Pulmonary Hypertension with Hepatic Cirrhosis

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A variety of circulatory changes can accompany portal cirrhosis: these include a high cardiac output, peripheral vasodilatation, an increase in plasma volume, and arterial desaturation. The mechanism of these changes is unknown, but portopulmonary shunts have been postulated on the basis of anatomical (Calabresi and Abelman, 1957) and physiological (Shaldon *et al.*, 1961) studies, and in a few patients multiple pulmonary arteriovenous fistulae have been described (Rydell and Hoffbauer, 1956; Murray, Dawson, and Sherlock, 1958).

There is also evidence that haemodynamic and pathological changes may occur in the pulmonary circulation in patients with portal hypertension (Mantz and Craige, 1951; Murray *et al.*, 1958; Naeye, 1960; Kerbel, 1962). We have recently seen a patient with post-necrotic cirrhosis who had severe pulmonary hypertension for which none of the usual causes could be found.

Case Report

A 43-year-old man, a progress chaser, was admitted to hospital in 1962, having suddenly collapsed at work with what appeared to be an epileptic fit. There was no previous history of epilepsy, but since childhood he had suffered from psoriasis on the legs, and had developed a urethral discharge while serving in the navy during the 1939-45 war. At this time he began drinking heavily, mainly spirits, and continued to do so until a year before his death. In 1951 he had had an attack of "pneumonia and pleurisy", but a chest radiograph after recovery was normal, and though he smoked 10 cigarettes daily he denied that he had ever had a chronic cough or sputum. In 1952 he was found to have hepatic cirrhosis at an emergency operation for a ruptured appendix.

He was a tall man of good physique weighing 75 kg., but was initially somewhat confused and disorientated. He was mildly jaundiced and had spider naevi on the face and arms and palmar erythema. The spleen could be felt at the level of the umbilicus and was very hard; the liver was not palpable. The blood pressure was 115/65 mm. Hg, and the jugular venous pressure was

not raised, though there was slight peripheral oedema. The heart was not enlarged, but there was a left parasternal heave, and auscultation revealed a split pulmonary second sound with accentuation of the pulmonary component and an ejection systolic murmur in the pulmonary area. The lungs were normal on examination and there were no focal neurological signs.

The chest x-ray film showed cardiac enlargement with accentuation of the bronchovascular markings and prominent central pulmonary vessels. The electrocardiogram showed sinus rhythm and right axis deviation, with dominant R and inverted T waves in the right chest leads. Liver function tests showed serum bilirubin 2.5 mg./100 ml., alkaline phosphatase 13.8 King-Armstrong units, thymol turbidity 4.1 units, albumin 2.8 g./100 ml., globulin 3.3 g./100 ml., with an excess of γ -globulin on paper electrophoresis. A barium swallow demonstrated extensive oesophageal varices.

Cardiac catheterization (see Table) was undertaken to try to establish the cause of the severe pulmonary hypertension. At rest the cardiac output was increased above the normal range (Segel *et al.*, 1964). Arterial oxygen saturation was normal and plasma volume was increased (Hart and Metz, 1962). Both pulmonary

TABLE
CARDIAC CATHETERIZATION FINDINGS

	Rest	Exercise
Oxygen uptake (ml./min./sq. m.)	185	521
Pulmonary ventilation (l./min./sq. m.)	7.2	18.9
Arteriovenous oxygen difference (vol. %)	3.8	10.2
Arterial oxygen saturation (%)	98.3	96.5
Cardiac output (l./min./sq. m.)	4.9	5.1
Plasma volume (ml./kg.)	53.5	—
Pressures (mm. Hg)	Mean	Mean
Brachial artery	153/73 110	195/109 132
Pulmonary artery	88/37 56	109/52 73
Pulmonary wedge	15	16
Right atrium	12	27
Free hepatic vein	13	—
Wedged hepatic vein	35	—
Pulmonary vascular resistance (dynes/sec./cm. ⁻⁵)	854	4500

FIG. 1.—Muscular pulmonary artery showing some medial hypertrophy, and pronounced intimal fibro-elastic thickening. (Elastic van Gieson. $\times 250$.)

artery and wedged hepatic vein pressures (normal 8–12 mm. Hg) were increased. During exercise the cardiac output did not increase, while the mean pulmonary

FIG. 2.—Plexiform lesion in muscular pulmonary artery. (Elastic van Gieson. $\times 250$.)

artery pressure and vascular resistance rose considerably. Arterial oxygen saturation remained normal.

Progress. Despite occasional episodes of fluid retention he remained well for two years, but after a febrile illness in 1964 he rapidly became confused and jaundiced. The signs were those of portal systemic encephalopathy, and in spite of neomycin and glucose infusions he died in three days.

Necropsy. The heart weighed 432 g. and showed no congenital defect. There was pronounced hypertrophy and dilatation of the right ventricle; its free wall weighed 156 g. (normal 65 g., Fulton, Hutchinson, and Jones, 1952) and measured 0.8 cm. in thickness. The remaining chambers and the valves were normal. The coronary arteries showed slight fatty streaking and the myocardium was healthy. Numerous atheromatous plaques were present in the pulmonary trunk and pulmonary arteries. The main pulmonary veins were normal. The lungs were examined by slicing after distension with formol saline and fixation: the cut surfaces showed prominence of the pulmonary arteries but no evidence of emphysema or interstitial fibrosis.

The liver was small (1020 g.) and showed an irregular nodularity. The portal vein and its tributaries were dilated and thickened, with foci of calcification in their walls. The hepatic veins were normal. The spleen was greatly enlarged and firm (1230 g.). Varices were present in the lower two-thirds of the oesophagus, and there was a chronic benign peptic ulcer on the lesser curvature of the stomach.

There were no thrombi in the femoral, pelvic, portal, or oesophageal veins.

Histology. The liver showed the features of post-necrotic cirrhosis. The configuration of the elastic fibres in the pulmonary trunk was of the adult type. The muscular pulmonary arteries showed medial hypertrophy and intimal fibro-elastic thickening (Fig. 1). Some of the smaller arteries were occupied by cellular proliferations characteristic of plexiform lesions (Fig. 2). An acute necrotizing arteritis was present in some of the larger vessels; their walls showed fibrinoid necrosis and infiltration by neutrophil polymorphs (Fig. 3). The pulmonary veins were normal.

Discussion

Mantz and Craig (1951) were probably the first to describe death from "cor pulmonale" in a woman who had an enormous shunt between portal and innominate veins but a normal liver. Proliferative changes were present in the pulmonary arteries as well as emboli in the small branches. Murray *et al.* (1958) encountered a young man with portal cirrhosis and multiple pulmonary arteriovenous fistulae, who at cardiac catheterization had a pulmonary artery pressure of 44/26 (mean 34) mm. Hg at rest. Pulmonary vascular resistance was 655 dynes per second per cm.^{-5} . These authors were

FIG. 3.—Muscular pulmonary artery showing acute necrotising arteritis. (Haematoxylin and eosin. $\times 150$.)

unable to establish the cause of the pulmonary hypertension. Naeye (1960) reported necropsy studies in 6 cirrhotic patients described as having "primary" pulmonary hypertension: 3 showed thrombosis of the portal vein and 5 out of the 6 had multiple pulmonary emboli which were thought to be the cause of the pulmonary hypertension. An increase in thromboplastic material or pulmonary arteriovenous shunts were postulated as possible mechanisms.

In a review of the circulatory changes associated with cirrhosis, Heinemann (1960) alluded to unpublished observations of raised pulmonary artery pressure and histological changes in pulmonary vessels in some patients. Kerbel (1962) described a 20-year-old negress with cirrhosis, in whom radiography revealed right ventricular hypertrophy and a grossly dilated pulmonary artery with poorly filled peripheral branches. The mean pulmonary artery pressure was 60 mm. Hg and subsequent necropsy showed that many of the small branches of the pulmonary artery were thickened and constricted, a change corresponding to grade IV of Heath and Edwards (1958). More recently the association of pulmonary hypertension with "active juvenile cirrhosis" has been reported (Cohen and Mendelow, 1965), but here the process may have been part of a single immunological response which could involve many organs.

The patient reported in this study had a raised blood volume and cardiac output, both of which might have contributed to the pulmonary hypertension. Some degree of pulmonary arterial hypertension has been found in a proportion of patients with cirrhosis, both at rest and during exercise (Segel *et al.*, 1963; Bayley, Segel, and Bishop, 1964), and has been attributed to increased total blood volume. That an increase in pulmonary blood flow may passively raise the pulmonary arterial pressure is well known (Harris and Heath, 1962). However, it seems unlikely that the magnitude of change in either blood volume or pulmonary blood flow could have been the only factor in the present case, since the degree of pulmonary hypertension was proportionately much greater than the observed changes in blood volume and cardiac output. In addition, the pulmonary vascular resistance was greatly increased, and this is not a feature associated with the latter changes. It is also unlikely that anoxia played any part in pathogenesis, since the arterial oxygen saturation was normal at rest and during exercise. None of the usual causes of pulmonary hypertension (congenital or acquired heart disease, recurrent pulmonary emboli, interstitial pulmonary fibrosis, pulmonary emphysema or pulmonary veno-occlusive disease) was found at necropsy, and it is, therefore, necessary to seek alternative explanations for its presence.

It is possible that the patient may have had a high pulmonary blood flow since 1952 and this could have initiated the rise in pulmonary vascular resistance which, over the ensuing years, led to permanent and progressive pulmonary vascular disease, as in some patients with long-standing septal defects. Alternatively, the pulmonary hypertension may have been caused by an endogenous, circulating vasoconstrictor agent. The circulatory changes in cirrhosis have been ascribed to failure of the liver to inactivate a systemic arterial vasodilator substance (Shorr, Zweifach, and Furchgott, 1948). If there were large portal-systemic shunts, such a substance would initially fail to reach the liver and could enter the pulmonary circulation via portal-azygos communications. Although there is no evidence that it would then cause vasoconstriction of the pulmonary vessels, the effect of humoral agents on the pulmonary circulation is not necessarily the same as that on the systemic circulation. Plasma kinins, serotonin, or oestrogens might be implicated in such a dual action.

Pulmonary hypertension is uncommon in patients with cirrhosis even when haemodynamic changes are present in the systemic arterial circulation. The reason for this is not clear, but it seems probable that a humoral rather than a mechanical agent

is the causative factor. The constrictive response of the pulmonary circulation to such a humoral agent might be variable or might require an initial intrinsic defect in the pulmonary vascular bed. Alternatively, the humoral substance might act only on pulmonary vessels previously exposed to a chronically increased pulmonary blood flow or to an agent normally removed by the healthy liver.

Summary

A patient with post-necrotic cirrhosis was found to have the clinical, haemodynamic, and histological features of severe pulmonary hypertension. The usual causes for pulmonary hypertension were excluded. It is suggested that humoral mechanisms may be responsible for an association between portal and pulmonary hypertension.

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