related in large measure to the large ventricular septal defect. Since the patient has not yet been recatheterized, there is no way of knowing whether the pressure has remained at this level. In this case, it may be reasonably suggested that the ductus arteriosus, in spite of the right-to-left shunt, did not constitute a critical “avenue of escape.” Closure at the time of coarctation repair failed to embarrass the right cardiac chambers, indicating that the resistance in the pulmonary vascular bed alone was not critical to continued functioning of the right ventricle. The additional possibility must be considered that left ventricular failure, elevated left ventricular diastolic pressure, and hence elevated left atrial and pulmonary venous pressure accompanied the coarctation, and contributed to the elevation of the pulmonary artery pressure as in chronic left ventricular failure in adults. Relief of the coarctation, then, diminished the burden on the left ventricle. This point of view is supported by the intractable heart failure prior to operation, and the relative clinical improvement since. Furthermore, the atresia of the isthmus may have acted to increase the left-to-right shunt through the ventricular septal defect. The major argument against this is the normal right ventricular diastolic pressure. In the presence of a large ventricular septal defect and left ventricular failure with elevated left ventricular diastolic pressure,
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this should be reflected in an increased right ventricular diastolic pressure.

The experience with the cases of coarctation associated with reversed flow through the distal ductus suggests that the increased resistance in the pulmonary vascular bed is reversible in some of these cases. This may have significant implications for all lesions in which reversal of flow through the ductus is based on the primary increase in resistance beyond the pulmonary arteriolar bed. With the burgeoning of open heart surgery, complete correction for all these anatomic malformations may be feasible, and it seems reasonable to suppose that the closure of the ductus when normal anatomic channels elsewhere have been restored need not necessarily be a hazard in spite of the obvious increase in pulmonary resistance.

Summary

In a number of different congenital cardiac anomalies, the ductus arteriosus serves as a site of continued fetal (veno-arterial) flow after birth. In all these conditions, the pulmonary arteriolar resistance must be significantly elevated to permit flow into the descending thoracic aorta. Beyond this, the common denominator of all these malformations in which right-to-left flow persists is the presence of a site of obstruction to blood flow in the pulmonary vessels, left heart, or aorta at some point beyond the pulmonary origin of the ductus arteriosus but proximal to its aortic insertion. The ductus serves as an "avenue of escape" in most of these lesions: in no other way could blood leaving the right ventricle reach all or part of the systemic circulation without precipitating or increasing right or left heart failure. The anatomic basis of persistent fetal ductus function after birth, the factors involved in increased pulmonary arteriolar resistance in these anomalies, and the therapeutic implications of the surgical approach to a specific group of these cases are discussed.

Acknowledgment

Many of the cases described in this paper were patients of Dr. Saul J. Robinson, who graciously permitted their inclusion. Cardiac catheterization studies were performed under the direction of Dr. Herbert Hullgren.

Summary in Interlingua

In un numero de differente congenite anormalitates cardiae, le ducto arterioso servivit como sito de un continuation postnatal del fetal fluxo veno-arterial. In omne iste conditiones le resistentia pulmono-arteriolar debe esser significativamente elevate pro permetter le fluxo a in le descendente aorta thoracie. In plus, un tracto commun del malformaciones con persistentia del fluxo dextero-sinistre es le presentia de un sito de obstruction al fluxo sanguinee in le vasos pulmonar, le corde sinistre, o le aorta a un puncto trans le origine pulmonar del ducto arterioso sed in su insertion aortie. In le majoritate de iste lesiones, le ducto servi como "via de escappamento," proque il existe nulle altere curso per que le sanguine veniente ab le ventriculo dextere pote attinger le complete circulation systemie o un parte de illo sin precipitar o augmentar disfallimento dextero-o sinistro-cardiac. Es discutite le base anatomic de persistentia del function del ducto fetal le nascientia, le factores que contribue al augmentate resistentia pulmono-arteriolar in iste anormalitates, e le valor therapeutie del tractamento chirurgie de un grupo specific de casos.

References


This is a summary of 16 pathologically proved instances of aortic rupture with dissection where conventional roentgenograms of the chest were available for review. The most characteristic roentgenographic finding was a definite change in the diameter of the aorta occurring between 2 successive examinations. Increased prominence of either the ascending or descending portions of the aorta, particularly when associated with contour irregularities, also was highly suggestive of the diagnosis. Loss of clear contour formation was seen once; hemorrhage into the superior mediastinum, into the right middle lobe of the lung, and into the pericardium, once each. Plaques of calcium within the inner aspect of the aortic wall several millimeters from the outer margin provide reliable evidence of thickening of the aortic wall. The author indicates that conventional roentgenographic findings are often diagnostic. This does not imply that definite diagnosis cannot be established by other means (angiocardiography).
Persistence of Fetal Ductus Function after Birth: The Ductus Arteriosus as an Avenue of Escape
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_Circulation._ 1958;18:206-226
doi: 10.1161/01.CIR.18.2.206

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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