Pulmonary oedema in lung disease

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Pulmonary extravascular fluid volume has been estimated during cardiac catheterization, using a double isotope dilution technique, in 28 patients with lung disease: 20 of these patients had obstructive airway disease and 8 had primary pulmonary vascular obstruction.

In the patients with obstructive airway disease, 4 of the 8 patients who had a history of congestive heart failure had much increased values of pulmonary extravascular volume, whereas values in patients with no such history of heart failure, or in those with primary vascular obstruction, were either normal or only marginally raised. Though coronary artery disease or some other form of heart disease cannot be excluded in these patients, it suggests that left ventricular failure, perhaps as a result of hypoxia, results in left atrial hypertension, and may be the basis of this interstitial pulmonary oedema.

Pulmonary hypertension in cor pulmonale is ascribed chiefly to hypoxia (Borden *et al.*, 1950; Dexter *et al.*, 1951; Ferrer *et al.*, 1950; Ferrer and Harvey, 1954; Ferrer, 1965; Harvey, 1965; Harvey, Ferrer, and Courmand, 1953; Harvey *et al.*, 1951; Mounsey *et al.*, 1952), though other factors such as anatomical restriction of the pulmonary vascular bed, hypercapnoea, acidosis, polycythaemia, with increased blood viscosity and increased blood volume, may all contribute (Borden *et al.*, 1950; Bristow, Morris, and Kloster, 1966; Harvey, 1965; Harvey *et al.*, 1951; Lewis *et al.*, 1952; Lovejoy *et al.*, 1952; Segel and Bishop, 1966). The early studies of Dexter and associates (1951) showing normal pulmonary wedge pressures appeared to eliminate left atrial hypertension as a factor. The extensive experience of Harvey (1965), and Ferrer and associates (1954, 1965) confirmed that pulmonary arterial pressure may rise without an increase in wedge pressure, thus apparently exonerating the left heart.

Pathological studies, on the other hand, have by no means excluded the left heart in cor pulmonale. Necropsy studies have shown repeatedly that left ventricular hypertrophy, in the absence of systemic hypertension or coronary artery disease, is common in patients dying from cor pulmonale (Fluck, Chandrasekar, and Gardner, 1966; Kountz, Alexander, and Prinzmetal, 1936; Michelson, 1960; Parker, 1940; Pearce, Yamashita, and Beazell, 1965; Schepers, 1957; Scott and Garvin, 1941; Spain and Handler, 1946; Spatt and

Grayzel, 1948; Zimmerman and Ryan, 1951). This strongly supports Altschule's concept that cor pulmonale is a 'disease of the whole heart' (Altschule, 1962). Some reasons suggested for this left ventricular hypertrophy have been anoxia, high cardiac output, or increased bronchial flow, but the evidence of any of these or other factors being a direct cause is not conclusive.

Since the left ventricle at necropsy is so frequently involved in cor pulmonale, one might expect to find evidence of left ventricular failure during life in at least a proportion of these patients. Clinically it may be difficult to distinguish the auscultatory features of pulmonary oedema in the presence of obstructive airway disease, and raised left atrial pressures during cardiac catheterization are exceptional, though they have occasionally been reported (Fowler *et al.*, 1952; Herles, Daum, and Bednář, 1960; Herles, Ježek, and Daum, 1968). In a recent study, Williams *et al.* (1968) were unable to show abnormal left ventricular function in patients with chronic obstructive airway disease. A normal left atrial pressure at rest does not, however, exclude incipient left ventricular failure with increase of pressure only on exertion.

A diffusible indicator method of measuring pulmonary extravascular water volume has been used in the assessment of pulmonary oedema in both animals and man (Anthonisen and Crone, 1956; Chinard, 1951; Chinard, Enns, and Nolan, 1962; Levine, Mellins, and Fishman, 1965; Lilienfeld *et al.*, 1955; Pearce *et al.*, 1965; Ramsey *et al.*, 1964). In a group of patients with valvular heart disease, pul-

monary extravascular water volume was found to be directly related to left atrial pressure (McCredie, 1967). It was only increased if left atrial pressure exceeded 12 mm. Hg and was invariably increased when it exceeded 25 mm. Hg. This method has been applied in a group of patients with either obstructive airway disease or pulmonary vascular obstruction, but no evidence of other heart disease, to determine the presence of pulmonary oedema in lung disease.

Subjects and methods

Twenty-eight patients were studied (Tables 1 and 2), 18 men and 10 women, whose ages ranged from 28 to 73 years. Twenty patients had obstructive airway disease, 12 had no history of congestive heart failure, and 8 had been in congestive heart failure (Table 1). The other group of patients was classified as primary pulmonary vascular obstruction: 4 were diagnosed as thromboembolic pulmonary hypertension and 4 as idiopathic pulmonary hypertension, one of whom had a history of congestive heart failure (Table 2).

Clinical, radiographic, and electrocardiographic assessment was made in all patients, and the diagnosis of airway obstruction was confirmed by ventilatory function tests. None of these patients had clinical evidence of ischaemic heart disease. Three patients had mild or moderate systemic hypertension (Cases 7, 14, and 24 - Tables 1 and 2). Three patients (Cases 13, 18, and 21 - Tables 1 and 2), when first seen in congestive heart failure, had radiological evidence of interstitial pulmonary oedema (Kerley B lines) and T wave inversion in the electrocardiogram extending from V₁ to V₆. These patients were studied after control of heart failure.

Right heart catheterization was performed in all patients. Left atrial pressures were obtained transeptally in 6 patients with primary vascular obstruction and 3 of the group with obstructive airway disease (Tables 1 and 2). Technically satisfactory pulmonary arterial wedge pressures were obtained in a further 7 patients. Oxygen saturation was determined spectrophotometrically.

The measurement of pulmonary extravascular fluid volume has been described in detail elsewhere (McCredie, 1967). A mixture of ¹³¹I-labelled serum albumin (RISA) and tritium-

TABLE 1 *Physical and haemodynamic data and values of pulmonary extravascular fluid volume in 20 patients with obstructive airway disease*

Case No.	Age (yr.)	Sex	BSA (m. ²)	P _{BA} (mm. Hg)	P _{FA} (mm. Hg)	P _{LA} (mm. Hg)	Cardiac index (l./min./m. ²)	S _a O ₂ (%)	Pulm. extravasc. vol. (ml./m. ²)
<i>No congestive heart failure</i>									
1	44	F	1.43	—	28	—	2.5	97	64
2	71	M	1.62	—	—	—	4.1	—	146
3	54	M	1.91	—	—	—	2.1	94	87
4	73	M	1.96	—	29	—	2.6	80	100
5	28	M	1.82	104	13	—	3.1	95	122
6	38	F	1.50	82	12	—	2.8	99	88
7	68	M	1.73	140	18	8	3.5	95	115
8	35	M	1.93	89	13	—	3.8	96	132
9	57	M	1.47	84	17	6*	3.4	98	108
10	47	M	1.71	68	12	8*	2.8	97	161
11	52	M	1.84	72	—	—	2.9	95	126
12	66	M	1.79	84	22	7*	3.2	93	104
Mean	53		1.73	90	18	7	3.1	94	113
SD	14.9		0.18	23	7	1	0.6	5.1	27
<i>History of congestive heart failure</i>									
13	48	M	1.88	86	36	17*	4.7	84	203
14	50	F	1.45	120	54	—	2.1	75	79
15	56	F	1.41	85	26	14*	3.8	93	147
16	51	F	1.57	97	—	—	1.9	92	156
17	56	F	1.47	90	60	—	1.4	88	80
18	60	M	2.08	84	35	7	2.9	83	179
19	58	M	1.79	102	31	17	2.2	96	233
20	33	F	1.35	93	58	8*	4.4	76	177
Mean	52		1.63	95	45	13	2.9	86	157
SD	8.6		0.26	12	14	5	1.2	7.6	55

BSA is body surface area. P_{BA}, P_{FA}, P_{LA} are brachial arterial, pulmonary arterial, and left atrial mean pressures. S_aO₂ is arterial oxygen saturation.

* Pulmonary arterial wedge pressures.

TABLE 2 Physical and haemodynamic data and values of pulmonary extravascular fluid volume in 8 patients with pulmonary vascular obstruction

Case No.	Age (yr.)	Sex	BSA (m. ²)	P _{BA} (mm. Hg)	P _{FA} (mm. Hg)	P _{LA} (mm. Hg)	Cardiac index (l./min./m. ²)	S _a O ₂ (%)	Pulm. extravasc. vol. (ml./m. ²)
<i>Thromboembolic</i>									
21	47	M	1.69	80	37	21	2.0	98	147
22	62	F	1.64	—	45	12	2.6	89	70
23	45	M	2.12	103	27	—	3.0	82	133
24	57	M	1.75	118	21	4*	2.8	94	75
<i>Idiopathic</i>									
25	32	F	1.58	89	47	5	2.9	96	87
26	53	M	1.26	—	32	6	2.4	88	98
27	40	M	1.56	84	116	10	3.8	76	66
28	43	F	1.54	91	45	9	2.3	96	160
Mean	48.1		1.68	91	45	10	2.7	90	105
SD	9.3		0.24	12	26	6	0.6	75	37

Key to abbreviations is at foot of Table 1.

labelled water (THO) was injected into the right atrium or right ventricle and timed samples were withdrawn rapidly from a peripheral artery. ¹³¹I and tritium activities were counted separately in these samples and indicator dilution curves constructed. RISA is confined to the vascular compartment whereas THO diffuses rapidly through the capillary walls, and, during a single passage through the lungs, is distributed through the pericapillary water space as well. Blood flow and mean transit times were calculated for each indicator, thus allowing the calculation of volume of distribution of each indicator (Hamilton *et al.*, 1932), and the difference between these two volumes represented the pulmonary extravascular water volume.

Values of pulmonary extravascular volume were expressed in ml./m.² body surface area. Previous work has shown that the standard deviation of this measurement is ± 15 ml./m.² and the average normal value is 107 ml./m.², with a range of 62 to 152 ml./m.² (McCredie, 1967).

Results

Results are listed in Tables 1 and 2. The mean value ± standard deviation of pulmonary extravascular volume in the group with obstructive airway disease was 131 ± 45/ml./min./m.², and in the group with pulmonary vascular obstruction 105 ± 37 ml./m.² Neither of these mean values differs significantly from the normal range.

The 8 patients with obstructive airway disease who had a history of congestive heart failure had a mean pulmonary extravascular volume of 157 ± 55 ml./m.² and, as seen in Fig. 1, this was higher than the mean value for the 12 patients in this group with no such history—113 ± 27 ml./m.² (p < 0.05). It was also higher

than the mean value for the group with pulmonary vascular obstruction (p < 0.05) and from a previously studied normal group (p < 0.05) (McCredie, 1967).

The group with a history of congestive heart failure had a higher average pulmonary arterial pressure and lower average arterial oxygen saturation than the patients with ob-

FIG. 1 Values of pulmonary extravascular fluid volume in patients with obstructive airway disease with and without a history of congestive cardiac failure and in patients with pulmonary vascular obstruction.

FIG. 2 Relation of pulmonary extravascular fluid volume to mean left atrial pressure (P_{LA}) in patients with obstructive airway disease (open circles) and pulmonary vascular obstruction (closed circles).

structive airway disease with no history of failure ($p < 0.01$ in both cases), but these values did not differ significantly from those found in the pulmonary vascular obstruction group (Table 2).

Fig. 2 shows the relation between pulmonary extravascular volume and mean left atrial or pulmonary arterial wedge pressure in 16 patients. The correlation coefficient for the 9 patients with obstructive airway disease was $+0.71$ ($p < 0.05$) and for the 7 patients with pulmonary vascular obstruction was $+0.47$ ($0.30 > p > 0.20$): for the whole group $r = +0.72$ ($p < 0.02$). There were no significant correlations between pulmonary extravascular volume and mean pulmonary arterial pressure ($r = -0.20$), cardiac index ($r = +0.20$), or pulmonary vascular resistance ($r = -0.27$).

Discussion

There are certain errors and limitations in this method which have been discussed in detail in a previous report on the measurement in valvular heart disease (McCredie, 1967). In pulmonary vascular disease with significant veno-arterial shunting, there is the theoretical possibility of underestimates of pulmonary extravascular volume, which are, however, unlikely to be significant. There is no theoretical reason for high values of pulmonary extravascular volume to be the result of any systematic error. In a number of studies with both animals and man (Anthonisen and Crone,

1956; Levine *et al.*, 1965; Lilienfield *et al.*, 1955; McCredie, 1967; Pearce *et al.*, 1965; Ramsey *et al.*, 1964) this measurement of pulmonary extravascular volume appears to be an index of interstitial pulmonary oedema. Thus, of the 28 patients studied, 7, mostly with obstructive airway disease and a history of heart failure, had increased values of pulmonary extravascular volume and therefore, presumably, had interstitial pulmonary oedema.

The association of a high pulmonary extravascular volume with a history of congestive heart failure in patients with obstructive airway disease suggests that there was an element of left ventricular failure present in these patients as well, perhaps related to hypoxaemia. Turino *et al.* (1968) have carried out the same measurement in patients with chronic bronchitis and found an abnormally low value except when they were in the stage of congestive failure. Systemic hypertension was not present in any of those with a high level and there was no evidence of coronary artery disease, though, of course, it cannot be excluded in patients in this age-group.

The mechanism of production of pulmonary oedema in lung disease probably differs from that of high altitude pulmonary oedema (Jackson, 1968) in which normal left atrial pressures have been found (Fred *et al.*, 1962; Hultgren *et al.*, 1964; Roy *et al.*, 1969). The relation of high left atrial pressure to high pulmonary extravascular volume may lend some support to the role of left ventricular failure in these patients.

Most of this work was done during tenure of a Senior Research Fellowship of the National Heart Foundation of Australia, and was supported by Grant-in-Aid G.571/380 from the Foundation. Miss Pamela Watson gave invaluable technical assistance.

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