THE CLINICO-PATHOLOGICAL SYNDROME PRODUCED BY CO-EXISTING PULMONARY ARTERIAL AND VENOUS HYPERTENSION

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In the last decade cardiac catheterization has demonstrated that the pressure in the pulmonary arteries and veins may greatly influence the clinical picture and prognosis in various forms of heart disease. Cases with severe pulmonary arterial hypertension show the clinico-pathological syndrome of hypertensive pulmonary vascular disease (Heath and Whitaker, 1956a). Severe pulmonary venous hypertension, following left ventricular failure due to diffuse myocardial disease, is associated with a clinical picture similar to that of constrictive pericarditis and the pathological features of pulmonary congestion and haemosiderosis. The purpose of this communication is to report the association of pulmonary arterial and venous hypertension in a case of diffuse myocardial fibrosis, a state of affairs which represents the fusion of the two main clinico-pathological pressure syndromes. The histology of the lung and the results of cardiac catheterization are described. These findings are compared and contrasted with similar observations from previously reported cases of each of the pressure syndromes. The role of a raised pressure in the pulmonary veins in the aetiology of pulmonary arterial hypertension is discussed.

CASE REPORT

A man aged 22 years, known to have had diabetes mellitus for eight years, was admitted cyanosed and breathless. Five years before admission he had developed a severe unexplained anaemia with radiological evidence of pulmonary congestion from which he had made an apparently complete recovery.

On examination he had the signs of pulmonary arterial hypertension in the form of a right ventricular heave, diastolic shock, and a widely split second sound in the pulmonary area that was louder than the aortic second sound. He was in congestive cardiac failure, with hepatomegaly, a jugular venous

pressure raised 4 cm. at 60°, and exhibiting giant "a" waves and peripheral systemic oedema. The haemoglobin level was 14.8 g.%. An electrocardiogram showed evidence of diffuse myocardial damage. The teleradiogram was not typical of hypertensive pulmonary vascular disease in that it showed marked cardiomegaly and an uncharacteristic cardiac silhouette (Fig. 1A). A typical teleradiogram from a case of hypertensive pulmonary vascular disease is shown in Fig. 1B. There was radiographic proof of pulmonary venous hypertension in the form of hilar congestion, pulmonary oedema, and evidence of pulmonary haemosiderosis.

The results of cardiac catheterization were as follows :

BLOOD PRESSURES (Fig. 2) (mm. Hg above level of the back)		
Left pulmonary artery		90/60 to 80/50
Right ventricle		80/20
Right atrium		15/10
Wedge left pulmonary capillary mean pressure		35

Thus pressures were high both in pulmonary arteries and in pulmonary veins.

BLOOD OXYGEN SATURATIONS (%)		
Superior vena cava		40
Inferior vena cava		38
High right atrium		36
Low right atrium		35
High right ventricle		36
Left pulmonary artery		37
Pulmonary capillary		66
Femoral artery		93

The progressive congestive cardiac failure did not respond to treatment and the patient died.

NECROPSY REPORT

The heart weighed 625 g. The left ventricle was dilated and thinned, and, on sectioning the myocardium, about 50 areas of firm fibrous tissue were found. The right ventricle was hypertrophied. There was antemortem thrombus in both ventricles in the region of the apex. The valves and coronary arteries were normal. The left atrium was opaque. The pulmonary artery was dilated and atheromatous, but the aorta was small. The appearances were those of idiopathic diffuse myocardial fibrosis, sometimes referred to as Fiedler's myocarditis.

FIG. 1A

FIG. 1B

FIG. 1A.—Teleradiogram showing gross cardiac enlargement. The lung fields show congestive changes and stippling indicative of pulmonary haemosiderosis.

FIG. 1B.—Teleradiogram from a patient with ventricular septal defect and severe pulmonary hypertension to illustrate in contrast to Fig. 1A the radiographic features of hypertensive pulmonary vascular disease. There is only slight cardiac enlargement with prominence of the pulmonary arteries and their main branches. The peripheral lung fields are clear.

FIG. 2.—Blood pressure tracings taken at cardiac catheterization. A, Right pulmonary artery, blood pressure 88/60 mm. Hg. B, Wedged pulmonary capillary blood pressure, taken to equal pulmonary venous blood pressure, varies from 32 to 38 mm. Hg. C, Right pulmonary artery (blood pressure 80/44 mm. Hg) to right ventricle (80/20 mm. Hg).

The upper and lower lobes of the left lung and the middle lobe of the right were brown and firm and showed abundant free iron due to pulmonary haemosiderosis. The appearances were those of brown induration. The mediastinal lymph nodes were plum coloured and showed free iron on testing with Perles' reagents. The small pulmonary arteries were grossly atheromatous. There was a nutmeg liver, a cricket-ball spleen, and congestion of the other abdominal viscera.

Histological examination of the heart showed diffuse fibrosis throughout the myocardium with a sparse chronic inflammatory reaction. The main pulmonary arteries showed atherosclerosis and numerous foci of fibrosis with loss or derangement of elastic fibrils in all but the peripheral layer of the (less than $1,000\ \mu$ in external diameter) were also media. The smaller elastic pulmonary arteries atheromatous. Measurements of the arteries were made by the technique of Best and Heath (1957).

FIG. 3.—Section of lung stained by Perles' reagents to demonstrate severe pulmonary haemosiderosis, a condition frequently associated with pulmonary venous hypertension, $\times 75$.

FIG. 4.—Transverse section of a muscular pulmonary artery, $560\ \mu$ in diameter, showing adventitial fibrosis, medial hypertrophy, and intimal fibroelastosis, $\times 105$.

FIG. 5.—Transverse section of a pulmonary arteriole, $60\ \mu$ in diameter, showing a distinct muscular media with internal and external elastic laminae. Normal arterioles are lined only by a single lamina with no muscular media, $\times 150$.

Figs. 4 and 5 are stained for elastic by the Lawson modification of the Weigert-Sheridan method to show the characteristic features of hypertensive pulmonary vascular disease.

FIG. 6

There was a marked difference in the appearance of the alveoli and small pulmonary vessels between those lobes which showed brown induration and those that did not. In the lobes showing brown induration there were many intra-alveolar foci of haemosiderin-containing macrophages measuring up to $500 \times 200 \mu$ in size (Fig. 3). Many of the alveoli were lined by cuboidal cells which contained granules that gave a positive reaction with Perles' reagent. All stages were found to suggest a transition from flattened cells lining the alveoli to swollen, cuboidal cells which had ingested haemosiderin and then passed into the alveoli with many other similar cells to form foci of pulmonary haemosiderosis. The thickness of the alveolar walls was increased to 30μ as a result of distended pulmonary capillaries lying between the cuboidal cells described above. There was no ferrous impregnation of the elastica of the vessels or alveolar walls and no granulomatous giant cell reaction to the haemosiderin. In these lobes the small pulmonary blood vessels showed the characteristic changes of hypertensive pulmonary vascular disease. The muscular arteries (100 to $1,000 \mu$ in external diameter) showed a thickened media. The mean medial thickness was 13.4% of the external diameter of the vessel and the mean area of muscle in cross section was $6,050$ sq. microns. Corresponding figures for vessels

FIG. 7

FIGS. 6 and 7.—Stained to show elastic by the Lawson modification of the Weigert-Sheridan method and counterstained with Van Gieson's stain. Transverse sections of muscular pulmonary arteries from one of the lobes without pulmonary haemosiderosis. There is practically no intimal fibroelastosis. Compare with Fig. 4. Note that the media is much thinner. Fig. 6 about 360μ in diameter, $\times 105$. Fig. 7 about 160μ in diameter, $\times 150$.

from the lower lobes of 16 controls, consisting of patients with no heart or lung disease, were 3.1% , and $2,260$ sq. microns. Proliferation of fibroelastic tissue in the intima severely reduced the lumina of many vessels (Fig. 4) and there was a thick fibrous adventitia. Pulmonary vessels below 100μ in diameter were also abnormal, showing a muscular media with internal and external elastic laminae (Fig. 5). In the lower lobe of the normal lung, in sharp contradistinction to the lingula, vessels below 100μ in diameter with a muscular media are rarely found. In the present case the mean medial thickness in this class of vessel was 11.5% of the external diameter, and the mean area of muscle in cross section was 815 sq. microns. The latter figure is much smaller than the mean value for the normal muscular pulmonary artery, indicating that these muscular vessels below 100μ in diameter are more likely to be pulmonary arterioles with abnormal development of muscle than constricted muscular pulmonary arteries, 100 to $1,000 \mu$ in diameter. These hypertensive arterioles were numerous in the haemosiderotic lobes, but unlike the smaller pulmonary arteries showed practically no intimal fibroelastosis. The veins and

venules, however, showed intimal fibrosis exceeding the normal age change. There was no arterial medial necrosis and no evidence of thin-walled collateral branches of muscular pulmonary arteries so frequently noted in the lung in cases of congenital heart disease with pulmonary arterial hypertension.

In sharp contrast, the small pulmonary vessels in the lobes not affected by gross pulmonary haemosiderosis were normal. In particular, the vessels below 100 μ in diameter did not show a muscular media but were lined by a single elastic lamina and showed only the normal age change of intimal fibrosis. The mean medial thickness of the muscular pulmonary arteries was 2.9% of the external diameter of the vessel and the mean area of muscle in cross section was 1,707 sq. microns. These values are normal, the corresponding figures in the upper lobes of the 16 controls studied being 3.1% and 1,850 sq. microns. There was no intimal fibroelastosis (Figs. 6 and 7). The veins showed the age change of intimal fibrosis. There were many small foci of haemosiderosis and emphysema in these lobes.

DISCUSSION

Many cardiac diseases are associated with severe pulmonary arterial hypertension to produce the clinico-pathological syndrome of hypertensive pulmonary vascular disease (Table II); others are characterized by diffuse myocardial disease and pulmonary venous hypertension to produce a clinical picture reminiscent of constrictive pericarditis (Table III). Mitral stenosis and left ventricular failure due to aortic disease or systemic hypertension may be associated with severely raised left auricular pressure and resultant pulmonary arterial hypertension (Tables II and V), but do not exhibit the pericarditis-like clinical picture as neither has a severe diffuse affection of the myocardium. However, in the present case diffuse myocardial fibrosis is associated with pulmonary arterial and venous hypertension and a clinical picture that represents a true fusion of the clinico-pathological syndromes resulting from the doubly elevated pressures (Table IV).

CLINICO-PATHOLOGICAL SYNDROME ASSOCIATED WITH PULMONARY ARTERIAL HYPERTENSION.—Patients with pulmonary artery blood pressures chronically elevated to levels of the order of the systemic blood pressure form a distinct clinico-pathological group termed hypertensive pulmonary vascular disease. This condition, which may complicate ventricular septal defect, patent ductus arteriosus, aorto-pulmonary septal defect, atrial septal defect, and mitral stenosis, or may occur as idiopathic pulmonary hypertension (Tables II and V), presents a clinical picture that is domi-

TABLE I
NORMAL VALUES GIVEN FOR PULMONARY ARTERY AND "PULMONARY CAPILLARY" BLOOD PRESSURES IN PREVIOUS REPORTS

Author	Year	Pulmonary Artery Mean Blood Pressure (mm. Hg)	"Pulmonary Capillary" or Left Atrial (*) Mean Blood Pressure (mm. Hg)
Lagerlöf and Werkö	1948	15	
Cournand	1950	13	5 (*4)
Dexter and others	1950	15	9

nated by signs and symptoms characteristic of severe pulmonary arterial hypertension, which often mask the underlying cardiac anomalies. Members of this group, with the exception of mitral stenosis, exhibit only a slightly raised pulmonary capillary blood pressure not exceeding 20 mm. Hg (Table II), the normal being in the region of 5 mm. Hg (Table I), as illustrated by reports of cardiac catheterization by various authors. All forms of hypertensive pulmonary vascular disease reflect the high pulmonary artery blood pressure in the form of definitive changes in the pulmonary vasculature, as illustrated in Figs. 3, 4, 6, and 7. These are atheroma in the elastic pulmonary arteries (more than 1,000 μ in diameter), medial hypertrophy and intimal fibroelastosis in the muscular pulmonary arteries (100 to 1,000 μ in diameter), and pulmonary arterioles (less than 100 μ in diameter) with a distinct media and internal and external elastic laminae. Similarly throughout this group, the absence of severe pulmonary congestion and haemosiderosis suggests only a slight elevation of the pulmonary capillary pressure. Both pulmonary congestion and haemosiderosis appear to be more closely related to pulmonary venous than arterial hypertension (Heath and Whitaker, 1956b).

CLINICO-PATHOLOGICAL SYNDROME ASSOCIATED WITH PULMONARY VENOUS HYPERTENSION AND DIFFUSE MYOCARDITIS.—Balchum, McCord, and Blount (1956) have analysed the clinical and pulmonary haemodynamic pattern in diseases associated with diffuse myocardial changes; such diseases present the clinico-pathological syndrome of pulmonary venous hypertension with severe congestive cardiac failure. This group includes Fiedler's myocarditis, endomyocardial fibroelastosis, severe myocardial fibrosis secondary to coronary atherosclerosis, cardiac amyloidosis, the myocardial damage associated with scleroderma and possibly that found in Freidrich's ataxia, haemochromatosis and glycogen storage disease, and fatty and neoplastic infiltration of

TABLE II

PULMONARY ARTERY AND "PULMONARY CAPILLARY" BLOOD PRESSURES IN SOME PREVIOUSLY REPORTED CASES OF HYPERTENSIVE PULMONARY VASCULAR DISEASE

Disease	Authors	Year	Pulmonary Artery Mean Blood Pressure (mm. Hg)	"Pulmonary Capillary" Mean Blood Pressure (mm. Hg)
(A) Congenital heart disease				
Eisenmenger's complex	Dexter and others	1950	78	8
			81	2
			102	13
" "	Heath and Whitaker	1956b	90	12
Atrial septal defect	Heath and Whitaker	1957	70	17
Idiopathic pulmonary hypertension	Heath and others	1957	100	15
" "	Shepherd and others	1957	58	4
			80	8
			57	13
			96	8
			105	5
			69	3

Pulmonary artery, 12 observations, mean = 82.2 mm. Hg, range = 57-105, S.D. = 23.50.

Pulmonary capillary, 12 observations, mean = 9.0 mm. Hg, range = 2-17, S.D. = 4.65.

(B) Mitral stenosis (no diffuse myocardial disease)

Dexter and others	1950	78	40
		80	30
		75	27
		63	35
		66	28
Epps and Adler	1953	75	30
		52	25
Whitaker and Lodge	1954	70	35
		75	33
		78	34
		80	36
		81	29
Heath and Whitaker	1956b	88	36
		64	33
		65	37
		66	42
		69	23
		74	37
		82	30
		90	34

Pulmonary artery, 20 observations, mean = 73.6 mm. Hg, range = 52-90, S.D. = 8.6.

Pulmonary capillary, 20 observations, mean = 32.7 mm. Hg, range = 25-42, S.D. = 4.8.

(C) Cardiac failure (no diffuse myocardial disease)

Dexter and others	1950	55	36
		48	32
		50	28
		58	35
		55	42

Pulmonary artery, 5 observations, mean = 53.2 mm. Hg, range = 48-58, S.D. = 3.7.

Pulmonary capillary, 5 observations, mean = 34.6 mm. Hg, range = 28-42, S.D. = 4.6.

the myocardium. The clinical picture is like that of constrictive pericarditis with diminished amplitude of the radial pulse, pulsus paradoxus, congestive cardiac failure, and pulmonary congestion. The electrocardiogram shows changes similar to that of pericardial disease, while the

TABLE III

PULMONARY ARTERY AND "PULMONARY CAPILLARY" BLOOD PRESSURES IN SOME PREVIOUSLY REPORTED CASES OF PULMONARY VENOUS HYPERTENSION SYNDROME

Disease	Authors	Year	Pulmonary Artery Mean Blood Pressure (mm. Hg)	"Pulmonary Capillary" Mean Blood Pressure (mm. Hg)
Endocardial fibrosis	Clark and others	1956	32	25
"Chronic myocarditis"	Balchum and others	1956	40	32
"Non-specific myocarditis"	Balchum and others	1956	40	28

Pulmonary artery, 3 observations, mean = 37 mm. Hg, range = 32-40, S.D. = 6.25.

Pulmonary capillary, 3 observations, mean = 28 mm. Hg, range = 25-32, S.D. = 5.3.

teleradiogram shows a globular cardiac silhouette with diminished cardiac activity on fluoroscopy. As in hypertensive pulmonary vascular disease, the findings at cardiac catheterization are most characteristic (Table III). Hansen, Eskildsen, and Göttsche (1951) originally described the intracardiac pressure tracings in constrictive pericarditis as showing atrial pressures with a maximum greater than normal and a saddle-shaped plateau. The ventricular pressure curves show a maximum that is not abnormal but a diastolic pressure that does not fall as low as normal and rises steeply in diastole to reach a high level which is maintained until systole begins. Similar pressure curves in this pulmonary venous hypertension group have been reported in myocardial fibrosis secondary to coronary atherosclerosis by Burwell and Robin (1954), in endocardial fibrosis by Clark, Valentine, and Blount (1956), and in non-specific myocarditis by Balchum and others (1956). The striking contrast to hypertensive pulmonary vascular disease lies in the slight elevation of pulmonary artery blood pressure which may approach levels of the order of 40 mm. Hg (Table III), which is solely accounted for by the very elevated pulmonary capillary blood pressure, usually 25 mm. Hg or over, even with an arterial pressure as low as 32 mm. Hg (Table III). This is reflected in the histology of the lung, which shows normal blood vessels but pulmonary congestion and haemosiderosis.

The Present Case.—The present case illustrates the co-existence of these two clinicopathological syndromes (Table IV). So far as we are aware the association of diffuse myocardial fibrosis with pulmonary arterial hypertension has never been reported, although in the first report of endomyocardial fibroelastosis by Bedford and Konstam (1946) a raised pulmonary

TABLE IV

PULMONARY ARTERY AND "PULMONARY CAPILLARY" BLOOD PRESSURES IN SOME PREVIOUSLY REPORTED CASES OF DISEASES WITH SEVERE HYPERTENSION IN BOTH PULMONARY ARTERIES AND VEINS

Disease	Author	Year	Pulmonary Artery Blood Pressure (mm. Hg)	"Pulmonary Capillary" Mean Blood Pressure (mm. Hg)
Mitral stenosis	Whitaker and Lodge	1954	88 (mean)	36
Myxoma of left atrium	van Buchem and Eerland	1957	120/50	40
Diffuse myocardial fibrosis	This case	1957	72 (mean)	35
Mediastinal mass occluding pulmonary veins	Edwards and Burchell	1951	90/45	..

artery blood pressure was suggested by their description of a much accentuated second sound in the pulmonary area and a prominent pulmonary artery and conus in the telerradiogram. The relation of this case to other diseases showing pulmonary venous and/or arterial hypertension with pulmonary congestion and haemosiderosis and/or hypertensive changes in the pulmonary vasculature is shown in Table V.

Pulmonary arterial hypertension in the present patient was probably related to the raised left auricular blood pressure. Other diseases with elevated pressure in both the pulmonary arteries and veins are mitral stenosis (Table II), left ventricular failure following aortic stenosis or systemic hypertension (Dexter, Dow, Haynes, Whittenberger, Ferris, Goodale, and Helles, 1950; Courmand, 1950), myxoma of the left atrium (Van Buchem and Eerland, 1957), and obstruction of pulmonary veins by a mediastinal mass (Edwards and Burchell, 1951). Dexter and others (1950) realized that elevated pulmonary

capillary pressures were consistently found in patients with mitral stenosis and in those with left ventricular failure. When the "pulmonary capillary" pressure rose to values of about 25 mm. Hg, the pressure in the pulmonary artery rose proportionately but the pulmonary artery-pulmonary capillary pressure gradient and the pulmonary arteriolar resistance remained normal. With "pulmonary capillary" pressures in excess of 25 mm. Hg, pressure in the pulmonary artery rose disproportionately, the artery-capillary pressure gradient widened, and the pulmonary arteriolar resistance increased on occasions to 20 or more times the normal value. Such clinical observations suggest that in man a pressor reflex may exist between the left atrium and pulmonary arteries, as suggested by the experimental work on animals by Ferri, Rovati, Panesi, Romanelli, and Righini (1956), Kleinerman, Chitescu, Busu, Enescu, and Lupu (1956), and Rovati, Ferri, Romanelli, Panesi, and Righini (1956). These workers have shown that experimental occlusion of the pulmonary veins in animals may induce reflexly a rise in pulmonary artery blood pressure. However, only a percentage of patients, apparently lower in diffuse myocarditis than in mitral stenosis, with a raised left auricular blood pressure develop pulmonary arterial hypertension, so that the problem appears to be more complex than a straightforward causal relationship between the two. Conditions similar to those produced in the animal experiments mentioned were found by Edwards and Burchell (1951) in a woman of 26 years who had severe acquired venous stasis in all except one pulmonary lobe due to a mediastinal mass. Cardiac catheterization demonstrated pulmonary arterial hypertension and a normal pulmonary blood flow. The

TABLE V
CARDIAC DISEASES ASSOCIATED WITH RAISED BLOOD PRESSURE IN THE LUNG

	Severe Pulmonary Arterial Hypertension with Normal or Only Slightly Elevated Blood Pressure in the Pulmonary Veins	Severe Pulmonary Arterial Hypertension with Severe Pulmonary Venous Hypertension	Slight to Moderate Pulmonary Arterial Hypertension with Pulmonary Venous Hypertension	Normal or Slightly Elevated Pulmonary Artery Blood Pressure with Severe Pulmonary Venous Hypertension
Without valvular lesions or septal defects	Idiopathic pulmonary hypertension	Some cases of diffuse myocardial disease associated with pulmonary arterial hypertension, as in the present instance Some cases of myxoma of the left atrium. Mediastinal masses occluding pulmonary veins	Left ventricular failure due to systemic hypertension	Some cases of Fiedler's myocardial endomyocardial fibroelastosis, myocardial fibrosis due to coronary artery disease, scleroderma heart disease. Possibly haemochromatosis, van Gierke's disease, Friedreich's ataxia, fatty and neoplastic infiltration of the heart
With valvular lesions or septal defects	Eisenmenger's complex, atrial septal defect, ventricular septal defect, patent ductus arteriosus, aorto-pulmonary septal defect } with pulmonary arterial hypertension	Many cases of mitral stenosis	Some cases of mitral stenosis. Left ventricular failure due to aortic valve disease	

lobe without significant venous stenosis had normal arterioles and small arteries, but in the remaining lobes there were severe occlusive vascular changes similar to those seen in some cases of mitral stenosis. In the present patient too, hypertensive changes in the small pulmonary vessels occurred only in those lobes with severe venous hypertension, as shown by pulmonary haemosiderosis. It appears that in cases with elevated pressure both in arteries and in veins the obstructive arterial lesions are directly related to pulmonary venous hypertension, which may exert its effect by inducing a reflex vasoconstriction in the pulmonary arteries, comparable to that produced experimentally in animals. The level of pulmonary arterial blood pressure alone does not appear to be directly responsible for the vascular changes, for, although there was pulmonary arterial hypertension, as proved by cardiac catheterization, in the lobes free from gross pulmonary haemosiderosis and severe venous hypertension in both the present case and that reported by Edwards and Burchell, there were no arterial changes in those lobes. In this connexion O'Neal, Thomas, and Hartroft (1955) have suggested that small pulmonary vessels below $100\ \mu$ in diameter with a distinct muscular media, the hall-mark of hypertensive pulmonary vascular disease, are vasoconstricted muscular arteries rather than muscularized pulmonary arterioles.

SUMMARY

The clinical and pathological features of a fatal case of diffuse myocardial fibrosis are described.

The pulmonary histology represented a fusion of the patterns produced by hypertension in the pulmonary veins and arteries respectively.

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