Anomalous Inferior Vena Cava Draining into the Left Atrium Associated with Intact Interatrial Septum and Multiple Pulmonary Arteriovenous Fistulae

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Congenital cardiac defects involving the venous return to the heart and those affecting the partitioning of the atria should probably be considered as a group. The most commonly encountered and simplest to correct are defects in the interatrial septum of the ostium secundum type. Due to the lower resistance to emptying into the right ventricle from the two communicating atria, the shunt in such instances is left to right unless obstruction to flow is present in the tricuspid valve, in a hypoplastic right ventricle, in the pulmonary valve, or because of high pulmonary vascular resistance.

Associated with defects in the interatrial septum various degrees of anomalous pulmonary venous drainage are also encountered. The simplest form involves drainage of the right pulmonary veins into the right atrium, with those from the left lung being normally inserted into the left atrium. Other variants include drainage of right-sided veins into the superior vena cava, and finally total anomalous pulmonary venous drainage into the superior vena cava system.

Isolated anomalies of the venae cavae alone have also been described.1 The commonest is drainage of the superior vena cava into the coronary sinus or, more rarely, into the left atrium. This is generally associated with an interatrial defect but on occasions the superior vena cava is found to drain into the left atrium with an intact interatrial septum, resulting in a partial right-to-left shunt.2

Taussig3 has described one instance of both venae cavae draining into the left atrium associated with an interatrial septal defect and underdeveloped right atrium and right ventricle. Other instances of total absence of the inferior vena cava have also been described but these were not associated with right-to-left shunt, since the blood was returned to the right heart via the azygous system.

An extensive review of the literature has revealed only two instances in which an anomalous inferior vena cava drained into the left atrium with an intact interatrial septum. The first patient reported by Gardner and Cole4 was a woman who had lifelong cyanosis and slight dyspnea. She died suddenly at the age of 32. The condition was recognized only at postmortem examination and there was no associated anomaly.

Since the present case was studied, Meadows et al.4 have described another instance of anomalous inferior vena cava drainage into the left atrium with intact interatrial septum in an asymptomatic, 37-year-old Negro man. This patient had advanced pulmonary tuberculosis and surgical correction was not undertaken. The diagnosis was established by separate superior and inferior vena cava catheterization including dye injections and angiography. This patient also had clubbing of the fingers, cyanosis (arterial oxygen saturation 82 volumes per cent), left ventricular hypertrophy by electrocardiogram, and a hematocrit level of 74 per cent.

The following case is thought to represent the first instance in which drainage of the inferior vena cava into the left atrium with an intact interatrial septum was recognized during life and subsequently corrected by open-heart surgery. It should be of interest.

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to those engaged in corrective surgery for congenital heart lesions not only as a rare cause of cyanotic heart disease but because of the associated presence of multiple bilateral pulmonary arteriovenous fistulae. Whether these two defects will be commonly associated in other cases remains to be seen. It is hoped that our experience will be recalled by those who may consider the redirection of an anomalously draining inferior vena cava in the future.

Embryology *

Embryologically the inferior vena cava has a complex origin. It consists of contributions from (1) the iliac anastomosis of the postcardinal veins, (2) fusion of the two post-

* We are grateful to Dr. Gordon Vawter of the Department of Pathology at the Children's Medical Center, Boston, for many helpful suggestions concerning the embryology of this malformation.

Figure 1

Embryology of anomalous inferior vena cava (adapted after Arey). A. Situation at the third month of embryonic life. The right valve of the sinus venosus almost divides the right atrium into two chambers. B. Normal atrophy of the cephalic end of sinus venosus valve usually seen at 4 months. Persistence of the caudal portion of this valve and fusion with the septum secundum (z to x' and y to y') would establish the defect seen in this patient.
month and nearly divides the right atrium into two chambers. This valve normally atrophies, leaving only the Eustachian valve of the inferior vena cava and the Thebesian valve of the coronary sinus as remnants. If the portion that becomes the valve of the inferior vena cava were to fail to regress normally, and, in addition, were to fuse with the septum secundum closing the foramen ovale the defect seen in this patient would be established (fig. 1B).

The blood from the inferior vena cava would then be directed between the septum secundum and the septum primum, and thence into the left atrium via the ostium primum. This simple alteration in normal embryologic development of the two atria would explain the tunneling of the inferior vena cava between two leaves of the interatrial septum that was seen in the case being reported. These two leaves undoubtedly represent the unfused septum primum on the left and the septum secundum joined to the persistent valve of the sinus venosus on the right.

Congenital pulmonary arteriovenous fistulae result simply from a failure of full maturation of the pulmonary capillaries from the pulmonary plexus.

Case Report

M. J. B. was 30 years of age when she was first seen by us in February 1958. She had been cyanotic since birth and was found to have a cardiac murmur at the age of 12. During childhood she had developed normally and had been unrestricted in her activities. First symptoms began at the age of 16 when dyspnea and fatigue on vigorous exertion and climbing hills appeared. At age 29 she experienced an episode of left-sided numbness and paralysis for approximately 5 to 10 minutes associated with “pneumonia.” There were no residua from this nor was there any recurrence of neurologic symptoms. At approximately the same time she also noted edema of her lower extremities for the first time. Episodic tachycardia appeared and she began to experience paroxysmal nocturnal dyspnea although she was able to sleep flat most of the time. There was no cough or hemoptysis. At the time of her first admission to the hospital she had dyspnea on
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one flight of stairs and had stopped working because of symptoms.

She was moderately cyanotic with marked clubbing of fingers and toes. Many minute pinhead telangiectases were noted over the skin of the back but none in the mucous membranes. The left breast was underdeveloped. Examination of the heart revealed a prominent left ventricular impulse in the midclavicular line and a soft grade-I systolic murmur over the upper left sternal border. There were no murmurs over the lung fields. There was 2+ peripheral edema, and the liver was enlarged one fingerbreadth beneath the right costal margin.

The electrocardiogram showed normal sinus rhythm with a P-R interval of 0.23 second. There were low voltage, abnormal nonspecific T-wave changes, and left ventricular hypertrophy.

The x-rays of her chest (fig. 2) revealed a 10-per cent increase in transverse diameter. In the oblique views the left ventricle was moderately enlarged. There was, in addition, a bulge along the upper right cardiac border in the region of the azygous vein. The lung fields were honeycombed with a tracery of minute vessels, interpreted as bronchial collateral vessels. In retrospect nodular densities could be seen behind the dome of the right diaphragm.

Right-sided cardiac catheterization* revealed a brachial arterial oxygen saturation of 70 per cent. The pulmonary artery pressure was within normal range (20/10 mm. Hg with a mean of 14). Dye-dilution curves following injection in the right ventricle, pulmonary artery, and right atrium were normal with no evidence of a right-to-left shunt. Dye injection from a vein on the dorsum of the foot showed very rapid appearance at the brachial artery, indicating a large right-to-left shunt.

As the result of this observation a second catheterization was carried out several days later through the right saphenous vein. The catheter could not be passed into the right atrium but repeatedly entered the left atrium and left ventricle as well as into the right inferior pulmonary vein. The oxygen saturation in the inferior vena cava was 60 per cent, in the left atrium and left ventricle 70 per cent, and in the right inferior pulmonary vein 87 per cent. The significant desaturation of the last was interpreted at the time as due to retrograde mixing from the left atrium but in retrospect was undoubtedly a clue to the presence of pulmonary arteriovenous fistulae. The mean pressure in the left atrium was 7 mm. Hg and the pulmonary venous mean was 9 mm. Hg. Fifteen milliters of 90 per cent sodium diatrizoate (Hypaque) were injected through the catheter in the inferior vena cava. Rapid filling of the inferior vena cava, left atrium, left ventricle, and aorta occurred without any dye entering the right heart (fig. 3). The calculated pulmonary blood flow was 2.6 L./min./M.2 and the systemic flow was 8.5 L./min./M.2. The mean pressure in the inferior vena cava was 11 cm. of water in contrast to a left atrial mean of 7 and a right atrial mean of 6, suggesting some obstruction to free flow from cava to left atrium.

Seven months later she was readmitted to the hospital. Her edema had disappeared and her dyspnea had diminished as a result of digitalization, diuretics, and a low-salt diet. Her cyanosis was more marked and her hemoglobin had risen from 12.5 to 16.5 Gm. per cent as a result of oral iron therapy. The hematocrit value was 60. A phlebotomy of 500 ml. was performed, and the hematocrit value fell to 57.5. Operation was deferred at this time because of arthralgia and temperatures of 100 to 101 degrees. She was placed on salicylate therapy. The final admission was 1 month later, at which time the joint pains had entirely subsided and the patient was afebrile. Her hematocrit value had fallen to 47 per cent.

Operation was performed on November 13, 1958, through a median sternotomy incision. Correction of the defect on cardiopulmonary bypass was chosen in preference to attempts to anastomose the short inferior vena cava above the diaphragm to the right atrium either directly or by graft, as employed by Baffes for complete transposition to the great vessels.

The superior vena cava was found to drain normally into the right atrium and the dilated azygous vein joined this vessel in the usual location. There was no left superior vena cava. The aorta and pulmonary artery came off their respective ventricles in a normal fashion and were of approximately equal size. The right ventricle and right atrium were adequately developed although somewhat small. The pulmonary veins drained into the left atrium. The inferior vena cava came through the diaphragm in its usual location but entered the posterior surface of the heart in the interatrial groove (fig. 4). This fact is taken as evidence of a failure migration of the sinus venosus to the right. The mitral and tricuspid valves were normal. The foramen ovale was obliterated by a diaphragm and no interatrial defects were present. The coronary sinus entered the right atrium in normal position and had no valve.

The patient was placed on cardiopulmonary by-

* We are indebted to Dr. Abraham Rudolph, formerly of Children's Medical Center, Boston, Massachusetts, for the catheterization and angiographic studies.

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Figure 4

Diagrammatic representation of the anatomy of the malformation. A. The inferior vena cava deviates to the left to enter the interatrial septum. It empties into the left atrium through two large fenestrations near the cephalic end of the septum. B. Method of surgical correction—the interatrial septum is incised and the left lateral wall of the intraseptal vena cava is sutured to it. C. Completion of the suture line directs the entire inferior vena caval flow into the right atrium.

pass by cannulation of the superior vena cava via the right atrium and the inferior vena cava via the left femoral vein. The inferior vena cava was occluded just before its entry into the heart by a tourniquet.

An incision in the intact interatrial septum was made near the tricuspid valve, and the inferior cava was entered as it passed upwards through the interatrial septum. A finger could be inserted down to the constricting ligature above the diaphragm. By directing the finger cephalad the left atrium was entered through two fenestrations of approximately 1.5 cm. diameter each, close to the superior aspect of the interatrial septum. The inferior vena cava was thus found to tunnel through the interatrial septum with intact right and left lateral walls and to communicate with the left atrium only near the most cephalic part of the septum (fig. 4).

The band between the two fenestrations was divided, following which the inferior vena cava was redirected into the right atrium by suturing...
the cut edge of the septal incision to the left lateral wall of the inferior vena cava. An opening measuring an estimated 2.5 cm.² in the area was thereby created. When the constricting ligature on the inferior vena cava was released, a large flow of unoxygenated blood was obtained. When the inferior vena cava was occluded, however, a small amount of oxygenated blood welled up into the newly constructed inferior vena caval orifice suggesting additional minute communication with the left atrium. In view of the small volume of this shunt, no further attempt was made to locate it.

Except for some difficulty in returning the clotting time to normal, the early postoperative period was quite benign and uncomplicated. There appeared to be less cyanosis although it had not entirely disappeared. There was no evidence of congestive failure and the venous pressure was 13.2 cm. of water. By the tenth postoperative day, however, the patient developed weakness, nausea and vomiting, and a fall in serum sodium to 125 mEq./liter. This was treated with 300 ml. of 3 per cent saline with marked clinical improvement. On the fifteenth postoperative day she developed atrial flutter with a 2 to 1 response and a ventricular rate of 130 to 140.

This was brought under control with increased digoxin dosage. The arterial oxygen saturation was 67 per cent and rose only to 80 per cent on breathing of 100 per cent oxygen.

A repeat cardiac catheterization was then carried out on the twenty-fifth postoperative day. All circulation times were normal and catheterization via the superior vena cava revealed no shunt within the heart. In view of the persisting desaturation it was concluded that pulmonary arteriovenous fistulae were present.

Following catheterization, the patient developed a right brachial thrombophlebitis with fever, malaise, and dyspnea. Staphylococcus aureus, resistant to all of the common antibiotics, was isolated from the brachial incision. This was soon followed by infection of the left groin and sternotomy incisions, which had previously healed. The patient's course from this time was progressively more complicated with tachycardia, spiking fever, pulmonary edema, and eventually massive bleeding from a duodenal ulcer. She succumbed to these complications on the forty-seventh postoperative day.

Postmortem examination revealed an intact anastomosis between the inferior vena cava and right atrium with a widely patent lumen. There was a 1-mm. linear communication between the inferior vena cava and the left atrium 0.5 cm. distal to entry of the inferior vena cava into the heart. This small communication was thought not to be of physiologic significance. Within the right atrium there was a low muscular ridge running from a point to the right of the orifice of the superior vena cava to an unusually heavy vertical muscular mass in the posterior portion of the interatrial septum. This finding is interpreted as confirmatory evidence of a failure of regression
of the caudal portion of the valve of the sinus venosus.

The heart weighed 300 Gm. and there was a generalized dilatation of the left atrium and left ventricle. The right atrium and ventricle were not remarkable. The left atrium showed endocardial fibrosis, thought to reflect the abnormally increased blood flow before operation. There was focal calcification of the annulus fibrosus of the mitral valve but no evidence of valvulitis. All cardiac valves were otherwise normal.

The lungs had a multiplicity of pathologic changes. The most conspicuous and important were the multiple pulmonary arteriovenous fistulae (fig. 5). These were found in all lobes and represented basically two histologic types. The smaller and least conspicuous were the focal aggregates of capillary hemangiomatous lesions found deep within the pulmonary parenchyma. Histologically, these were multiple capillaries lined by a single layer of endothelium, which rested on the wall composed of collagen and fibrous connective tissue of varying thickness.

The most prominent pulmonary lesions were the plexuses of thin-walled channels lying close to and occasionally abutting on the pleural surface (fig. 6). These channels varied in internal diameter from 1 to 10 mm. Often they were seen lying back to back, but in other areas they were separated by one or two alveoli. The walls were lined by a single layer of endothelium that resembled mesothelium histologically. The walls varied in thickness, depending on the amount of supporting collagen and the inconstant presence of elastic tissue. In some of these channels there were old, organizing and recent thrombo-emboli, as well as focal fibrous intimal thickening. These larger arteriovenous fistulae were fed by large muscular pulmonary arteries having both internal and external elastic laminae. In many areas these muscular arteries were abruptly transformed into channels that were indistinguishable from veins (fig. 7). The pathologic sequelae of ruptured pulmonary arteriovenous fistulae (thrombosis, intrapulmonary hemorrhage, infarction, and fibrosis with compensatory emphysema) were present throughout the lungs.

The bronchial arteries were dilated, and there were many pleural adhesions with vascular communications between the pulmonary and intercostal arteries. These channels histologically resembled dilated capillaries and veins. They undoubtedly explain the reticular appearance of the pulmonary vascular pattern noted in the roentgenograms preoperatively.

An additional anatomic finding of major importance was the diffuse distribution of the histologic stigmata of hypertension in the pulmonary arterial tree. In the arterioles a distinct media was found and in the small muscular arteries medial hypertrophy often associated with marked intimal thickening and fibrosis was seen (fig. 8). In addition, diffuse arteriosclerotic changes were seen in all arteries but there was no evidence of arterial necrosis or arteritis.

Finally, there were multiple, fresh, organized and recanalized thrombo-emboli distributed diffusely in muscular arteries and arterioles (fig. 9). These were most prominent in the lower lobes.

The liver grossly and microscopically was chronically congested and histologically showed severe "cardiac fibrosis." It would seem logical to assume that this lesion was due to long-standing elevation of hepatic venous pressure and arterial oxygen desaturation.

There were multiple abscesses in all organs and staphylococci were cultured from them. The
cause of death was thought to be a staphylococcal septicemia complicated by acute gastric hemorrhage from two "stress" ulcers in a patient with an uncorrected large right-to-left shunt.

**Discussion**

This unusual lesion is of interest as a newly recognized variant in the spectrum of disorders of venous return and the development of the interatrial septum. The two other cases thus far reported were not associated with major bilateral pulmonary arteriovenous fistulae. The possibility of the association of these two lesions, however, should be noted by others who may encounter a similar case.

The identification of a single adequate explanation for the cyanosis in the present case seemed to preclude the necessity for further diagnostic investigation. In retrospect, more attention should have been paid to the nodular shadows behind the right diaphragm seen in the roentgenograms (fig. 2) and the desaturation of the pulmonary venous blood. The nodules undoubtedly represented the shadows cast by the large arteriovenous fistulae, which were eventually identified at postmortem examination. An angiocardiogram performed through the superior vena cava would have established the additional diagnosis.

In planning the surgical procedure for correction of the anomalous inferior vena cava a direct anastomosis to the right atrium by closed technic or with a graft was considered. In view of the shortness of the inferior cava from the hepatic veins to the heart, however, and the anticipated difficulties of exposure, this idea was abandoned. The simplest and most straightforward approach appeared to be to redirect the inferior vena cava into the right atrium by transposing the interatrial septum during cardiopulmonary bypass.

The conception and execution of this plan proved to be effective in correcting completely the one defect recognized preoperatively. The fatal outcome is traceable directly to the failure to eliminate an equally voluminous right-to-left shunt due to the pulmonary arteriovenous fistulae in addition to the complications of sepsis and gastrointestinal hemorrhage. Without the associated defect, it seems reasonable to believe that the patient would have been restored to health.

The pathologic findings in this case raise numerous questions and stimulate speculation. The peripheral arteriovenous fistulae in this case are identical in every detail with those described by Hales. He demonstrated in his own cases by vinylite casts and random histologic sections that these lesions are usually subpleural. They are fed by several arteries and drained by numerous veins with walls showing a discontinuous elastica, no media, and focally fibrotic intima. Prior to 1956 Hales stated that only seven cases had been reported in which cyanosis, clubbing, and erythrocytosis resulted from multiple small pulmonary arteriovenous communications. He added two more cases of his own and noted that, although these lesions are congenital, in the absence of other right-to-left shunts, they remain clinically insignificant until middle life.

Histologically, the pulmonary lesions in the present case were intermediate in size between the small spherical plexuses of hereditary telangiectasis (Rendu-Osler-Weber's disease) and the multiloculated saccular lesions commonly described in pulmonary arteriovenous aneurysms. It has been suggested that the large saccular type arises by progressive dilatation of one of the limbs of a small plexus. As one channel begins to enlarge, it is as-

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**Figure 9**

Photomicrograph. A representative small muscular pulmonary artery showing the marked intimal fibrosis and recanalization characteristic of thrombo-embolic changes.

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sumed that blood is shunted into this channel where there is less resistance in accordance with Laplace's law. The dilatation of the channel then becomes progressive, while reduced flow in others that are smaller leads to atrophy. As the dilatation progresses, the limiting pleural membrane causes the channel to coil and thus loops in close proximity to each other are formed, giving the appearance of a multiloculated sac. According to Hales, the only organ in which such a transformation of hereditary telangiectasia occurs is the lung. He thought this was due to the low tissue resistance in this organ. If this pathogenetic reasoning is correct, it provides a logical explanation for the tardy appearance of cyanosis in such cases.

It is impossible to apportion the relative blood flow through the pulmonary capillaries and the fistulae before operation in this patient. It is equally impossible to reconstruct the changes that took place after the total pulmonary flow was significantly increased by redirecting the inferior cava to the right atrium. It seems logical to assume that the flow through the fistulae was increased and probably to a greater relative extent than that through the pulmonary capillaries because of the associated diffuse pulmonary atherosclerosis and thrombo-emboli.

The etiology of the pulmonary atherosclerosis observed at autopsy is obscure, since this patient had no elevation of the pulmonary arterial pressure during cardiac catheterization preoperatively. Indeed there must have been only approximately one third of the normal pulmonary flow, if one accepts the usual figures for distribution between superior and inferior venae cavae. It is difficult to believe that such diffuse changes as were seen in the pulmonary arteries could have occurred in the 47 days following operation, although at the last catheterization the shunt through the pulmonary fistulae was calculated to be 7 liters per minute, or about 65 per cent of cardiac output. An increase in flow of this magnitude may well have opened previously dormant shunts.

The partially organized pulmonary thrombo-emboli are of interest, since the only venous blood flowing through this patient's lungs was from the superior vena cava until 47 days before her death. It is well recognized that thrombosis is a frequent complication of arteriovenous fistulae. On the basis of the histologic appearance it is impossible to state whether these were thrombi or emboli. If they were emboli, then they must have arisen from the veins draining into the superior vena cava or else complete organization of emboli from the lower extremities into intimal fibrous connective-tissue plaques must have occurred within 47 days. Either one of these assumptions is possible, since Wessler et al. have reported complete organization of serum-induced thrombo-emboli in dogs within six weeks.

Finally, the histologic changes characteristic of secondary pulmonary hypertension seen in this patient's lungs may also have been due to pulmonary embolization and thrombosis. Such a sequence has been observed experimentally in the dog.

Summary

A 30-year-old woman with cyanotic heart disease due to anomalous drainage of the inferior vena cava into the left atrium in the presence of an intact interatrial septum is reported. The diagnosis was established during life and the defect was successfully corrected by open-heart surgery. The patient failed to survive due to associated multiple pulmonary arteriovenous fistulae. The embryology of the intracardiac defect, the pathophysiology of these fistulae, and the associated advanced pulmonary atherosclerosis are discussed.

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vein to the left atrium; the syndrome of cyanosis and clubbing, "normal" heart, and left ventricular hypertrophy on electrocardiogram. Circulation 24: 669, 1961.


Student Days of William Harvey at Padua

Harvey, who proved to be Fabricius’ hardest-working student, became the spokesman of the small group of Englishmen and was elected their representative. Each nationality had such deputies, and every two years they participated in the election of the new rector. They would also hold conferences during which they often rose up to rail vociferously against the professors. The students at the law college also elected Harvey to be their representative, which was no small matter, since in the life of the University the law students were considered much more distinguished than the medical students and accordingly enjoyed more authority.

Harvey entered Fabricius’ institute which was then in the midst of the most intensive research and discussion. Fabricius had just collected the material for his book on the development of animals, after which he intended to summarize his findings on venous valves. Such ventures involve a tremendous amount of reading, dissecting, thinking, and the young medical student entering this whirlpool of scientific problems naturally tends to absorb an abundance of enthusiasm and assurance at being considered worthy to participate in such important matters. Harvey, who was small compared to his strapping compatriots, with black wavy hair, and who spoke with lively gestures in a manner more Italian than English, threw himself passionately into the problems of the development of the embryo and the movement of the blood.—TIBOR DOBY, M.D. Discoverers of Blood Circulation. From Aristotle to the Times of Da Vinci and Harvey. New York, Abelard-Schuman, 1963, p. 187.
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