Changes with exercise in dilution estimates of extravascular lung water in patients with mitral stenosis

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SUMMARY We carried out simultaneous transpulmonary indicator dilution studies with ^{51}Cr -erythrocytes, ^{125}I -albumin, and ^3H -water, in 6 patients with mitral stenosis, both at rest and during upright exercise and, from these, measured the central blood volume and extravascular space accessible to labelled water. The central blood volume increased with exercise. The water space, in the one patient with minimal mitral stenosis, fell within the normal range. In 3 patients, with moderate to severe mitral stenosis, who were under 35 years of age, it was substantially increased (values at rest of 4.5 to 5.5 g/kg, in comparison to maximal exercise values in normals of 2.45 ± 0.51 g/kg) and exercise induced further increases in the values, except in one patient who became faint under the stress of exercise. In the last two patients, who had long-standing moderate mitral stenosis and were over 55 years of age, the measured water space fell within the normal range despite raised capillary pressures and the development of frank pulmonary oedema with exercise in one patient. In these patients, with long-standing derangement and distortion of the pulmonary capillary bed, the dilution measurements appear to underestimate the water content.

In the 5 patients who underwent surgery, the clinical result obtained was closely related to the groups defined by the combined data from the dilution measurements and the right and left heart catheterisation. Only the patients with grossly raised water space values showed substantial functional improvement. We suggest that the preoperative measurement of extravascular lung water space may have value as a predictor of late results from operation in patients with isolated mitral stenosis.

In the normal lung, gravitational force induces a gradient in perfusion which increases from above downward (West and Dollery, 1960; Bake *et al.*, 1968). This gradient is most evident in the upright position but has been shown to decrease or even disappear during exercise as the upper parts of the lungs become better perfused (Bryan *et al.*, 1964; Bake *et al.*, 1968). Labelled water, introduced into the pulmonary circulation, will be delivered only to the areas of parenchyma perfused, and estimates of its extravascular distribution volume will provide a measure of the volume of tissue perfused. In normal subjects, in the upright position, we have shown that the accessible lung water space increases in the transition from rest to low level of exercise but increases no further at higher levels of exercise (Goresky *et al.*, 1975, 1977). We interpreted these findings to indicate complete recruitment of available pulmonary capillaries at the lower level

of exercise, with no further recruitment at the higher level.

Patients with significant mitral stenosis perfuse more of their lung capillaries at rest than do normals because of their higher pulmonary venous pressure. The apical regions in such patients have often been observed to have increased perfusion relative to the basal areas, the converse of the normal pattern (Jebavý *et al.*, 1970). In addition, in some of these patients, the capillary pressure will be expected to be so high that interstitial oedema will be present. Our previous study in normal adults provides values for the pulmonary parenchymal water space under conditions in which the capillary bed is fully recruited but no oedema is present. These data provide a way of assessing the significance of observed values for the extravascular water space in patients with mitral stenosis. In the present study we measure the accessible extravascular lung water volume in patients with mitral stenosis, in the upright position, under conditions of rest and exercise,

and compare these values with those in normal subjects. In addition, we attempt to relate the disparity between the observed values and normal values to the degree of haemodynamic and structural abnormality consequent to the mitral stenosis.

Methods

We studied 6 patients with isolated mitral stenosis. As part of the diagnostic work-up, right and left heart catheterisation was carried out, with the patient supine, within 10 days of the lung water studies. We recorded left ventricular, pulmonary arterial, and pulmonary capillary wedge pressures, and measured cardiac output by the direct Fick method, both at rest and during steady state exercise. Mitral valve areas were calculated by Gorlin's formula (Gorlin and Gorlin, 1951). Left ventricular angiograms excluded the presence of mitral regurgitation in these patients.

For the separate lung water study, we passed a 15-gauge catheter percutaneously via the medial basilic vein to the superior vena cava and slowly infused heparinised saline to maintain its patency. Using the Seldinger technique, we inserted a small polyethylene catheter (PE60) percutaneously into the left brachial artery. The patient was seated on a bicycle ergometer and kept at rest for 15 minutes to achieve cardiorespiratory stability after these manipulations. Resting arterial samples for blood gases were then drawn. Immediately thereafter, a multiple indicator dilution study was carried out (Goresky *et al.*, 1969). As rapidly as possible, a 2 ml mixture containing ^{51}Cr -labelled red cells, ^{125}I -labelled albumin, and tritium enriched water made up in plasma to a haematocrit matching that of the patient, was flushed into the superior vena cava with 10 ml blood, and serial blood samples were collected from the brachial artery.

After the resting study, each patient exercised for 6 minutes at a low workload (25 W) in order to achieve steady state conditions, and then, with exercise continuing, the study was repeated. After a 20-minute rest period, the study was again repeated in 3 of the 6 patients, with the workload increased to 50 W.

Blood and gas samples were analysed as described previously (Goresky *et al.*, 1975). In this experimental design, the vascular red cell and albumin transit patterns provide a precise basis for measuring both central blood volume and extravascular water space (Goresky *et al.*, 1975).

Results

The background description of each patient is given in Table 1. Table 2 presents the haemodynamic data

obtained at the time of cardiac catheterisation, in the supine position, during both rest and exercise. These indicate that case 4 is haemodynamically almost normal, that case 5 has moderately severe mitral stenosis, and that the others vary in their degree of severity. Table 3 presents the data obtained in the lung water studies.

CENTRAL BLOOD VOLUMES

The central blood volume was found to increase with flow, in each of the patients with mitral stenosis. The pattern of increase is shown in the upper panel of Fig. 1. In this panel and the one below, the shaded areas correspond to an area ± 1 SE about the relation fitted through the normal data. The increase in cardiac output with exercise is limited in the patients with mitral stenosis, so that the highest values attained correspond only to the values found in normal subjects at low level exercise. The upper parts of the normal range are, therefore, not displayed. Most of the resting values for the central blood volume begin in or close to the normal range but in 4 of 6 patients they increase slightly more steeply with exercise than do the normals. Case 4, with very mild mitral stenosis, was haemodynamically almost normal. The two oldest patients, cases 2 and 6, showed differing patterns: the values for case 2 were consistently low, and those for case 6 were consistently high.

EXTRAVASCULAR WATER SPACE

The extravascular lung water space in normal subjects increases about 18 per cent between rest and first level exercise, and then increases no further, with higher levels of cardiac output (Goresky *et al.*, 1975). The initial pattern of increase is outlined in the shaded area of the lower panel of Fig. 1. The individual values for the patients with mitral stenosis appear to subdivide themselves into two groups. In cases 1, 3, and 5, who were younger (< 35 years), the values recorded for the accessible extravascular water space at rest are high (they are, in fact, much higher even than the average values found in the normals at high level exercise, 2.45 ± 0.51 g/kg, when presumably all of the normal pulmonary capillary bed and accessible water space

Table 1 Background data

Case No.	Sex	Age (y)	Height (cm)	Weight (kg)	Surface area (m ²)	Haemoglobin (g/dl)	Arterial haematocrit
1	M	31	187.9	78.2	2.05	17.2	0.41
2	F	57	160	57	1.60	13.0	0.30
3	F	21	159	52.7	1.54	13.1	0.40
4	F	22	162.5	50	1.52	13.4	0.35
5	F	34	165	59.5	1.64	15.6	0.40
6	M	56	157	66	1.67	13.8	0.35

Table 2 Rest and exercise data (supine position, obtained at cardiac catheterisation)

Case No.	CI	Cardiac output (l/min)	Cardiac output (ml/s per kg)	Oxygen consumption (ml/min)	Pulmonary artery pressure (mmHg)	Pulmonary capillary pressure (mmHg)	Pulmonary vascular resistance (kPa/l per min)	Mitral valve gradient (mmHg)	Mitral valve area (cm ²)
1	Rest	3.41	7.0	1.49	277	32/16 (24)	0.11	6	2.0
	I	5.85	12.0	2.56	1486	85/40 (60)	0.06	35	
2	Rest	2.44	3.9	1.14	177	40/20 (28)	0.38	7	1.6
	I	3.56	5.7	1.67	550	73/37 (49)	0.26	29	
3	Rest	3.77	5.8	1.83	199	72/32 (48)	0.41	24	1.3
	I	5.29	7.4	2.34	553	115/50 (75)	0.63	38	
4	Rest	4.87	7.4	2.47	203	20/8 (14)	0.11	0	3.6
	I	8.62	13.1	4.37	735	23/8 (17)	0.1	16	
5	Rest	2.5	4.1	1.15	166	47/21 (33)	0.16	14	0.9
	I	6.71	11.0	3.09	779	94/43 (67)	0.11	43	
6	Rest	2.77	4.62	1.17	211	45/27 (30)	0.14	9	1.5
	I	3.78	6.31	1.59	650	88/52 (56)	0.13	23	

I = first level exercise.

Table 3 Data from multiple indicator dilution studies, obtained at rest and exercise, in erect position

Subject		Mean transit times*			Cardiac output (l/min)	Cardiac output (ml/s per kg)	Central blood volume (ml)	Extra- vascular lung water (g)	Oxygen consumption (ml/min)	Arterial blood Po ₂ (kPa)	Arterial blood PCo ₂ (kPa)	Arterial blood pH
		⁵¹ Cr-RBC (s)	¹²⁵ I-Alb (s)	THO (s)								
1	Rest	13.59	14.58	20.69	4.30	0.92	1015	388.6	198	13.7	3.4	7.46
	I	8.58	9.54	12.01	14.03	2.99	2141	551.1	1693	14.9	3.5	7.35
2	Rest	12.41	13.07	15.80	2.21	0.65	474	92.5	139	11.2	5.1	7.48
	I	7.50	8.02	9.37	4.93	1.44	646	105.2	711	10.8	4.1	7.44
3	Rest	13.34	14.14	19.73	3.56	1.12	819	292.9	181	10.8	4.9	7.47
	I	9.14	9.72	12.60	7.30	2.31	1155	315.9	883	11.2	3.8	7.42
4	Rest	9.66	10.18	11.87	4.26	1.42	710	110.7	173	12.1	4.7	7.45
	I	6.26	6.68	7.59	7.50	2.50	817	109.7	712	13.3	3.8	7.43
	II	5.46	6.22	7.11	8.33	2.80	853	121.8	1048	13.2	3.3	7.41
5	Rest	18.00	19.35	25.92	2.62	0.73	822	258.8	185	—	—	—
	I	11.95	12.86	15.44	5.22	1.46	1087	211.8	734	—	4.1	7.44
	II	12.42	13.44	15.61	4.98	1.40	1083	176.1	803	—	4.3	7.41
6	Rest	18.69	19.86	21.91	3.64	0.92	1440	119.8	205	11.2	3.6	7.58
	I	13.62	14.06	15.53	6.99	1.77	2110	157.9	1124	12.9	3.7	7.42
	II	11.64	12.06	13.35	7.84	1.98	2114	156.8	—	12.9	3.3	7.43

*Corrected for inflow and outflow catheter delays.

has been recruited). The increased values in these patients must then reflect the presence of chronic interstitial oedema as well as, perhaps, an increment in parenchymal tissue. Cases 1 and 3 were able to increase their cardiac output to a fair degree during exercise, accompanied by a further increase in their accessible extravascular lung water. Case 5, with the smallest calculated mitral valve area, had a limited increase in her cardiac output at the first level of exercise but was unable to increase it further at the second level of exercise. She became quite faint when her output was unable to meet the demands imposed by her exercising muscles. It is doubtful that she maintained her 'steady state' conditions at this time, rendering her output and accessible water space measurements less reliable at this second exercise level. The decrease in accessible water space with the first exercise load, at a time when cardiac output and central blood volume were increased, suggests that in some pathways the water label was being shunted past the capillary bed, so that a part of the extravascular water space was no longer accessible to the label.

The values for cases 2, 4, and 6 fall within the normal range. Case 4 was haemodynamically almost normal and her accessible extravascular lung water increased normally during exercise. Cases 2 and 6 were much older (56 and 57 years, respectively), with long-standing disability. Case 2 had a low resting cardiac output which increased only to a small extent with exercise, yet her accessible water space fell within the normal range. Case 6 increased his cardiac output more significantly with exercise but again the water space fell within the normal range during rest and exercise. With exercise, however, he developed new basilar râles and protracted dyspnoea indicating the development of pulmonary oedema. In the presence of these findings, the lack of an increase in the water space must be taken to imply either a lack of perfusion of some of the oedematous areas (Goresky *et al.*, 1971), so that the measured value is falsely low, or the presence of a destructive process in the microvascular bed associated with mitral stenosis which has reduced and distorted the total capillary bed so that a smaller than normal (albeit oedema-

Fig. 1 Manner in which the superior vena cava—brachial artery central blood volume (CBV) and estimated extravascular lung water space change with cardiac output, during upright exercise. Both ordinate and abscissal values have been normalised in terms of body weight. The stippled area corresponds to a band ± 1 SE about the regression lines developed by data from normal subjects (Goresky et al., 1975). The data points from the rest studies on the patients with mitral stenosis are represented by solid circles; those from first level exercise by half-filled circles; and those from second level exercise, by open circles.

tous) space is being measured. The decrease in pulmonary vascular resistance with exercise, as well as the demonstrated increase in blood flow to the lower lobes of patients with mitral stenosis on exercise (Bjure et al., 1971) suggest that the former is a more likely explanation.

On admission to hospital for catheterisation, each patient was assessed with respect to functional classification (NYHA) by an independent cardiologist not participating in our study. All patients,

except case 4, underwent closed mitral commissurotomy on the advice of their treating physician. Three months later, the operated patients were again classified with respect to functional ability (NYHA) by the same cardiologist who initially assessed them. Table 4 presents this assessment. It is clear that cases 1, 3, and 5 had an excellent functional result while cases 2 and 6 received no significant benefit from surgery. The latter two are the patients whose measured extravascular lung water values appeared normal, despite increased capillary pressures, and changed relatively little on exercise.

Table 4 Results of operation: functional assessment

Subject	Functional class (NYHA)	
	Preoperative	Postoperative
1	III	I
2	III	II-III
3	II	I
4	I	Not operated
5	III	I
6	II-III	II-III

Discussion

This small number of patients, the total presenting to our institution with isolated mitral stenosis over a 2-year period, reflects the decreasing incidence of this disease in our community. Despite the small number of patients studied, the results have been so striking that we report them here. In this group, the severity of disease varies considerably from patient to patient and cannot be judged on mitral valve area alone. The independent functional classification combined with the measured degree of stenosis and pulmonary venous pressures appears to give the most meaningful assessment of severity. In this light, 5 of the 6 patients presented are in the moderate to severe range, the sixth patient (case 4) being classified as very mild.

CENTRAL BLOOD VOLUMES

The most appropriate volume to measure in this kind of study is the pulmonary blood volume. The catheter placement necessary for this entails a small hazard in the upright and exercising patient. Because of this, we used the more unreliable central blood volume (superior vena cava—brachial artery) measurements. Despite this compromise in experimental design, interesting trends are apparent.

In the normal lung, acute increases in pulmonary venous pressure result in immediate recruitment and distension in the pulmonary vascular tree (Vreim and Staub, 1973). In patients with long-standing rises of pulmonary venous pressure, as in

mitral stenosis, expanded pulmonary or central blood volumes have not been characteristic. Rapaport *et al.* (1956) studied a group of patients with rather severe mitral stenosis in the supine position and found central blood volumes at rest which were normal or slightly low when compared with normals (Luepker *et al.*, 1971) similarly studied. The values were found to increase modestly with exercise when cardiac output increased, but showed no increase when the output was restricted. Most of our values correspond to these observations. In comparison with upright normal subjects, the resting values are normal or low with the exception of case 6 who had an apparently increased central blood volume. All increased with exercise. Though we cannot tell in this study whether the increased volume occurred in the pulmonary circulation or in the more peripheral components of the central blood volume, two recent studies of the pulmonary blood volume itself (carried out by simultaneous pulmonary artery and transseptal left atrial catheterisation) have described its increase with exercise in patients with mitral stenosis who were supine (Luepker *et al.*, 1971; Austin *et al.*, 1976).

In patients with long-standing, severe mitral stenosis, there are distinct changes in the pulmonary vasculature, increasing in severity from above downwards (Parker and Weiss, 1936). In advanced stages the alveolar wall is perfused with sparse dilated vessels and the whole becomes thickened, with an overlying cuboidal rather than flat alveolar epithelium. The alveolar wall is converted from a structure optimal for the equilibration of tracer water throughout its substance to one whose structural characteristics appear poor.

Functionally our studies and the others quoted above suggest that the distorted pulmonary vasculature in patients with long-standing severe mitral stenosis still shows some capacitance characteristics, that it is not completely rigid, and that there is probably both dilatation and recruitment as the basis for the increases in pulmonary blood volume seen with exercise. The pattern, however, will differ from that in the normals, where there is a recruitment of the vasculature in the upper lung fields (Goresky *et al.*, 1969, 1975; Jones *et al.*, 1976). In the patients with mitral stenosis with advanced pulmonary changes, the normal perfusion gradient disappears and an inverse gradient is found. Bjure *et al.* (1971) reported that in these patients with mitral stenosis, who have a relatively low basal blood flow in the erect position at rest, exercise results especially in an increased basal blood flow. In the patient with very advanced pathological changes, the increase in flow will be occurring through the sparsely distributed large

distorted vessels which have taken the place of the normal alveolar sheets. Vasodilatation as well as increased flow will be occurring, under the influence of the pronounced increase in the left atrial and pulmonary arterial pressures, and these large vessels may well become the site of shunt-like effects.

The severity of the chronic pulmonary vascular changes present in our patients is difficult to assess accurately. Despite the degree of mitral valve obstruction, only 2 patients (cases 2 and 3) had clearly raised pulmonary vascular resistance at rest in the supine study; and only in 1, case 3, with the highest resistance level, was there an increase with exercise. Nevertheless, one would expect a correlation both with the degree of obstruction and, perhaps even more importantly, with the duration of the process.

EXTRAVASCULAR LUNG WATER

In patients with a variety of disorders, increases in the accessible extravascular lung water have been correlated with increased left atrial pressures (McCredie, 1967; Luepker *et al.*, 1977). In our results, the already raised water space in cases 1, 3, and 5 at rest (values in the range 4.5 to 5.5 g/kg versus maximal exercise values of 2.45 ± 0.5 g/kg in normals) suggests that this relation holds true in our younger patients at least. The values correlate well with the average reported by Brigham *et al.* (1976), 5.1 g/kg, for a group of patients about to undergo prosthetic mitral valve replacement. It also seems likely that the further increase in the accessible water space in cases 1 and 3 with increasing cardiac output and increasing left atrial pressure represents formation of oedema fluid, as suggested by Luepker *et al.* (1971) rather than vascular recruitment of additional abnormal lung tissue.

In our oldest patients, cases 2 and 6, both with moderately severe mitral stenosis, one would expect relatively advanced pulmonary vascular changes with a larger than normal proportion of the water space which is inaccessible because of the structural changes in the alveolar wall. This supposition appears to be at least partly upheld by the development of clinically evident alveolar oedema (in case 6) at a time when concomitant dilution measurements of the extravascular lung water are in the normal range.

RESULTS WITH SURGERY: CAN THESE BE PREDICTED?

In Fig. 2 we present the combined results from the cardiac catheterisation and dilution studies on our patients. The upper panel illustrates the relation between the accessible extravascular water space

Fig. 2 The relation between the extravascular lung water space and the pulmonary capillary wedge pressure; and that between the pulmonary capillary wedge pressure and cardiac output. The shaded areas correspond to normal values, in each case.

and the pulmonary capillary wedge pressure; and the lower panel, that between pulmonary capillary wedge pressure and cardiac output. In the upper panel the young patient with very mild mitral stenosis occupies an area to the left and deviates little from the normal range. Of those with more severe stenosis, the younger patients, with presumably less severe chronic pulmonary vascular changes, have high resting accessible water spaces, and in the 2 with more flexible cardiac outputs these increase further with increasing flow. Case 5, with the most severe mitral stenosis and limited increases in cardiac output, did not increase her accessible water space as expected. This was presumably because of the alteration in flow pattern, with a shunt-like effect in the lower lobes as described, or because of her relatively non-stable 'steady-state'. The oldest patients, cases 2 and 6, with long-standing mitral obstruction are clearly separated by their low and relatively fixed cardiac outputs and their low and relatively fixed accessible water

spaces. In this latter group, we have concluded that the measured water volume must be an unreliable estimate of true extravascular lung water volume, caused by the structural changes in the alveolar wall.

The assessment in Table 4 after operation subdivides the 5 patients into 2 groups: those that improve, and those that do not. It is clear from this Table and Fig. 1 and 2 that those patients with high accessible water spaces are those with the best clinical results after operation. Thus a high measured water volume appears to identify those patients with less chronic obstructive and more reversible lesions. The older patients who experienced little or no benefit from operation, presumably because of the irreversible pulmonary lesions present, had low or normal, and probably unreliable, estimates of extravascular water space. The difference in the water space differentiates these two groups, even though their pulmonary wedge pressures and pulmonary vascular resistances are not characteristically different.

Our series is admittedly small, but the apparent separation of our patients into two groups strongly suggests that measurement of accessible lung water at rest and with exercise may be an important predictor of later benefit from operation. It is not always clear from presently available haemodynamic techniques, which patient will not benefit from operation. We feel that the potential utility of lung water measurement in this area needs further study. It may well be a useful addition to current diagnostic techniques.

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