Pulmonary veno-occlusive disease: antemortem diagnosis from roentgenographic and hemodynamic findings

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A 17-year-old boy with pulmonary veno-occlusive disease underwent Swan–Ganz catheterization. A normal pulmonary capillary wedge pressure was recorded in the presence of severe pulmonary arterial hypertension and roentgenographic evidence of pulmonary venous congestion. This triad of findings permitted an unequivocal diagnosis of pulmonary veno-occlusive disease, which was later confirmed at autopsy. The hemodynamics of this condition and of others included in the differential diagnosis are presented schematically.

Un garçon de 17 ans souffrant de maladie veino-occlusive pulmonaire a subi un cathétérisme de Swan–Ganz. Une pression capillaire pulmonaire normale a été enregistrée en présence d'une hypertension artérielle pulmonaire sévère et de signes roentgenographiques de congestion veineuse pulmonaire. Cette triade a permis de poser un diagnostic positif de maladie veino-occlusive pulmonaire, confirmé ultérieurement à l'autopsie. Les variables hémodynamiques de cette affection et d'autres comprises dans le diagnostic différentiel sont présentées schématiquement.

Most patients with pulmonary arterial hypertension have a clinically evident predisposing condition, the more common of which include chronic hypoxia, congenital cardiac disorders, mitral stenosis, arteriosclerotic coronary artery disease and hypertensive heart disease. "Unexplained pulmonary hypertension", with no evident predisposing condition, has been called primary pulmonary hypertension and includes three distinct pathologic entities: classical vasoconstrictive hypertensive pulmonary vascular disease (also referred to as primary pulmonary hypertension and now renamed plexogenic pulmonary arteriopathy),[1] recurrent pulmonary thromboembolism and pulmonary veno-occlusive disease. The diagnosis of pulmonary veno-occlusive disease is usually made histologically and frequently only at autopsy. We contend that the diagnosis can be made in the presence of characteristic roentgenographic and hemodynamic findings. The following case report is illustrative.

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Case report

A 17-year-old man had experienced frequent episodes of rhinorrhea, itchy eyes, fever and cough until the age of 14 years, when exertional dyspnea and postexertional cough developed.

At age 15½ years his height was 156 cm (less than the third percentile) and his weight 37 kg (less than the third percentile). No abnormality of the cardiovascular or respiratory system was detected by physical examination. An electrocardiogram showed sinus rhythm and an axis of 105°. A chest roentgenogram showed a mild perihilar haze. The hemoglobin concentration was 17.7 g/dl. The serum immunoelectrophoretic pattern, the sweat chloride concentration and the α_1-antitrypsin value were normal, and a wide range of allergic skin tests and tests for serum precipitins gave negative results. Pulmonary function tests demonstrated a moderately severe nonobstructive ventilatory defect. He achieved 90% of the predicted power output on progressive treadmill exercise testing, with an excessive heart rate response, an appropriate ventilatory response and a decrease in arterial oxygen saturation (measured by ear oximetry) to 80% from a resting value of 91%.

Despite the administration of 20 mg of prednisone on alternate days and the removal of pet chinchillas from his home, he became more dyspneic. A lung biopsy performed 6 months later in another city was reported as demonstrating pulmonary fibrosis. The prednisone dosage was increased, but exertional dyspnea progressed over 8 months to dyspnea with minimal exertion as well as orthopnea. Two months later he was admitted to hospital because of acute dyspnea and peripheral cyanosis with a heart rate of 125 beats/min and a blood pressure of 110/70 mm Hg. He had a visible parasternal heave, a palpable P2, a grade 2/6 apical systolic ejection murmur, 2 cm of jugular venous distension but no edema or hepatic pulsation, and a right anterior pleural rub but no wheezing or rales. An electrocardiogram revealed right ventricular systolic overload, and a chest roentgenogram showed evidence of pulmonary arterial hypertension and venous congestion. The forced expiratory volume in 1 second (in litres) was 1.8 and the vital capacity 3.2 (predicted values 2.0 and 3.6 respectively). While the patient was breathing room air the arterial oxygen tension was 60 mm Hg (oxygen saturation 92%), the carbon dioxide tension 11 mm Hg, the pH 7.46 and the serum bicarbonate concentration 8 mmol/l. M-mode echocardiography confirmed right ventricular enlargement and normal left atrial and left ventricular sizes.

Although the patient's condition improved initially with bed rest as well as therapy with oxygen, steroids and digoxin, the dyspnea and orthopnea worsened. On the fifth hospital day a third heart sound gallop over the right ventricle and rales throughout both lungs were heard, and evidence of diffuse interstitial

and intra-alveolar pulmonary edema, with prominent Kerley's B lines, was apparent on a chest roentgenogram (Fig. 1). Swan–Ganz catheterization on the seventh hospital day showed a pulmonary arterial pressure of 135/60 mm Hg, with a mean of 63 mm Hg, and a mean pulmonary capillary wedge pressure of 10 mm Hg (Fig. 2). Distinct a and v waves, respiratory cycle variation and an abrupt change to a pulmonary arterial pressure tracing with balloon deflation several times indicated that the pulmonary capillary wedge pressure tracings were technically valid. Pressures were not measured in other lung segments since the patient was in distress, and the diagnosis of pulmonary veno-occlusive disease had been established by the recording of a low pulmonary capillary wedge pressure in the presence of generalized pulmonary edema and severe pulmonary arterial hypertension. The pulmonary edema resolved with diuretic, oxygen, morphine and digitalis therapy, but death ensued on the eighth hospital day, when a progressive fall of the arterial oxygen saturation was followed by sinus bradycardia, complete atrioventricular block and asystole.

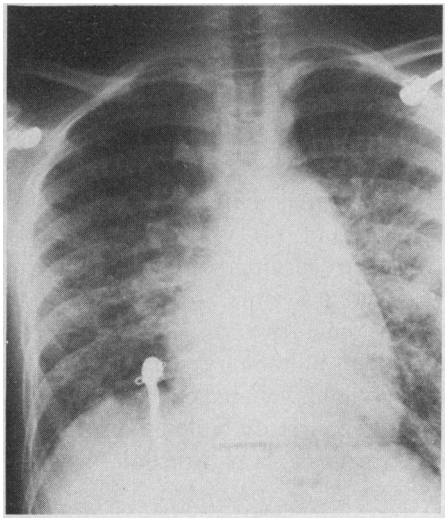

FIG. 1—Cardiomegaly, marked enlargement of main pulmonary artery, diffuse interstitial and intra-alveolar pulmonary edema, with prominent Kerley's B lines, in patient with pulmonary veno-occlusive disease.

Necropsy revealed pronounced right ventricular hypertrophy and widespread narrowing or occlusion of pulmonary veins and venules by fibroelastic tissue that was sometimes perforated by several vascular channels, suggestive of old organized and recanalized thrombus (Fig. 3). Some veins showed "arterialization", with the development of a distinct muscular media bounded by intimal and external elastic laminae. There were foci of intense congestion of alveolar capillaries related to occluded venous segments, and these were associated with the presence of hemosiderin-laden macrophages in the alveolar spaces. The pulmonary arterioles showed secondary hypertensive changes, and the muscular pulmonary arteries showed medial hypertrophy and intimal fibrosis. There was iron encrustation of the elastic laminae of blood vessels and of the elastic fibres in the alveolar walls. Prominent dilated lymphatic channels were noted in the perivascular and interlobular fibrous tissue. Review of the lung biopsy specimen obtained 1 year before death also showed the typical features of pulmonary veno-occlusive disease.

Discussion

This case illustrates the usual course of pulmonary veno-occlusive disease,[2,3] with progressive dyspnea and cyanosis terminating fatally within a few years of the onset of symptoms. The correct interpretation of the features of the lung biopsy specimen was only available post mortem. Thus, the clinical problem presented was unexplained pulmonary arterial hypertension. If the pulmonary edema had been due to mitral stenosis, cor triatriatum or a large pulmonary vein stenosis the pulmonary capillary wedge pressure would have been considerably elevated. Kerley's B lines and generalized pulmonary edema are not features of plexiform pulmonary arteriopathy, and would be present in association with recurrent pulmonary thromboembolism only if there were left ventricular failure and an elevated pulmonary capillary wedge pressure. The adult respiratory distress syndrome does not result in more than mild to moderate pulmonary hypertension. Pulmonary veno-occlusive disease is the only condition known to produce the triad of severe pulmonary arterial hypertension, pulmonary congestion with Kerley's B lines on chest roentgenograms and a normal pulmonary capillary wedge pressure.

Disagreement exists in the literature regarding the usefulness of measuring the pulmonary capillary wedge pressure in patients with pulmonary veno-occlusive disease. Carrington and Liebow[4] have pointed out that the usually low or normal wedge pressure, together with roentgenographic evidence of pulmonary congestion, is evidence for obstruction of small veins or venules.

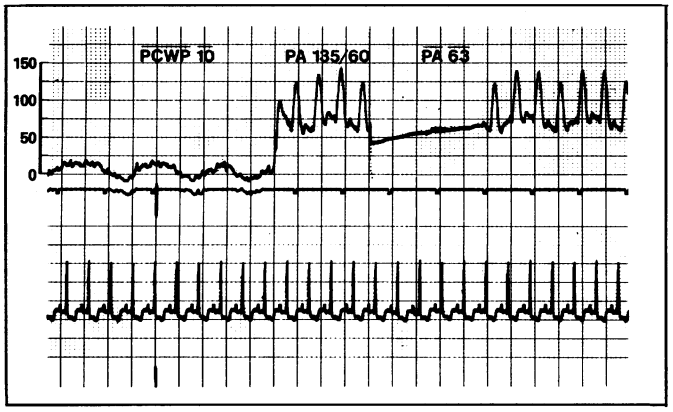

FIG. 2—Pulmonary hemodynamics.

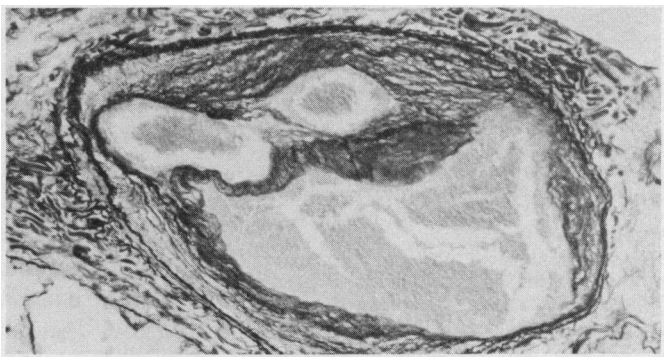

FIG. 3—Pulmonary vein: lumen narrowed by proliferation of fibroelastic tissue perforated by several vascular channels (elastic–Van Gieson stain; ×147, reduced 50%).

Wagenvoort and Wagenvoort[5] referred to the low or normal wedge pressure and stated that the pulmonary capillary wedge pressure may not help to distinguish pulmonary veno-occlusive disease from primary pulmonary hypertension (plexogenic pulmonary arteriopathy). Thadani and colleagues[2] discussed the patchy involvement and the variable degree of venous obstruction in pulmonary veno-occlusive disease. They suggested that this results in a range of values for the pulmonary capillary wedge pressure, depending on the segment of lung sampled, and thus reduces the value of measuring this pressure in this disease. Heath and Oakley[6] also stated that a range of values for this pressure may be recorded in this disease. Others,[3,7-10] however, have suggested that measurement of the pulmonary capillary wedge pressure can be very useful in diagnosis, with a low or normal value distinguishing pulmonary veno-occlusive disease from pulmonary arterial hypertension associated with mitral stenosis or a large pulmonary vein stenosis.

Thirty detailed case reports of pulmonary veno-occlusive disease have been published.[2,3,7,10-16] Liebow and associates[17] described briefly a further 16 patients, and Liebow, Moser and Southgate[7] mentioned a personal collection of 27 cases. Many more cases have been described briefly in pathology reviews. Right heart catheterization was performed in 22 of the 30 cases described in detail, and the pulmonary capillary wedge pressure was recorded in 20; the pressure was less than 20 mm Hg in all 20 and was less than 13 mm Hg in 16. Chest roentgenograms showed Kerley's B lines or evidence of pulmonary congestion in 20 of the 26 patients for whom there was a description of the roentgenograms; these findings were absent in 4 and equivocal in 2. Liebow and colleagues,[7] in their description of 16 patients, stated that Kerley's B lines were often present and the pulmonary capillary wedge pressure was often normal. Therefore, a normal or slightly elevated pulmonary capillary wedge pressure in the presence of roentgenographic evidence of pulmonary venous congestion is generally found in pulmonary veno-occlusive disease. In the presence of pulmonary congestion and severe pulmonary arterial hypertension a normal pulmonary capillary wedge pressure is diagnostic and a mildly elevated pressure is highly suggestive of pulmonary veno-occlusive disease.

Probable explanations for the normal or low pulmonary capillary wedge pressure in pulmonary veno-occlusive disease have been provided by Brown and Harrison[18] and by Carrington and Liebow.[4] An extension of their ideas, with a consideration of other conditions leading to pulmonary arterial hypertension, is presented in Fig. 4. When a wedged catheter occludes a vessel, downstream pressure is recorded by the transducer. The downstream pressure will reflect the left ventricular end-diastolic pressure as long as there is no obstruction between the catheter tip and the left ventricle. If there is downstream obstruction the pressure recorded at the catheter tip will exceed the left ventricular end-diastolic pressure only if blood flows into the downstream circuit distal to the catheter tip and proximal to the obstruction, and if there is no run-off of blood around the obstruction. Thus, in the presence of a large pulmonary vein stenosis, cor triatriatum or mitral stenosis (C, D or E) there will be an inflow of blood from the pulmonary veins to the downstream circuit proximal to the obstruction, and the wedged catheter will record an elevated pressure. If plexogenic pulmonary arteriopathy or recurrent pulmonary embolism is present there will be no inflow of blood distal to the catheter tip and proximal to the stenosis, and a normal pulmonary capillary wedge pressure will be recorded (A). In pulmonary veno-occlusive disease, if the occlusive process is confined to the small venules subtending capillary networks, no inflow will occur between the catheter tip and the stenosis, and there will be a static column of blood from the catheter tip to a point distal to the stenosis; thus, a normal pulmonary capillary wedge pressure will be recorded (B). Even with patchy involvement of venules the wedge pressure will be normal in all parts of the lung. The normal pressure might also be explained by the exit of tributaries from the occluded vein proximal to the stenosis and their connection with nonoccluded veins eventually reaching the left atrium (BB). However, if the disease also involves larger pulmonary veins, the inflow of blood distal to the catheter tip but proximal to the site of occlusion would result in an elevated wedge pressure, as it would with stenosis of the large pulmonary veins. Again, the pressure would be elevated only if there were no tributaries existing from the oc-

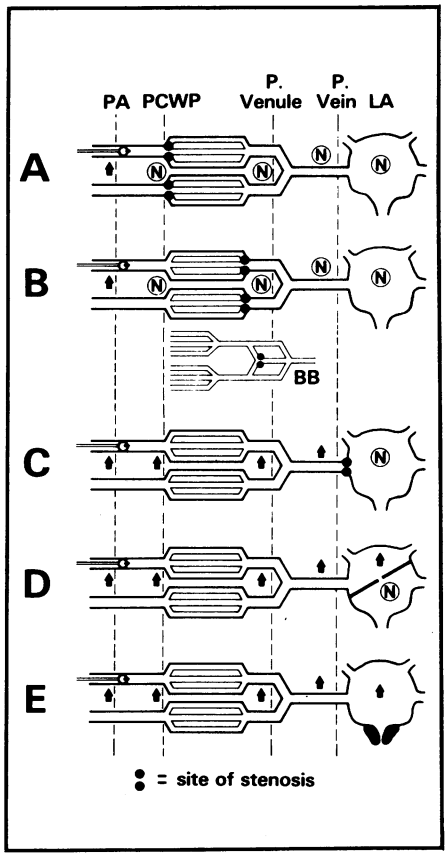

FIG. 4—Pulmonary hemodynamics in pulmonary arterial hypertension of various causes. Pressures, expressed as elevated (↑) or normal (Ⓝ), with Swan–Ganz catheter in place. A = plexogenic pulmonary arteriopathy or recurrent pulmonary thromboembolism; B and BB = pulmonary veno-occlusive disease; C = large pulmonary vein stenosis; D = cor triatriatum; E = mitral stenosis; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; P. = pulmonary; LA = left atrium.

cluded vein proximal to the stenosis and connecting with the left atrium through nonstenotic pathways.

The difficulty of obtaining satisfactory measurements of the pulmonary capillary wedge pressure in patients with severe pulmonary hypertension is well recognized. The standard end-hole catheter may repeatedly fail to wedge or may impinge on an occluded segment, with marked damping. The balloon floatation catheter has been used in many cardiac catheterization laboratories and usually permits the recording of a satisfactory wedge pressure in patients with severe pulmonary hypertension in whom the wedge pressure could not be recorded with conventional end-hole catheters.[19,20] Ideally the pressure should be measured in several pulmonary segments to ensure that a given pressure is not simply a local phenomenon or in error. The finding of oxygen saturation at arterial levels in blood aspirated from the catheter confirms that the catheter is wedged. In our patient the catheter was repeatedly withdrawn and advanced, and the balloon was inflated to various degrees. The abrupt change from the pulmonary artery pressure to the pulmonary capillary wedge pressure was repeatedly observed. It is likely that all the recordings were made from one lung segment, however, since the catheter was not drawn back to the right ventricle and fluoroscopy was not done. The phasic tracing with respiratory cycle variation and the replicability of the findings were considered evidence of the reliability of the normal values for the wedge pressure and, therefore, of the left atrial pressure. Hence, blood was not aspirated, although the results of analysis could have provided stronger confirmation. Further confirmatory measures were considered to be contraindicated in view of the patient's severe distress.

In the severely distressed patient in whom a lung biopsy would be dangerous, Swan–Ganz catheterization may permit an easy, rapid diagnosis. In the patient we have described, the diagnosis of pulmonary veno-occlusive disease was made by measurement of the pulmonary capillary wedge pressure rather than post mortem, as is the usual case. Although therapy is generally unsuccessful, improvement has been reported with azathioprine,[11] heparin[16] and a combination of anticoagulants, methylprednisolone, acetylsalicylic acid and dipyridamole.[10] Earlier diagnosis and treatment might improve the prognosis and permit more intensive study of the disease.

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continued from page 1518

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