Multiple Small Pulmonary Arteriovenous Fistulas
Diagnosis by Cardiac Catheterization

By J. S. Sanders, M.D., and J. M. Martt, M.D.

The antemortem diagnosis of pulmonary arteriovenous fistula was made for the first time by Smith and Horton in 1939. The lesion was suspected from the appearance of the chest x-ray and subsequently proved by injection of contrast media into an arm vein with visualization of the abnormal vascular communication in the right lung. Since then many such lesions have been suspected from clinical findings and proved by angiocardiography. The classical clinical findings are cyanosis, polycythemia, clubbing of the digits, and murmurs over the lung fields in the absence of cardiac disease. Surgical excision has resulted in cure of the disease with disappearance of cyanosis and clubbing when the lesion or lesions are localized to one or two segments of a lung. The complications resulting from pulmonary arteriovenous fistulas, if untreated, include the following:

1. Rupture with massive hemorrhage. 2. Cardiac decompensation. 3. Cerebral thrombosis secondary to polycythemia. 4. Cerebral emboli due to passage of emboli from the periphery through the fistulas. 5. Brain abscess or meningoencephalitis, presumably secondary to septic emboli. 6. Impairment of cerebral function from chronic anoxemia. Cyanosis, polycythemia, and clubbing of the digits are found in patients in whom the pulmonary arteriovenous communications are of sufficient size or number to produce these findings. It is estimated that 5 Gm. of reduced hemoglobin per 100 ml. of blood or a right-to-left shunt of 20 per cent of the systemic cardiac output are necessary for cyanosis to be apparent clinically. The presence of even minimal shunting of venous blood into the arterial circuit, however, can be demonstrated by determination of arterial oxygen saturation after inhalation of 100 per cent oxygen for 20 to 30 minutes. Under these circumstances the arterial oxygen saturation is invariably below the normal level of 100 per cent + 1.5 vol. per cent dissolved in plasma.

Although the number of reported cases of pulmonary arteriovenous fistula now approximates 400, a very small number of these are of the multiple minute type involving all five lobes of the lungs. In a recent review in which 350 reported cases of pulmonary arteriovenous fistulas are summarized, only five cases are of this type. Two cases have since been added. The lesions are often suspected from clinical data, but the diagnosis is frequently difficult to prove even with chest x-rays and angiocardiography. Cardiac catheterization has not been of benefit except to rule out associated cardiac lesions that might contribute to the patient's cyanosis. In the case reported here, however, the presence of a congenital heart lesion (atrial septal defect) allowed the diagnosis to be established with reasonable certainty by cardiac catheterization.

Case Report
A 16-year-old white girl was admitted to the University of Missouri Medical Center on May 30, 1960, for evaluation of cyanosis and dyspnea on exertion.

The patient was born prematurely after one uncomplicated 7-month pregnancy. Her mother noted that the patient's skin and mucous membranes were "blue" shortly after birth. During childhood there was a slight but definite progression in the cyanosis. There was a history of squatting. Childhood illnesses included measles, mumps, whooping cough, and chickenpox. There were no complications. At the age of 9 years it was believed that she was definitely mentally retarded and for this reason she did not attend school past the fifth grade. At the age of 12 years cardiac studies including right heart catheterization...
terization were performed at another hospital. A diagnosis of atrial septal defect with a left-to-right shunt was made. A summary of the results of this catheterization as they were reported to us are tabulated in Table 1. A cause for her cyanosis was not found. Because of her cardiac disease she was advised to restrict her activity. With exertion she noted increasing cyanosis and severe shortness of breath. Eighteen months prior to the present admission she developed jaundice with hepatosplenomegaly; the diagnosis was infectious hepatitis. Dyspnea on exertion became more severe at this time, and she was forced to discontinue any activity that required more than minimal exertion. She was not bothered by orthopnea or paroxysmal nocturnal dyspnea. There was no hemoptysis at any time.

Family History: There is no history of cardiac disease or cyanosis in the family. Six younger siblings are all living and well with no evidence of cardiac or pulmonary disease.

Physical Examination: The patient was a well developed, fairly well nourished, cyanotic white girl. The blood pressure was 112/60 mm. Hg in both arms, the pulse was 110 and regular, and the respirations were 22 per minute. The temperature was 98.6° F. There was obvious cyanosis of the mucous membranes and funduscopic examination revealed the retinal veins to be slightly dilated. The neck veins were prominent but not pulsating. Hepatojugular reflux was not elicited. There was obvious clubbing of all the digits. The lungs were clear to percussion and auscultation. Cardiac examination revealed the left border of cardiac dullness to be 1 cm. lateral to the left midclavicular line. The heart rhythm was regular. No murmurs were audible, and there was no evidence, clinically, of ventricular enlargement.

Abdominal examination revealed no hepatomegaly or tenderness in the right upper quadrant. A firm, nontender spleen was palpated 7 cm. below the left costal margin. No other abdominal masses were palpable. Examination of the extremities revealed the previously mentioned clubbing and cyanosis. Peripheral pulses were equal in all extremities. Several small spider angiomata were present on the shoulders and over the upper anterior chest. No other vascular lesions were noted on the skin or mucous membranes.

Laboratory Data: The admission hemoglobin was 16.8 Gm. per cent and the hematocrit level was 53 per cent. Bone marrow aspiration revealed moderate hyperplasia of both granulocytic and erythrocytic elements. Chest x-rays with barium revealed no abnormality of the heart or aorta. The lungs appeared to be hypervascularized (Fig. 1). An esophagogram revealed no evidence of esophageal varices, but esophagoscopy revealed small varices in the lower esophagus. Liver function studies were as follows: Bromsulphalalin retention 17.9 per cent (45 minutes); serum cholesterol 110 mg. per cent; alkaline phosphatase 8.6 King Armstrong units; thymol turbidity 5.1 units; cephalin-cholesterol flocculation 4+ (24 hours); serum glutamic oxaloacetic transaminase 34 units, and prothrombin time 16.2 seconds (control 13 seconds).

Cardiopulmonary Studies: The electrocardiogram revealed right axis deviation and sinus

Figure 1
Erect posteroanterior roentgenogram of the chest showing diffuse increase in pulmonary vascular markings.

Figure 2
angiogram performed from the superior vena cava showing multiple small flocculent densities in peripheral lung fields.
Table 1
Right Heart Catheterization. Data Observed Elsewhere from Cardiac Catheterization in 1956

<table>
<thead>
<tr>
<th>Location</th>
<th>O₂ Content (Vol. %)</th>
<th>Pressure (mm. Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior vena cava</td>
<td>12.95</td>
<td>6</td>
</tr>
<tr>
<td>Right atrium</td>
<td>15.50</td>
<td>14/8</td>
</tr>
<tr>
<td>Inferior vena cava</td>
<td>14.15</td>
<td>6/4</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>14.80</td>
<td>32/16</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>15.00</td>
<td>32/16</td>
</tr>
<tr>
<td>Systemic artery</td>
<td>15.60 (86%)</td>
<td>110/80</td>
</tr>
</tbody>
</table>

Diagnosis: Atrial septal defect with L-R shunt.

tachycardia. Right heart catheterization was performed on June 13, 1960. There was no evidence of left-to-right shunting of blood in the right atrium, the right ventricle, or the pulmonary artery. The catheter passed readily, however, from the right atrium to the left atrium through a low-lying posteriorly located atrial septal defect. This was confirmed by the presence of arterialized blood (an increase in oxygen content of 2 to 2.5 vol. per cent). The catheter was then passed into the pulmonary vein of the lower lobe of the right lung. Blood samples were then taken from the vein and from the distal pulmonary vein (wedge position). Oxygen saturation values by the euveette method were 76.0 per cent in the pulmonary vein and 100.5 per cent in the pulmonary vein wedge position. Later during the catheterization the catheter was passed to the left ventricle and pressures and saturations were obtained. It was then withdrawn and passed into the inferior vena cava, the hepatic vein, and wedged in a branch of the hepatic vein in the right lobe of the liver. Results of this study are given in table 2.

Biplane angiocardiography from the superior vena cava was performed after completion of the catheterization. This revealed a strikingly abnormal appearance of the peripheral pulmonary vasculature with multiple small flocculent densities throughout both lung fields. It was thought that this finding was compatible with the clinically suspected entity of multiple small arteriovenous fistulas (fig. 2).

Hospital Course: The patient tolerated all the above procedures without incident. Because of slight mental retardation it was difficult to obtain complete studies of pulmonary function.

No gross abnormalities were detected in the ventilatory examination, and the diffusion by the carbon monoxide single-breath method was within normal limits. At the time of discharge the patient showed no significant change in her condition. It was decided to follow her with periodic visits to the Cardiac Out Patient Clinic.

Discussion

The presence of an atrial septal defect was fortuitous in this patient, as it allowed the catheter to be passed into a pulmonary vein. The oxygen saturation of 100 per cent in the pulmonary vein wedge position indicated that the shunting of blood occurred distal to this site and that the pulmonary capillaries were normally oxygenated. The normal pulmonary diffusion capacity confirmed the latter finding. The oxygen saturation of 76 per cent with the catheter near the wedge position in a branch of the pulmonary vein indicated that the shunting of blood must have occurred at the level of the smallest branches of the vein. The location of the catheter during this portion of the examination is diagrammatically illustrated in figures 3 and 4. The diffuse na-
ture of the disease and the probability that these communications were from pulmonary artery to pulmonary vein are suggested by the appearance of the lungs on the angiocardiogram. A somewhat similar appearance has occasionally been reported in the past in cases of multiple pulmonary arteriovenous fistulas.10, 12

The patient's history is somewhat unusual for the diagnosis of pulmonary arteriovenous fistulas in that she had been cyanotic since infancy. Congenital pulmonary vascular communications may produce cyanosis early in life, although it is more common for this finding to appear in adolescence or later.4 It is thought by many observers that congenital pulmonary arteriovenous fistulas are a part of the syndrome of hereditary hemorrhagic telangetasias (Osler-Weber-Rendu disease), even though cutaneous and mucosal manifestations of this disease may be absent or delayed in appearance.5, 11, 13 The atrial septal defect would not appear to be a likely cause of cyanosis during childhood in this patient in view of (1) the absence of pulmonary hypertension on both catheterizations; (2) the demonstration of a left-to-right shunt at the atrial level during the first catheterization; (3) marked desaturation of the pulmonary vein on the most recent study, indicating that the right-to-left shunt occurs before the blood is returned to the left atrium.
A second possible etiology for the syndrome of multiple small pulmonary arteriovenous fistulas is chronic hepatic disease with secondary portal hypertension. There has been considerable investigation of the cardiopulmonary effects of cirrhosis of the liver in recent years. The combination of cyanosis, clubbing, and chronic hyperventilation with cirrhosis of the liver has been noted in many of these studies. One of the early descriptions of this condition was by Evans and Sheldon in 1937. The etiology of the cyanosis and clubbing in the 12-year-old patient described was not found, but it was suspected that an associated "lung lesion" accounted for the arterial oxygen desaturation. Since that time numerous cases have been described in which no obvious cause for the cyanosis has been detected. Several mechanisms have been postulated, including the following: 1. Ventilatory distribution defects due to elevation of the diaphragm secondary to ascites. 2. Intrinsic pulmonary disease with a diffusion defect. 3. A change in the hemoglobin molecule leading to a shift in the oxygen dissociation curve. 4. Right to left shunting of blood through portal-pulmonary communications and multiple pulmonary arteriovenous fistulas.

It has been found that in most of the patients with cyanosis, administration of 100 per cent oxygen does not result in a rise in the arterial oxygen saturation to the expected normal value (100 per cent plus 1.5 vol. per cent). This finding indicates that the cyanosis can only be due to right-to-left shunting of blood at the cardiac or pulmonary level. As cardiac anomalies leading to a shunt of this type can usually be excluded by cardiac catheterization, the presence of fistulous connection with the pulmonary venous system seems the most likely etiology. The antemortem localization of the sites of the lesions has been difficult, but both pulmonary artery-to-pulmonary vein and portal vein-to-pulmonary vein communications have been demonstrated with special postmortem studies. Calabresi and Abelman have demonstrated portal-pulmonary communications by dye studies in two of 10 cadavers with portal cirrhosis. These lesions have been suspected though not proved to be present in other adults dying with portal cirrhosis and cyanosis. Rydell and Hoffbauer succeeded in demonstrating multiple small pulmonary arteriovenous fistulas in a 22-year-old patient dying with postnecrotic cirrhosis, cyanosis, and clubbing. Routine postmortem examination revealed no abnormal pulmonary vascularity, but injection of a plastic substance into the pulmonary artery resulted in demonstration of communications between small branches of the pulmonary arteries and veins.

The patient under consideration had (1) abnormal liver function tests (increased bromsulphalein retention, decreased serum cholesterol, 4+ cefalin flocculation, and elevated prothrombin time), (2) splenomegaly with probable secondary hypersplenism, and (3) ancillary signs suggestive of cirrhosis of the liver ("spider" angiomata, without associated "pinhead" angiomata characteristic of hereditary hemorrhagic telangectasis). The attack of "infectious hepatitis" 17 months prior to admission may have resulted in worsening in her condition, as she complained of increased fatigability and dyspnea on exertion after this illness. However, this could not have been an etiologic factor in the patient's pulmonary vascular disease, as the cyanosis preceded the attack by several years. In any case it is interesting to speculate that
so-called "juvenile cirrhosis" appearing in infancy might have been a predisposing factor in the development of the pulmonary vascular lesions. The association of cyanosis with juvenile cirrhosis in a 9-year-old boy has recently been reported.24 The etiology of the cyanosis was never determined though portal pulmonary venous communications were suspected.

A liver biopsy would have been of considerable interest in our patient but, because of the elevated prothrombin time and depressed platelet count, it was not done.

Surgical therapy for this condition has not been possible because of the diffuse nature of the lesions. Medical therapy consists of control of polycythemia, which may require occasional phlebotomies, and management of heart failure, should it become manifest. Any localized infection should be treated vigorously because of the danger of septic emboli passing to the brain through the vascular communications. It is thought by some that when these lesions are secondary to chronic hepatic disease, portal hypertension is the etiologic factor, although the mechanism for the production of the fistulas is not known.17,21 If portal hypertension is responsible, it is possible that a shunting procedure (portacaval or splenorenal) to relieve the hypertension might result in closure or decreased function of the fistulas, especially if this is done soon after the appearance of cyanosis. This procedure has never been attempted in this condition. It was not considered in this case because of the long history of cyanosis and the possibility that the pulmonary and hepatic disease were unrelated.

Summary

The condition of multiple small pulmonary arteriovenous fistulas is discussed with regard to diagnosis, complications, and possible etiology. The lesions are believed to be either congenital in origin or secondary to cirrhosis of the liver with portal hypertension. Surgical therapy has not been attempted in this condition because of the diffuse nature of the lesions.

A case is discussed wherein the diagnosis of diffuse small pulmonary arteriovenous fistulas was made by cardiac catheterization. The catheter was passed through an atrial septal defect into a pulmonary vein. Difference in oxygen saturation between the pulmonary vein and pulmonary capillaries (pulmonary vein wedge) revealed conclusive evidence of a right-to-left shunt in this area. Etiologic and therapeutic considerations are discussed in view of recent literature on this subject.

References


Thomas Sydenham
1624–1689

Sydenham stands as the representative of the clinical or bedside approach to the problems of disease, just as his immortal contemporary and fellow townsman William Harvey stands as the prototype of the experimental investigator. He is entitled to a perpetual place in Medicine's Hall of Fame.—David Riesman, M.D. Thomas Sydenham, Clinician. New York, Paul B. Hoeber, Inc., 1926, Preface, pp. 7 and 9.
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