Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation in Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension

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Seven cases of patent ductus arteriosus with pulmonary hypertension and reversal of the usual direction of flow are described. Breathing of a low oxygen mixture either initiated or increased the reversed shunt, and breathing 100 per cent oxygen produced the reverse effect. Differences in oxygen saturation and dye-dilution curves recorded simultaneously from the radial and femoral arteries have allowed calculation of differences in the proportion of shunted blood flowing in these arteries and demonstrate that retrograde movement of blood in the aortic arch may occur.

It has been reported from this clinic and by others that a patent ductus arteriosus may be associated with severe pulmonary hypertension and that, as a consequence, a reversal of the arteriovenous shunt usual in this condition may occur. The reversal of flow may be intermittent, or if permanent, a characteristic clinical picture of cyanosis of the feet with slight or absent cyanosis of the hands and face may be observed. Also, because the left subclavian artery is anatomically sometimes nearly opposite the aortic aperture of the ductus, the left hand may be cyanotic while the right is not. The general arrangement of the origins of the major arteries from the aortic arch are illustrated in figure I, from which it may be deduced that a principal effect of the flow of venous blood from the pulmonary artery to the aorta would be a decrease in the oxygen saturation of the blood passing to the lower part of the body by way of the descending aorta, while the blood passing to the upper part of the body would be affected to a lesser extent or not at all.

In 1946, von Euler and Liljestrand found that in the cat the blood pressure in the pulmonary artery was increased when the animal breathed mixtures low in oxygen content, and similar findings have been reported in man. These reports suggested to us an investigation of the effect of breathing varied oxygen mixtures on the degree of venous shunt in cases of congenital cyanotic heart disease, and of the quantitative effect of such mixtures on the shunt from the aorta to the pulmonary artery in cases of patent ductus arteriosus associated with pulmonary hypertension. It was suggested that the effects of breathing differing oxygen mixtures, including 100 per cent oxygen, might be of diagnostic value in some cases of patent ductus arteriosus with transient reversal of the shunt.

This communication presents data on seven patients with patent ductus arteriosus and pulmonary hypertension in whom either (1) the breathing of 100 per cent oxygen caused a disappearance or decrease in flow from the pulmonary artery to the aorta or (2) the breathing of a low oxygen mixture either caused the appearance of a flow, or accentuated the flow already present, in this direction.
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METHOD

Cardiac catheterization was carried out on each patient utilizing a photokymographic recording assembly and associated equipment described elsewhere. Blood oxygen content, blood pressures and arterial dilution curves of T-1824 were recorded simultaneously from the radial and femoral arteries. Oxygen saturation was determined both by manometric techniques and by photoelectric technics. Estimation of venous-arterial shunts from dye-dilution curves was carried out as described elsewhere.

At 2 years of age, the patient was in the hospital for two weeks with pneumonia. On our examination there was a loud basal systolic murmur. The heart was enlarged roentgenographically, and the electrocardiogram was interpreted as indicative of left ventricular hypertrophy. Catheterization was carried out under anesthesia, and the data indicated the presence of a patent ductus arteriosus (table 1). Surgical exploration was carried out on October 24; the heart was found to be very large and the pulmonary artery large and tense. A large patent ductus was present, being more than a centimeter in diameter, which was successfully closed by multiple ligation. The postoperative course was satisfactory. After operation a harsh short systolic murmur over the precordium persisted, and it was suspected, as before operation, that there was an associated subaortic stenosis. The patient returned for examination in August, 1951, at which time there was a thrill in the suprasternal notch and a grade 2 systolic murmur in the aortic area. The heart had decreased markedly in size on roentgenologic study and the vascularity of the lung was less notable than on preoperative study. The general condition was very satisfactory.

Case 1. A boy, aged 5 years, was brought to the clinic in August, 1951, for evaluation of his heart disease. He had been admitted to the clinic previously at the age of 10 months for treatment of an acute bronchitis, at which time a loud rough systolic murmur had been noted in the midsternal area. On the occasion of the second admission there was a grade 2 systolic murmur maximal in the second and third intercostal spaces and well transmitted toward the left clavicle and back. The blood pressure was 92 mm. Hg systolic and 60 mm. diastolic. The heart was moderately enlarged roentgenologically and the pulmonary vascular shadows were increased. The electrocardiogram was interpreted as indicative of biventricular hypertrophy. The diagnosis of patent ductus arteriosus was confirmed by cardiac catheterization (table 1), the catheter passing through the

<table>
<thead>
<tr>
<th>Table 1.—Cardiac Catheterization Data From Patients With Patent Ductus Arteriosus and Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case</strong></td>
</tr>
<tr>
<td>-----------</td>
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<tr>
<td></td>
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<tr>
<td>1</td>
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<td>5</td>
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<tr>
<td>6</td>
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<td>7</td>
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</table>

CLINICAL DATA

None of the patients had a typical loud continuous murmur, four had a systolic murmur at the base, and two of the adults had a prolonged basal diastolic murmur. Apart from case 1, in which it was thought both preoperatively and postoperatively that the patient had a subaortic stenosis, it was believed that no complicating congenital defects were present. All the patients represented complex diagnostic problems, and in every instance the diagnosis was assured only after cardiac catheterization and studies of the oxygen saturation of the blood from the radial and femoral arteries. Six patients underwent surgical exploration. Two of the patients died following surgical closure of the ductus and in these no associated defect was found post mortem.

Case 1. The patient, aged 3½ years, first registered at the Mayo Clinic in October, 1950. The birth was normal but at 6 months of age a roentgenogram showed cardiac enlargement, and the home-town physician stated that there was a congenital heart defect with pulmonary congestion.
ductus. Following successful surgical closure of the ductus, no murmurs were present and convalescence was uneventful.

Biopsy of the lung disclosed increased thickness of the media and prominence of the internal elastic lamina of the small pulmonary arteries, but these arteries were free of intimal disease. The walls of the arterioles were of increased thickness with an increased degree of cellular structure, but the difference from normal could be graded only mild to moderate.

Case 3. The patient was first seen at the clinic in November, 1950, at the age of 21 years, when he was admitted to the hospital with heart failure. A heart murmur was said to have been noted at birth, and during his childhood he had been restricted in his activities. In 1946, while suffering from an upper respiratory infection, he was said to have been bluish in color. In October, 1949, there had been swelling of the abdomen and discomfort in the right upper quadrant. The legs and ankles became swollen, and paracentesis had been carried out 22 times in the year prior to November, 1950.

Our examination disclosed a loud rough apical systolic murmur and thrill, and a short early diastolic murmur at the apex and xiphoid area. The clinical findings indicated marked right ventricular hypertrophy and pulmonary hypertension. No definite cyanosis could be recognized. Clinically, the most likely diagnosis was thought to be a ventricular septal defect with aortic insufficiency. It was believed that tricuspid insufficiency might be an associated condition. A roentgenogram showed marked cardiac enlargement with prominence of the left border. The electrocardiogram (fig. 2, case 3) showed an intraventricular conduction disturbance, the QRS measuring 0.10 second, and was characterized by right axis deviation, a wide high R in V1 and a triphasic QRS in V6. In aVR, not illustrated, Q and R deflections were of approximately equal amplitude.

Following catheterization studies during which the aorta was entered through a ductus, exploratory thoracotomy was carried out on November 7. A large patent ductus was found and ligated, although at the time of exploration the heart dilated and slowed and it was necessary to resort to cardiac massage for a time to maintain cardiac function. The postoperative convalescence was satisfactory.

The patient returned 10 months later, in September, 1951, stating that he was able to do his farm work but had slight dyspnea if he overworked. There had been no swelling of the feet but there had been occasional soreness in the hepatic region. He had not required any further paracentesis. He had discontinued use of digitalis in May and had had recurrence of mild symptoms, requiring treatment with mercurial diuretics and resumption of his use of digitalis. At the time of re-examination he had remarkably good exercise tolerance. There was a grade 2 apical systolic murmur. The preoperative pressure in the pulmonary artery had averaged 100 systolic and 70 diastolic. Catheterization on Sept. 11, 1951, 10 months after operation, revealed a pulmonary pressure that averaged 55 systolic and 22 diastolic; the pressure in the right ventricle was 54/0.

Case 4. The patient was first admitted at the age of 24 years, on Aug. 19, 1952, because of pregnancy. A heart murmur was known to have been present since the age of 3, and some cyanosis of the feet had been noticed since the age of 13. During the school years it was said that she was moderately dyspneic on effort. She carried her baby to term satisfactorily and was delivered of a live baby, low forceps being used, on October 16. There was blood in the amniotic fluid and the placenta showed evidence of a recent premature separation. The day following delivery she complained of increased dyspnea and palpitation and noted deeper cyanosis of the nails. On October 22 there was repeated hemoptysis. She was dismissed from the hospital on November 2, and returned for further investigation six weeks later. The main auscultatory finding was a grade 3 diastolic murmur that was maximal in the left infraclavicular area. A short systolic murmur was also present in the pulmonary area. The second sound in the pulmonary area was moderately accentuated. Roentgenograms showed that the size of the heart was within normal range in the anteroposterior view, but there was marked prominence of the pulmonary artery. In the oblique roentgenograms there was evidence of right ventricular hypertrophy. The electrocardiogram was interpreted as indicative of right ventricular hypertrophy (fig. 2, case 4). Surgical exploration was carried out on January 10, and a huge patent ductus, exceeding the size of the aorta, was successfully divided and its ends sutured. About two hours after the completion of the operation, marked hypotension developed without any prior warning symptoms, and death occurred in about 20 minutes.

The postmortem examination did not reveal any specific reason for the death. The heart showed no complicating defect. The right ventricle (fig. 1c) was thick, being approximately equal to the thickness of the left ventricle, which was of normal size. The large pulmonary arteries were unobstructed; the small arteries had a varied structure, some appearing to be dilated, others moderately thick-walled, and still others occluded by intimal changes.

Case 5. The patient was first registered at the clinic in 1939 at the age of 18 years, at which time a diagnosis of severe scoliosis and patent ductus arteriosus was made. A "machinery" murmur was noted by the consultant. The patient returned in 1942 for a re-evaluation of the scoliosis and the cardiac condition; at that time she was noted to
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Fig. 1(a and b). Two normal aortas from which the anterior half of the wall has been removed to demonstrate the relationship of the aortic arch vessels to the ligament of the ductus arteriosus. While the ligament is distal to these branches, it is more definitely so in a than in b. In the latter it may be noted that the left vertebral artery arises as a separate branch of the aorta, a not uncommon arrangement. It is to be emphasized that considerable variation in the arrangement of the origin of these vessels occurs. (c) The great vessels in case 4. The divided and sutured ends of the ductus are indicated by the arrows. The hypertrophy of the right ventricle (R. V.) is evident. It is of interest that blood shunted through the ductus could be detected in the right radial artery in this case (fig. 5).

(These photographs of specimens are used through the kindness of Dr. J. E. Edwards, Section of Pathologic Anatomy, Mayo Clinic.)

Fig. 2. Electrocardiograms from five adult patients with patent ductus arteriosus and pulmonary hypertension. These tracings were taken during the admission during which cardiac catheterization was performed.

have adequate cardiac reserve, and it was thought best to defer surgical treatment. On her return in November, 1951, the cardiac status had worsened considerably, the patient being much more disabled. She gave a history of having had, in November and December, a prolonged illness called "septicaemia" which was treated with penicillin and streptomycin for seven weeks. It was apparently believed that she had had a subacute bacterial endocarditis or endarteritis. The possibility of thyrotoxicosis also had been suggested, but the clinical evaluation supported by radioiodine studies indicated that she was euthyroid. The auscultatory findings were a grade 3 systolic murmur and thrill in the third left intercostal space with a grade 1 continuous murmur to the left of the sternum. An interesting phenomenon was observed in that following her occasional extrasystoles, there was the occurrence of a marked, prolonged diastolic murmur and accentuated pulmonic second sound. The problem of surgical therapy again arose, and at that time (November, 1951) it was believed that, in spite of the severe scoliosis, such treatment might be carried out safely and perhaps with benefit. When the patient returned on her last visit in August, 1952, her condition had further deteriorated. The feet were slightly cyanosed when the hands were not. The heart was enlarged, but its size was difficult to assess because of the kyphoscoliotic deformity. The vital capacity was 860 cc. The electrocardiogram showed right axis deviation and evidence of right ventricular hypertrophy (fig. 2,
Cardiac catheterization was carried out (table 1) to determine pulmonary arterial pressure, which was found to exceed the systemic pressure. It was the final opinion that surgical treatment could not then be recommended.

Case 6. The patient first registered at the clinic in January, 1950, at the age of 35. He reported that at the time of birth the physician had said that he had a weak heart. His development was normal and he engaged in routine athletic activities during his school years. He considered himself in good health until 1945, when he began to notice orthopnea and was hospitalized and given digitalis and mercurial diuretics. He got along relatively well on a program of restricted activity until January, 1949, when there was an increase in dyspnea, but improvement occurred with restriction in his activities. In April, 1949, he had further exacerbation of the dyspnea, and edema of the legs developed. He was admitted to the hospital, and improvement occurred with loss of the edema. His condition had been relatively unchanged until his admission here.

On examination, his weight was 143 pounds, and his blood pressure was 150 systolic and 90 diastolic. A long loud diastolic murmur was present in the second and third left intercostal spaces and this was well heard also at the apex. Roentgenographically, the heart was huge and there was prominence of the pulmonary artery and vascular shadows. The electrocardiogram (fig. 2, case 6) showed right axis deviation and evidence of right ventricular hypertrophy in the precordial leads. The final clinical assessment was that a severe pulmonary hypertension and right ventricular hypertrophy related to congenital cardiac disease were present. Cardiac catheterization (table 1) proved the presence of a ductus.

Surgical treatment was carried out on March 11, 1950. The pulmonary artery was found to be extremely large and sclerotic. The ductus was approximately 2.5 cm. in diameter and very short. It was impossible to use transfusion sutures, but two braided silk ligatures were passed around the ductus and tied down as tightly as was thought reasonable with regard to the structural changes in the ductus and pulmonary artery. The patient's condition was critical throughout the operation and his postoperative course was stormy. A prolonged basal diastolic murmur was still present at the time of his dismissal. The question was raised at this time whether the ductus would remain closed.

The patient returned for re-examination in October, 1950. He had continued to have chronic congestive failure without much change in the general picture. Cardiac catheterization was carried out again and the ductus demonstrated to be open. When the patient returned in January, 1952, his general condition appeared somewhat better and he had been able to get along satisfactorily without mercurial diuretics, but with digitalis medication and sodium restriction. The results of cardiac examination were as before.

Case 7. The patient was first seen at the age of 45, in August, 1952, with the complaint of shortness of breath for many years and "constant cold" of four years' duration. A cardiac murmur was said to have been first discovered at the age of 10. For many years the patient had continued to work as a clerk for eight hours daily. There had been no orthopnea, and there had been no recent progression of symptoms. Her weight was 130 pounds and her blood pressure was 130 systolic and 80 diastolic. There was a prolonged grade 2 plus diastolic murmur that was maximal to the left of the sternum from the fifth rib to the left infraclavicular area. The pulmonic second sound was accentuated. No systolic murmur was heard. The roentgenogram showed marked prominence of the pulmonary artery segment and the pulmonary vessels. The electrocardiogram (fig. 2, case 7) was interpreted as presenting evidence of biventricular hypertrophy, showing an "M" QRS complex in V1, and a high R and small S in V5. At cardiac catheterization the presence of a patent ductus arteriosus was established.

Surgical exploration was carried out on September 10 and an aneurysmal dilatation of the pulmonary artery was found. The patent ductus arteriosus was of about the same diameter as the aorta and was approximately 1 cm. in length. It was possible to divide the ductus and suture its ends. The patient's immediate postoperative course was satisfactory. There was persistence of a diastolic murmur to the left of the sternum. On the seventh postoperative day there were two episodes of pain in the right shoulder and slight dyspnea, and a few hours later severe dyspnea with cyanosis, shock and death.

Postmortem examination showed the sutured ends of the ductus to be in good condition, and the exact cause of death was not determined. The right ventricle was markedly thickened. No associated cardiac defect was present. The pulmonary vascular changes were not uniform, some vessels showing relatively minimal change, while others showed medial hypertrophy and intimal change of advanced degree. The histopathologic picture did not approach the severe degree that has been described in other cases of patent ductus arteriosus. 35

Laboratory Data

The laboratory data on the seven patients are summarized in tables 1 and 2. In table 1 are given the more routine findings on cardiac catheterization, where it may be noted that in the group generally the pulmonary and systemic arterial pressures were nearly equiv-
alent, the exceptions being case 1, a young child, in which the pulmonary arterial pressure was significantly lower, and case 5, in which it was significantly higher than the systemic pressure. In cases 4, 5 and 7 there was insufficient arteriolarization of the blood in the pulmonary artery, so that from the routine data given in this table the diagnosis would not have been obvious during the catheterization procedure had not the catheter entered the aorta. In case 4 no data on the pressure or calculated across the ductus. The anatomic relationship of the ductus to the branches of the aortic arch (fig. 1) determines a preferential flow of blood from the ductus to the descending aorta. Hence the presence in the femoral artery of blood with an oxygen saturation significantly lower than that of a sample drawn simultaneously from the radial artery is positive evidence of a right-to-left shunt through a patent ductus arteriosus. Further evidence of the presence of this condition may

Table 2.—Effect of Variation in the Oxygen Content of Inspired Air on Pulmonary and Systemic Arterial Pressures and on Differences in Oxygen Content of Simultaneously Withdrawn Radial and Femoral Arterial Blood (Patients With Patent Ductus Arteriosus and Pulmonary Hypertension)

<table>
<thead>
<tr>
<th>Case</th>
<th>100% Oxygen*</th>
<th>Room a'ir*</th>
<th>Low oxygen mixture*</th>
</tr>
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<tbody>
<tr>
<td>1†</td>
<td>15.7</td>
<td>16.1</td>
<td>67/42</td>
</tr>
<tr>
<td>2‡</td>
<td>18.9</td>
<td>18.6</td>
<td>88/47</td>
</tr>
<tr>
<td>3</td>
<td>19.3</td>
<td>19.3</td>
<td>108/11†</td>
</tr>
<tr>
<td>5</td>
<td>20.0</td>
<td>16.0</td>
<td>150/90</td>
</tr>
<tr>
<td>6</td>
<td>26.9</td>
<td>26.5</td>
<td>137/81</td>
</tr>
<tr>
<td>7</td>
<td>24.2</td>
<td>23.2</td>
<td>140/74</td>
</tr>
</tbody>
</table>

* Gas mixture being breathed.
† Catheter in right ventricle.
‡ Avertin anesthesia.
§ Descending aorta.
† Pulse badly damped by clot in intra-arterial needle.

Abbreviations: PA, pulmonary artery; RV, right ventricle.

The low oxygen mixture differed for individual patients. Mixtures containing 10 to 14 per cent of oxygen in nitrogen were used.

oxygen saturation of the blood in the radial artery were obtained during catheterization.

In table 2 are shown data obtained during additional studies on the arterial pressure and oxygen saturation of blood withdrawn simultaneously from femoral and radial arteries while the patient breathed differing oxygen mixtures. The figures given in the two tables do not correspond exactly, as in some instances a second study was done on a different day. While the systolic systemic arterial pressures and the pulmonary arterial pressure, where recorded in table 2, were taken simultaneously, the former are not a sufficiently accurate reflection of the aortic pressure to allow instantaneous pressure gradients to be derived from dye-dilution curves recorded following injection of Evans blue dye into the pulmonary artery via a cardiac catheter.26

Each case has features of special interest regarding the laboratory data. In case 1 catheterization was done under anesthesia, and after the diagnosis of arteriovenous shunt between the aorta and pulmonary artery was established, arterial needles were inserted into both the femoral and radial arteries in order to obtain arterial blood samples and hence to differentiate between a patent ductus arteriosus and an aortic-pulmonary fistula of the base of the great vessels. To increase the diagnostic potency of this test a mixture containing 10 per cent oxygen was also administered. The
results gave confirmatory evidence to the diagnosis of patent ductus arteriosus, but the hypoxemia produced by 10 per cent oxygen was more profound than was wished; it was thought possible that the lungs were practically excluded from the circulation temporarily toward the end of the test period, the blood samples from the pulmonary and femoral arteries having an extremely low oxygen content and the radial blood sample having only a slightly higher content (fig. 3). If the reversed shunt had taken place at the origin of the great vessels (aortic-pulmonary fistula), its effect on the blood in the vessels originating from the arch should have been approximately equal to the effect on the blood in the descending aorta. The possibility that left ventricular failure related to the concomitant subaortic stenosis could have occurred is to be considered, but there were no signs of pulmonary congestion or later untoward effects.

In case 2 the patient was also catheterized under anesthesia and the catheter entered the aorta through the ductus. The pressures and oxygen saturations at various sites of the catheter tip are shown in table 2 and figure 4. A difference between the oxygen content of the right radial artery and that of the descending aorta existed when the patient was breathing air, but this difference disappeared when he breathed 100 per cent oxygen. No lowoxygen mixture was administered to this patient.

In case 3 there was no difference between the oxygen content of the radial and femoral blood samples when the patient breathed 100 per cent oxygen or air, but there was a small though significant difference (0.7 volume per cent) when 12 per cent oxygen was breathed. The catheter was made to enter the aorta several times and the continuous record showed no readily demonstrable pressure
difference on withdrawal until the right ventricular pressures were recorded. This was so, despite the fact that approximately 30 per cent of the left ventricular output was being shunted into the pulmonary artery via the ductus. The record showed some artefact related to catheter movement which, along with a cardiac irregularity, vitiated accurate measurements of pressure. Whether there was a persistence of the left-to-right shunt, as well as the slight reversal on the breathing of 12 per cent oxygen, is unknown, since during this period the catheter tip was in the right ventricle. It may be mentioned again that 10 months after surgical closure of the ductus the pulmonary arterial pressure was 55/22 and no shunt was demonstrable.

The cases are arranged in order of age, but actually case 4 was the one most recently studied. The early cyanosis of the feet in this case clinically suggested an associated coarctation of the aorta above the ductus. While the laboratory data would not necessarily exclude

**TABLE 3—Effect of Variation in the Oxygen Content of Inspired Air on Blood Oxygen Saturation at Various Sites in the Systemic Arterial System of a Patient with Patent Ductus Arteriosus and Pulmonary Hypertension**

<table>
<thead>
<tr>
<th>Site</th>
<th>100%</th>
<th>20%</th>
<th>14%</th>
<th>10%</th>
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<tr>
<td>Right radial artery</td>
<td>100</td>
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<td>86</td>
<td>69</td>
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<tr>
<td>Right ear</td>
<td>100</td>
<td>95</td>
<td>87</td>
<td>67</td>
</tr>
<tr>
<td>Left ear</td>
<td>100</td>
<td>95</td>
<td>77</td>
<td>62</td>
</tr>
<tr>
<td>Left radial artery</td>
<td>99</td>
<td>85</td>
<td>75</td>
<td>54</td>
</tr>
<tr>
<td>Right femoral artery</td>
<td>95</td>
<td>79</td>
<td>69</td>
<td>45</td>
</tr>
</tbody>
</table>

* Case 4. See text for details.

† Note increase in degree of desaturation at different arterial sites relative to their origin in the distal direction along the aortic arch.
such an associated defect, they were interpreted as favoring the absence of such a lesion; that is, the similarity in the radial and femoral pressures and the characteristic dye-injection studies to be described were so interpreted. Dye-concentration curves were obtained after the method of Nicholson and co-workers, and the quantity of blood shunted was calculated on the basis of the ratio of the area of the primary deflection to the area of the secondary deflection after the method of Swan and co-workers. The calculations of the shunt, expressed as the proportion of arterial flow composed of shunted blood, for the right radial, right ear, left ear, left radial and right femoral sites were: breathing 100 per cent oxygen, 6, 6, 14, 24 and 35 per cent, respectively; and breathing air, 10, 11, 16, 29 and 47 per cent, respectively (fig. 5). The per cent arterial oxygen saturation at various sites with the patient breathing various oxygen mixtures is given in table 3, which shows progressive desaturation from right to left in respect to the branches of the aortic arch. That a small venous shunt from the pulmonary artery via a ductus may affect the saturation in all vessels of the aortic arch is more readily and conclusively demonstrated by arterial dye-dilution curves than by the values for oxygen saturation of the blood samples.

In this patient (case 4), the fact that pulmonary arterial blood was reaching the innominate and right radial artery was clearly shown by the initial contour of the dye curve from the latter vessel when the values for oxygen saturation were inconclusive. The femoral arterial dye curve had the characteristic double-hump contour associated with a large venous shunt. Of further interest were the facts that the femoral and left radial oximetric records showed marked phasic variations related to the respiratory cycle, while the records from the two ear oximeters and right radial artery did not; and while no left-to-right shunt through the ductus was present when the patient breathed air, there was some evidence of it when she breathed 100 per cent oxygen, as ascertained by some arterialization of blood in the pulmonary artery. The arrangement of the aortic arch branches in this case are shown in figure 1.

Case 5 is of special interest in that the pulmonary arterial pressure grossly exceeded that in the systemic arteries. There had been marked recent increase in the disability, and how much of this might be attributed to con-
oxygen saturation between the radial and femoral arterial samples while the patient was breathing air, but the values were similar for samples taken from the two arteries when the patient was breathing 100 per cent oxygen.

Dye-dilution curves were recorded from radial and femoral arteries and both ears while the patient breathed 100 per cent oxygen and also 16 per cent oxygen. With 100 per cent oxygen the contours of the curves were similar for all four sites, but the time components were prolonged with a disproportionate increase in disappearance time indicative of a low cardiac output with pulmonary recirculation.\textsuperscript{23} When the patient breathed 16 per cent oxygen, the contours for all sites were again similar but differed from the first series in the occurrence of a premature deflection that returned to the base line. This was followed by a second deflection which corresponded in time and in contour to the curve seen when the patient breathed 100 per cent oxygen, except that the disappearance time was no longer disproportionately prolonged. These curves indicated that with 16 per cent oxygen a right-to-left shunt was occurring, while the left-to-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig7}
\caption{Pulmonary and systemic arterial pressures and oxygen content of simultaneously withdrawn blood samples in a patient with patent ductus arteriosus and pulmonary hypertension (case 6) while differing oxygen mixtures were being breathed. Note the similarity in pressures and contours of all three pulses in the three states studied, and that the pulmonary pressure was relatively decreased when the patient breathed 100 per cent oxygen. Note also the resulting differences in oxygen content between simultaneously withdrawn radial and femoral arterial samples; these differences are greatest when the patient breathe 10 per cent oxygen, and are present to a progressively less degree when room air and 100 per cent oxygen are breathed. The proportion of shunted pulmonary arterial blood in the femoral arterial flow amounted to 42, 12 and 5 per cent, respectively, when the patient breathed 10, 21 and 100 per cent oxygen.}
\end{figure}

right shunt that was evident with 100 per cent oxygen was no longer present. When the proportion of shunted pulmonary arterial blood present at each site was calculated from the dilution curve,\textsuperscript{17} it was found to be 13, 9, 15 and 34 per cent respectively in the right radial arterial, right ear, left ear and right femoral artery, indicating that under this circumstance a higher proportion of shunted blood was passing to the caudal than to the cephalic portion of the body.

In case 7, simultaneous dye-dilution curves
were recorded from the radial and femoral arteries while the patient breathed 100 per cent oxygen and air, with the dye injected via the catheter in the pulmonary trunk. In each instance, both the ear-piece curves and the

radial artery curve were within normal limits; however, the femoral dye-dilution curve showed a shortened appearance time with a double-hump contour on the build-up slope characteristic of a right-to-left shunt (fig. 8). Dye-dilution curves of this type from the femoral artery have also been noted by Bothwell and co-workers.9

![Dye dilution curves](image)

**Fig. 8.** Differences in dye-dilution curves recorded simultaneously from cephalic (radial artery and both ears) and caudal (femoral artery) sites in the arterial system of a patient with patent ductus arteriosus and pulmonary hypertension (case 7, see text for details). The patient was breathing 100 per cent oxygen. The comparative sensitivity of the different oximeters is shown by the oxygen saturation scale included for each oximeter. Except for differences in amplitude caused by variations in sensitivity, there is similarity in contour of the dilution curves recorded from the right and left ears and the right radial artery. The curve from the femoral artery was, however, significantly different from the other three, showing a shorter appearance time and an abnormal initial hump caused by dyed blood shunted via the ductus from the pulmonary artery to the descending aorta. Measurements on this curve indicate that approximately 20 per cent of the blood from the femoral artery had originated from a right-to-left shunt. The disappearance limbs of all four curves are prolonged to a degree compatible with a left-to-right shunt (pulmonary recirculation) amounting to 20 per cent of the pulmonary arterial flow.

**Comment**

As previously reported,15 the production of change in magnitude or direction of flow through a patent ductus arteriosus by variation of the oxygen content of the inspired air is a unique and unequivocal method of demonstrating a differential effect of oxygen on the pulmonary and systemic circulations. It is generally conceded that pressure in the pulmonary artery usually varies inversely with the oxygen tension of the respired gas. However, the mechanism of, and lack of uniformity in, the pulmonary vascular response in man and animals have been controversial issues.27 That the effect is mediated by the sympathetic nerves is indicated by the work of Stroud and Rahn,28 who found in animals absence of the response in the sympathectomized lung. The absence of the pulmonary pressor effect in animals as noted by Beard and co-workers29 when 8.5 per cent oxygen was breathed might in part be related to the narcotized state. The possibility that in our patients a rise in left atrial pressure could have contributed to a rise in pulmonary resistance cannot be excluded as a factor in the change on low oxygen breathing but does not find likely application in the explanation of the change related to the shift from air to 100 per cent oxygen or vice versa. The decrease in pulmonary arterial pressure on change from air to 100 per cent oxygen, illustrated in figure 7, was as clear-cut as the decrease on changing from 10 per cent oxygen to air. It is to be noted that frequently there was a bidirectional shunt through the ductus orifice. While this might be considered related in part to turbulence, it seems more likely related to variations in the direction of flow during the cardiac cycle. If the latter were true, a variation in heart rate, with change in the relative durations of systole and diastole, might cause a change in the magnitude of the shunt, but it is thought that such an effect, if it occurred, would be insignificant, as the changes in heart rate were minimal.

The fact that a venous-arterial shunt through a patent ductus affected the oxygen saturation of the blood in the aortic arch vessels that originate proximal to it, was noted in several
cases but particularly in case 5. This finding demonstrates retrograde movement of blood in the aorta probably in late systole or diastole. Whether this backflow occurs during closure of the semilunar valves at the end of systole or is due to phasic differences in ventricular ejection or capacity of the aorta and pulmonary artery to take up the stroke volume of the respective ventricles, or a high runoff from the proximal branches of the aortic arch, or to these and additional factors, is at present uncertain.

The phenomenon of reversal of the arteriovenous shunt in patent ductus arteriosus is not usual even when some degree of pulmonary hypertension is associated with the congenital lesion. Thus the over-all incidence of venoarterial shunt in patent ductus arteriosus is small, and the cases which we have discussed are distinctively atypical on hemodynamic and clinical grounds. We have seen two cases of patent ductus in which the magnitude of the pulmonary arterial pressures as related to the systemic arterial pressure was within the range of that of the seven cases presented above, but in which the use of differing oxygen mixtures failed to influence the magnitude of a shunt already present.

Further emphasis may be placed on the fact that the patient with the syndrome of patent ductus arteriosus and severe pulmonary hypertension may have a clinical picture, that is, basal systolic murmur, enlarged heart and vascular shadows, and electrocardiographic findings, which might suggest Eisenmenger's complex. Indeed, if only a routine catheterization of the heart were done and single samples of blood from the various chambers were obtained, the diagnosis of Eisenmenger's complex might be thought to have been supported. When the catheter passes through the ductus, the diagnostic importance of which has been emphasized by Limón Lason and co-workers, the problem is simplified but in the absence of such an event, comparison of the oxygen content of the blood in the radial with that in the femoral artery is a most important investigative procedure. It might be mentioned that the Eisenmenger complex in case 2 of Cosby and co-workers group of cases, as well as in such cases of our own, closely resembled the clinical complex of patent ductus and pulmonary hypertension with some reversal of flow through the ductus.

The problem of surgical exploration in adult cases of this type is a very difficult one, and the justification for exploration may be largely dependent on the fact that the immediate mortality is not prohibitive rather than on a real hope of "cure." Case 3 is of pertinent interest, as the heart failure seemed to have been alleviated and the pulmonary pressure was markedly reduced. Case 7 is of particular interest in that on postmortem examination the pulmonary vascular changes were not sufficiently extensive to make one believe that the pulmonary hypertension was necessarily irreversible. When this patient breathed 100 per cent oxygen there had been evidence of a shunt in the aortic-pulmonary direction. Shumacker advised against surgical treatment in one case of this type, and Dammann and co-workers have expressed the belief that the condition is primarily nonsurgical. De Camp reported one case in which death followed surgical treatment. In children, the problem is somewhat different in that one would not expect accumulated organic changes approaching irreversibility to be present. Here the question of an associated defect may be the main deterrent to surgical exploration. Exploration may be justified if studies of the type described give no indication of an associated intracardiac defect of severe nature. If the cyanosis has been present since early life, the likelihood of an associated defect is very great indeed.

Summary

In seven cases of patent ductus arteriosus with pulmonary hypertension a transient or maintained blood flow from the pulmonary artery to the aorta has been demonstrated. These patients were studied by cardiac catheterization and simultaneous blood sampling from radial and femoral arteries. Under given conditions in each case, the oxygen content of femoral arterial blood was demonstrated to be less than that of simultaneously withdrawn radial arterial blood.
It was possible to affect the magnitude and occasionally the direction of the aortic-to-pulmonary flow in each of these cases by varying the oxygen content of the gas mixture breathed.

This finding affords unequivocal evidence that in man systemic and pulmonary vascular pressures are affected differently by variations in oxygen content of the respired gas mixture. This effect affords a basis for tests which may be useful occasionally in the diagnosis of atypical ductus arteriosus since the pulmonary artery-to-aorta pressure gradient, and hence the flow in that direction, may be varied at will in the inverse direction to changes in oxygen tension of inspired air.

The injection of dye either into a peripheral vein or into the heart via the catheter and the recording of the dye-dilution curve from various sites in the arterial system, particularly the right radial and femoral arteries, has been of additional value, particularly in the quantitation of the magnitude of pulmonary artery-to-aorta flow. Dye entering the aorta via the ductus is demonstrable in the femoral artery, and on occasion may be detected in progressively diminishing concentration in arteries arising more proximally from the aortic arch. This last finding demonstrates that a significant degree of retrograde movement of blood may occur in the arch of the aorta in man.

ADDENDUM

Since this manuscript was prepared, an additional patient, 21 years of age, has been studied in the laboratory while breathing varied oxygen mixtures, and the findings were practically identical with those of case 4. This young woman also showed the evidence of retrograde flow of blood in the aortic arch and the characteristic differences in dye curves obtained from various sites of the arterial tree.

ACKNOWLEDGMENTS

Acknowledgment is made to Dr. Edward Morgan and Dr. Earl Beard, Fellows of the Mayo Foundation, who have made individual case presentations at local medical meetings. The help of Dr. J. E. Edwards of the Section of Pathologic Anatomy, Mayo Clinic, with particular regard to the post-mortem and biopsy material is also acknowledged with sincere appreciation. The cooperation of Drs. O. T. Clagett and J. W. Kirklin, Division of Surgery, in the study is appreciated.

SUMARIO ESPAÑOL

Siete casos de conducto arterioso patente con hipertensión pulmonar y reversión de la dirección usual de la circulación se describen. Respiración de una mezcla baja en oxígeno o inició u aumentó el "shunt" reversado, y respiración de oxígeno al 100% produjo un efecto inverso. Diferencias en saturación de oxígeno y en curvas de dilución de tinte registradas simultáneamente de las arterias radiales y femorales hicieron posible calculaciones de la diferencia en proporción de sangre desviada circulando en estas arterias y demuestra que movimiento retrogrado de sangre en la aorta puede ocurrir.

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Demonstration of Differential Effects on Pulmonary and Systemic Arterial Pressure by Variation in Oxygen Content of Inspired Air in Patients with Patent Ductus Arteriosus and Pulmonary Hypertension

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Circulation. 1953;8:681-694
doi: 10.1161/01.CIR.8.5.681

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

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