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Cardiovascular function at rest and on exercise in patients with cryptogenic fibrosing alveolitis

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ABSTRACT Cardiovascular complications are common in fibrosing alveolitis, but there have been few physiological studies of the pulmonary circulation in this condition, and those that have been carried out have usually depended on right heart catheterisation. This paper reports non-invasive measurements of effective pulmonary blood flow, oxygen uptake, pulmonary arteriovenous oxygen content differences, and estimates of mixed venous oxygen saturation in 20 patients with histologically proved cryptogenic fibrosing alveolitis at rest and while exercising on a motorised treadmill. Results were compared with those of 20 age and sex matched normal subjects, at rest and at an arbitrarily chosen oxygen uptake of 0·75 l/min. The latter results were obtained by linear interpolation. Effective pulmonary blood flow was normal at rest, but oxygen dispatch to the tissues (blood flow × blood oxygen content) was significantly reduced at rest (mean reduction 190 (SD 68) ml/l/min; $p < 0·01$) and at an oxygen uptake of 0·75 l/min (mean reduction 128 (50) ml/l/min; $p < 0·02$), reflecting the presence of systemic arterial hypoxaemia. Pulmonary arteriovenous oxygen content differences were similar in patients and normal subjects, but mixed venous saturation was lower in the patients at rest (mean % reduction 6·8 (2·6); $p < 0·02$) and at an oxygen uptake of 0·75 l/min (mean % reduction 9·6 (2·9); $p < 0·002$). It is concluded that the supply of oxygen potentially available to the tissues is reduced at rest and during exercise in patients with fibrosing alveolitis and hence, by analogy with normal people exercising under hypoxic conditions, that pulmonary blood flow is inappropriately low in this condition. The low mixed venous oxygen saturation may contribute to the development of pulmonary hypertension in some patients. The rebreathing technique used in this study may be of use in monitoring treatment; it could be applied many times to the same patient, and might be a suitable way of following the response to pulmonary vasodilators.

The pulmonary features of cryptogenic fibrosing alveolitis have been studied in detail. They include reductions in FEV_1, vital capacity, static lung volumes, and carbon monoxide transfer; decreased lung compliance; and systemic arterial hypoxaemia at rest and during exercise.[1-4] The cardiovascular consequences are less well characterised, despite the fact that pulmonary hypertension is common in life,[5,6] a quarter of patients die of cardiovascular causes,[7,8] and right ventricular hypertrophy is virtually universal at necropsy.[9] Most physiological studies of the cardiovascular system have depended on right heart catheterisation,[5,6,10] which cannot be repeated many times in the same patient.

This paper describes the application of a non-invasive, rebreathing method of measuring effective pulmonary blood flow ($\dot{Q}_{P}$.eff) and oxygen consumption ($\dot{V}O_2$) in patients with fibrosing alveolitis at rest and during exercise and the results of the derived measurements—namely, oxygen "dispatch" from the lungs, pulmonary arteriovenous oxygen content differences, and mixed venous saturation. The test can be used to monitor the progress of the disease and any responses to vasodilator treatment,[10] and the results may also help to throw light on the pathogenesis of pulmonary arterial hypertension in these patients.

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Methods

We studied 20 patients (12 of them men), of mean age 50·9 (SD 15·1), range 16–66 years. The diagnosis of fibrosing alveolitis was based on typical clinical and radiographic findings, and confirmed histologically by open lung biopsy (n = 19) or high speed drill biopsy (n = 1). No patient had clinical or electocardiogra-

phic evidence of cardiac disease. All the patients over the age of 30 had a normal 12 lead electrocardiogram during maximal exercise. None was taking drugs likely to affect the cardiovascular system.

All patients had standard lung function tests performed. Forced inspiratory and expiratory flow volume curves were obtained by using a dry rolling seal spirometer (Ohio 840). Absolute lung volumes and airway resistance were measured in a constant volume, whole body plethysmograph (Fenyves and Gut). Carbon monoxide transfer factor was measured with a 10 second breath holding time (PK Morgan model C apparatus). All patients also exercised on a motorised treadmill (PK Morgan) according to the Bruce protocol.

In the hour before the exercise test the patients were not permitted any food or caffeinated drinks. They came to the laboratory and were familiarised with the apparatus. Standard electrocardiographic leads were attached, and the electrocardiogram was displayed continuously. An ear oximeter (Hewlett Packard) was also positioned. They were shown how to perform the rebreathing manoeuvre exactly as described previously.[11] In summary, the subject rebreathed a volume of test gas just below vital capacity from a six litre anaesthetic bag. The test gas was 35% oxygen, 3·5% chlorodifluoromethane (freon-22), and 10% argon in nitrogen. It was rebreathed at 0·3–0·5 cycle/s for 30 seconds or until the respired oxygen (P_{O_2}) had fallen below 13·3 kPa, whichever was sooner. No attempt was made to impose a fixed pattern of breathing. The rebreathing manoeuvre was first performed with the subject seated after 10 minutes' rest, and then standing. At least seven standing baseline manoeuvres were performed at three minute intervals, and then the treadmill was started. The rebreathing test was repeated at the end of each stage of the Bruce protocol,[12] until the patient was unable to contine. The highest oxygen consumption attained was expressed as a percentage of the predicted maximum (% $\dot{V}_{O_2}$max), calculated from regression equations based on age, sex, and body weight.[13] Heart rate was measured from the electrocardiogram at the end of each stage, and arterial oxygen saturation was also recorded. All patients had a resting sample of blood taken within 48 hours of the exercise test for haemoglobin estimation by a Coulter counter.

Seventeen patients underwent a second exercise test within 24 hours of the first. The Bruce protocol was again used, but oxygen uptake was measured by the conventional open circuit, argon dilution method[14] in routine use in our laboratory. These results were used for the comparisons with oxygen consumptions measured by rebreathing. We also calculated the percentage of the alveolar tidal volume (that is, tidal volume minus the anatomical deadspace) reaching alveoli that were not perfused, an index of wasted ventilation. The calculation is based on the Bohr equation, which gives percentage alveolar deadspace equal to [(1 − end tidal P_{CO_2}/arterial P_{CO_2}) × 100]. This was measured at rest and on exercise in the same 17 patients at the time of their second exercise test. The end tidal P_{CO_2} was taken as the mean from at least six breaths, measured with the mass spectrometer probe mounted 1 cm from the lips. Arterial P_{CO_2} was taken to be the same as that in an arterialised earlobe blood sample drawn simultaneously.

The measurements made in all 20 patients were $\dot{Q}_{P}$.eff, $\dot{V}_{O_2}$, heart rate, and earlobe oxygen saturation (Sa_{O_2}). The following measurements were derived from the basic data:

Pulmonary arteriovenous oxygen content difference
$$(AVO) = \dot{V}_{O_2}/\dot{Q}_{P}.eff$$
Stroke volume index (SVI) $= (\dot{Q}_{P}.eff \times 1000)/$ (heart rate × body surface area)
Oxygen dispatch to tissues $= \dot{Q}_{P}.eff \times Sa_{O_2}$ 1·39 × haemoglobin concentration.

(The term oxygen dispatch is used throughout, rather than the more conventional "oxygen delivery," because the latter term implies that the distribution of blood within peripheral tissues is normal. We have made no measurements to show whether this is the case.)

By definition, if dissolved oxygen is neglected,
AVO = haemoblobin conc. × 1·39 × (Sa_{O_2} − mixed venous saturation).
Therefore
Mixed venous saturation = Sa_{O_2} − AVO/(1·39 × haemoglobin conc.).

All results were compared with those from 20 age and sex matched normal subjects (12 male), of mean age 49·4 (SD 14·0) years), who also underwent a Bruce protocol exercise test, with rebreathing estimates of effective pulmonary blood flow and oxygen uptake. None had any history or physical signs of cardiac or pulmonary disease, and all those over age 40 years had a normal 12 lead electrocardiogram during maximal exercise. For the normal subjects only, haemoglobin was assumed to be at the midpoints of the normal ranges (15·8 g/dl for men and 14·0 g/dl for women), and arterial oxygen saturation, corrected for age, was assumed from published data[15] (saturation calculated from: Pa_{O_2} (kPa) = 0·133 × [104 − 0·24 age]).

All the above procedures were covered by approval from the Brompton Hospital ethics committee, and all patients and normal subjects gave verbal informed consent.

Results

The results of the standard lung function tests on the 20 patients, expressed as percentages of predicted

normal values,[15] are shown in table 1, and the details of their exercise performance in table 2. Most of the patients with fibrosing alveolitis were too disabled to do more than one stage of the Bruce protocol, so comparisons with rate of change of variables at higher levels of exercise were not possible. All traces were inspected to check that the rebreathing manoeuvre had been performed satisfactorily. No patient had a significant slope to the argon plateau. We discarded any exercise result in which the measured bag-lung volume was more than 10% greater than the mean of the corresponding volume measured at rest.

In the companion paper[11] (p 268) we have shown that measurement of power output (watts) is not accurate because it is based only on vertical work. Consequently results were compared at rest and at the arbitrarily chosen values of oxygen consumption 0·75,

Table 1 *Lung function data (% predicted normal[15]) on 20 patients with cryptogenic fibrosing alveolitis*

Patient No	*FEV_1*	*FVC*	*TLC*	*RV*	*TLCO*	*KCO*
1	91·6	79·3	60·7	39·8	40·0	76·0
2	80·7	70·3	63·4	62·4	47·2	62·1
3	62·7	55·8	49·1	45·0	55·3	88·5
4	72·6	87·8	98·2	121·6	61·5	40·7
5	82·1	93·9	80·8	54·5	50·6	74·1
6	53·0	46·2	48·6	55·5	43·6	104·3
7	86·6	88·2	81·7	78·0	68·9	82·7
8	79·9	82·4	90·0	95·1	70·6	95·2
9	66·2	55·2	54·9	53·8	43·7	93·9
10	66·6	61·3	60·1	63·4	32·9	60·5
11	83·0	82·2	61·8	44·6	50·2	97·3
12	71·2	77·8	69·9	51·2	31·6	49·2
13	110·5	104·6	93·8	67·9	45·0	52·8
14	88·6	78·3	84·1	104·1	50·9	77·4
15	95·1	83·5	76·9	52·7	24·3	35·5
16	69·1	65·4	58·4	46·9	32·7	62·8
17	68·4	69·1	72·3	80·2	62·3	91·1
18	84·9	88·2	83·0	82·1	66·3	87·1
19	55·8	67·1	74·2	77·6	35·2	58·8
20	86·3	82·7	83·2	137·9	77·5	105·8
Mean	77·8	76·0	72·3	70·7	49·5	74·8
(SD)	(14·1)	(14·5)	(14·7)	(26·8)	(14·8)	(21·0)

FEV_1—one second forced expiratory volume; FVC—forced vital capacity; TLC—total lung capacity; RV—residual volume; TLCO—carbon monoxide transfer factor; KCO—transfer coefficient.

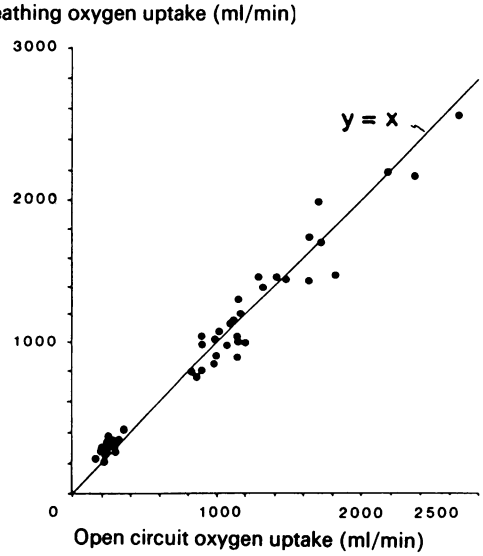

Fig 1 *Comparison of rebreathing and open circuit oxygen uptakes (47 observations on 17 patients). The line of identity is shown.*

Table 2 *Exercise data on 20 patients with cryptogenic fibrosing alveolitis*

Patient No	*Arterial oxygen saturation (%)*		*Work done (watts)*	*Maximum oxygen uptake (% predicted[13])*	*% Alveolar deadspace*	
	Res	*Exercise*			*Rest*	*Exercise*
1	98	92	61	54·0	0	4
2	96	85	85	71·2	6	4
3	97	84	63	47·4	0	0
4	98	94	111	104·3	0	3
5	99	96	61	69·3	0	0
6	97	84	56	57·0	—	—
7	97	93	85	63·4	0	0
8	99	96	86	69·6	0	0
9	97	91	51	43·2	7	0
10	98	82	66	46·3	—	—
11	99	92	48	63·1	0	0
12	100	86	84	67·6	8	26
13	96	83	62	61·1	—	—
14	96	99	39	50·6	0	1
15	97	79	47	57·3	16	38
16	94	84	62	38·5	0	1
17	98	86	247	78·4	0	0
18	96	90	169	59·6	0	0
19	96	84	101	40·4	0	0
20	98	89	129	57·8	0	0
Mean	97·3	88·5	85·7	60·0	2·2	4·5
(SD)	(1·4)	(5·5)	(49·3)	(15·1)	(4·5)	(10·6)

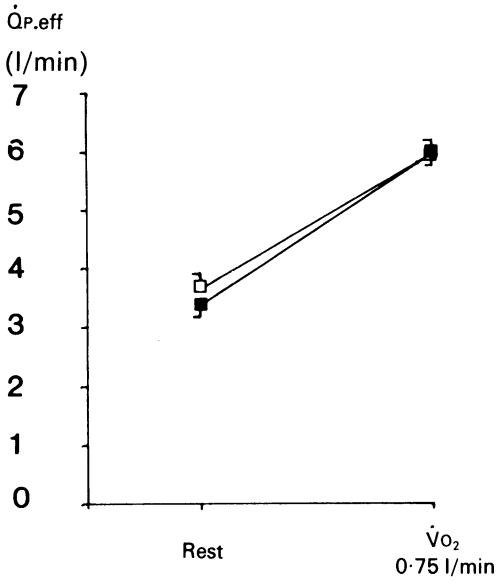

Fig 2 *Comparison of effective pulmonary blood flow (Q̇P.eff) at rest and at oxygen uptake 0·75 l/min. Open squares indicate normal subjects (n = 20) and closed squares patients with fibrosing alveolitis (n = 20). There are no significant differences.*

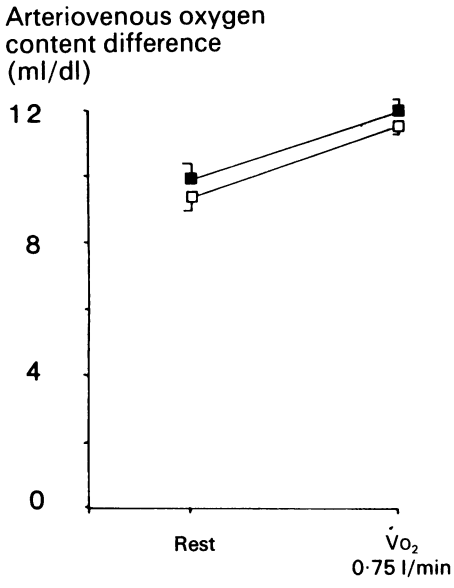

Fig 3 *Comparison of arteriovenous oxygen content difference at rest and at oxygen uptake 0·75 l/min. Open squares indicate normal subjects (n = 20) and closed squares patients with fibrosing alveolitis (n = 20). There are no significant differences.*

1·0, and 1·25 l/min. Results at these levels were found by linear interpolation; a similar approach has been used by others.[16] In the present study all patients attained an oxygen consumption of 0·75 l/min, but only 13 patients managed 1·0 l/min, and only six reached 1·25 l/min.

Oxygen consumption measured from the rebreathing traces was compared with values from open circuit argon dilution[14] (fig 1). There was good agreement (rebreathing oxygen consumption = (0·96 × argon dilution oxygen consumption) + 65, 47 observations on 17 patients; r = 0·98, p < 0·001]. The mean difference between the two methods was 26 (SD 17) ml (NS).

Direct comparisons of the data on patients and on normal subjects are possible for effective pulmonary blood flow, stroke volume index, and pulmonary arteriovenous oxygen content difference. The effective pulmonary blood flow (fig 2) and arteriovenous oxygen content difference (fig 3) were normal at rest and at oxygen uptake 0·75 l/min. The stroke volume index was significantly lower in the patients at rest (mean reduction 5·8 (SD 2·4) ml/m^2; p < 0·05). There was a trend (fig 4) for lower than normal values also at

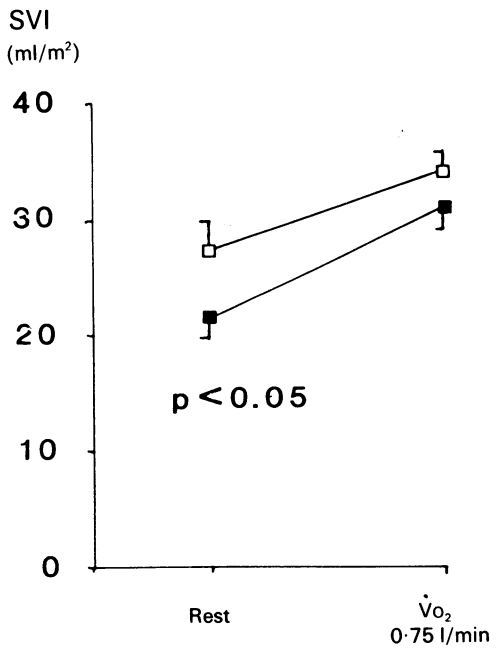

Fig 4. *Comparison of stroke volume index (SVI) at rest and at oxygen uptake 0·75 l/min. Open squares indicate normal subjects (n = 20) and closed squares patients with fibrosing alveolitis (n = 20). At rest SVI is reduced in the patients (p < 0·05), but the reduction during exercise is not significant.*

oxygen uptake 0·75 l/min (mean reduction 3·7 (2·0) ml/m^2; $p < 0.10$).

Haemoglobin and earlobe oxygen saturation were not available for the normal subjects, and their values were assumed to lie within the normal range. This means that oxygen dispatch and mixed venous oxygen saturation, which are derived from direct measurements in the patients, are compared with normal values based partly on assumptions. At rest one patient had an arterial oxygen saturation of less than 95%, and in all but one patient it fell during exercise (table 2). Calculated oxygen dispatch from the lungs (fig 5) was significantly lower in the patients than in the normal subjects at rest (mean reduction 190 (SD 68) ml/l/min; $p < 0.01$) and at oxygen uptake 0·75 l/min (mean reduction 128 (50) ml/l/min; $p < 0.02$). As the arterial oxygen saturation was reduced and pulmonary arteriovenous oxygen content differences were similar to normal, mixed venous oxygen saturation was lower in the patients (fig 6); at rest the mean value was 6·8% (SD 2·6%) lower than in normal subjects ($p < 0.02$), and at oxygen consumption 0·75 l/min it was 9·6% (2·9%) lower ($p < 0.002$).

Six patients achieved an oxygen consumption of 1·25 l/min. Their results were compared with those of the six matched normal subjects. At rest and at all three levels of oxygen uptake studied there were no significant differences between these two small groups for effective pulmonary blood flow, stroke volume index, oxygen dispatch, pulmonary arteriovenous oxygen content differences, or mixed venous saturation.

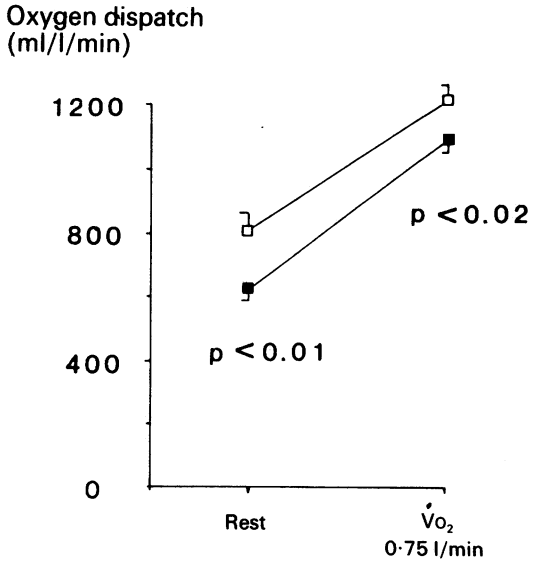

Fig 5. *Comparison of oxygen dispatch from the lungs at rest and at oxygen uptake 0·75 l/min. Open squares indicate normal subjects (n = 20) and closed squares patients with fibrosing alveolitis (n = 20). Oxygen dispatch is reduced at rest ($p < 0.01$) and during exercise ($p < 0.02$).*

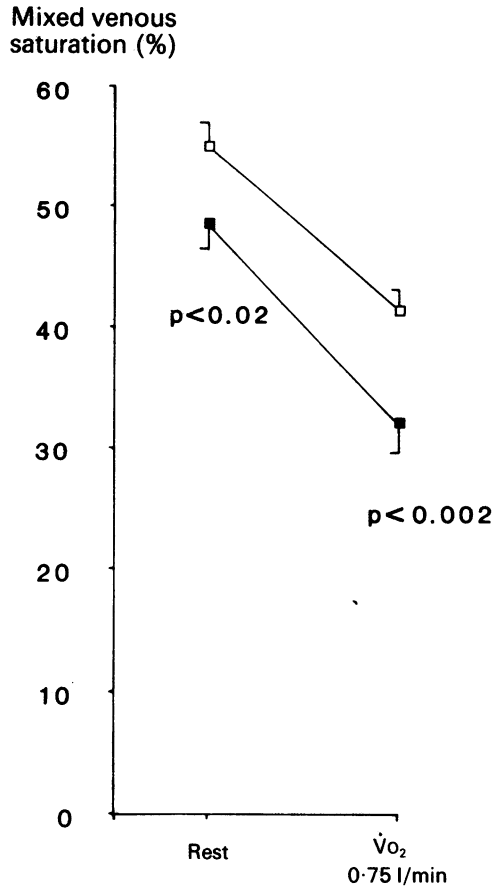

Fig 6. *Comparison of mixed venous oxygen saturation at rest and at oxygen uptake 0·75 l/min. Open squares indicate normal subjects (n = 20) and closed squares patients with fibrosing alveolitis (n = 20). Saturation is reduced at rest ($p < 0.02$) and during exercise ($p < 0.002$).*

Discussion

We have shown that the rebreathing technique can be performed at rest and during exercise by patients with moderately severe fibrosing alveolitis who were able to attain an average of only 60% of their predicted maximum oxygen consumption. Use of rebreathing methods in patients with lung disease depends on certain assumptions related to perfusion and ventila-

tion. In any patient with a large anatomical intrapulmonary right to left shunt cardiac output would be much greater than measured effective pulmonary blood flow. In normal subjects anatomical shunt is less than 5% of cardiac output.[17] Patients with fibrosing alveolitis have a normal or only slightly increased alveolar arterial oxygen gradient with 100% oxygen,[2 18] and shunt measurements using the labelled microspheres technique[19] and multiple inert gas infusion[20] are not greatly abnormal, suggesting that anatomical shunting is not a major feature of this condition. Further support for this comes from computer modelling of gas exchange in these patients.[21] This suggests that total and effective pulmonary blood flow may be very similar even in patients with pulmonary fibrosis.

The other possible confounding factor is the effect of maldistribution of ventilation. This should be minimised by rebreathing, and indeed none of our patients showed evidence of delayed gas mixing or a slope to the argon plateau. Computer modelling, however, suggests that effective pulmonary blood flow is underestimated in the presence of a large deadspace,[22] which may be present in patients with fibrosing alveolitis. We minimised this effect by discarding the first two breaths[22] when we analysed the data. In any case, most of our patients had an alveolar deadspace of less than 5%, the normal value for our laboratory. The results of the 15 patients with a normal or nearly normal deadspace did not differ significantly from those of the five patients in whom the deadspace was not measured or was found to be high. Furthermore, if the uptake of freon-22 were underestimated significantly owing to maldistribution of ventilation, the uptake of oxygen would be likely to be underestimated by the same mechanism. This was not the case. The differences between the estimates of oxygen uptake by the rebreathing and the open circuit methods reported here are very similar to the differences we found in normal subjects.[11] We believe that our measurements of effective pulmonary blood flow were not significantly affected by any abnormalities of ventilation in these patients.

Patients with fibrosing alveolitis commonly have cor pulmonale at death.[9] At first sight in the patients studied here the effective pulmonary blood flow at rest and during exercise was normal. All but one of the patients showed oxygen desaturation on exertion, however, and oxygen dispatch from the lungs, and thus the supply of oxygen potentially available to the tissues, was reduced. When normal people exercise at altitude they have alveolar and arterial hypoxaemia, but their cardiac output is increased to compensate for it.[23 24] This suggests that the pulmonary blood flow in the patients with fibrosing alveolitis is inappropriately low for the degree of hypoxaemia. Supportive evidence comes from a study in which hydralazine was given to patients with fibrosing alveolitis.[10] The drug resulted in an increase in cardiac output at rest and during exercise, with no change in pulmonary artery pressure. The likeliest explanation is that in patients with fibrosing alveolitis the right ventricle was unable to maintain pulmonary blood flow against a raised resistance.

We found that mixed venous saturation is reduced in the patients at rest and during exercise. The exercise estimates of mixed venous saturation assume that the haemoglobin concentration during exercise is the same as at rest. In normal people at the extremes of exercise haemoglobin rises by about 10%;[25] we are not aware of any studies on normal subjects or patients with fibrosing alveolitis on the effects of low levels of exercise on haemoglobin concentration. In the absence of such data, all the values for mixed venous saturation must be considered as estimates only. The finding of a reduction in mixed venous saturation in the patients in this study are, however, supported by direct measurements made by others.[10]

In animal models a low mixed venous saturation results in pulmonary hypertension.[26] Possible supportive evidence for the importance of mixed venous saturation in the control of pulmonary vascular resistance in man, independently of alveolar oxygen tension, comes from the study of patients having extracorporeal membrane oxygenation.[27] There are reports of substantial falls in resistance shortly after institution of prepulmonary membrane oxygenation, associated with a rise in mixed venous oxygen saturation with alveolar oxygen tension high and constant. Possibly a low mixed venous oxygen saturation contributes to the development of cor pulmonale in these patients. In addition, the level of mixed venous saturation is of prognostic importance in primary pulmonary hypertension,[28] and possibly also in chronic obstructive lung disease.[29] Its meaning in fibrosing alveolitis is not known.

Many factors may limit exercise in these patients.[16 30] They have a high respiratory rate, a small tidal volume, and an increased physiological deadspace; so ventilatory factors may reduce exercise tolerance.[31-33] Pulmonary hypertension is known to worsen with exercise,[5] and this study shows that oxygen dispatch falls below the normal range, oxygen consumption and arteriovenous oxygen content differences are normal, and mixed venous saturation falls below normal. These circulatory factors may be important in limiting exercise tolerance. Those patients with the least severe cardiovascular abnormalities attained a higher oxygen uptake but, as they also tended to have the least severe pulmonary function abnormalities and ventilation during exercise was not measured, no definite conclusions about the specific role of the

pulmonary circulation can be drawn from this.

In summary, in this study of effective pulmonary blood flow, oxygen dispatch from the lungs, pulmonary arteriovenous oxygen content differences, and mixed venous saturation in fibrosing alveolitis, oxygen dispatch and mixed venous saturation were reduced below normal at rest and during exercise, and the latter abnormality may contribute to the development of pulmonary hypertension in this condition. The rebreathing technique is non-invasive, and offers a means of following the response to pulmonary vasodilators, which have been shown in previous studies to increase pulmonary blood flow without changing pulmonary artery pressure.[10]

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