Respiration Physiology, 83 (1991) 155–166
Elsevier

RESP 01739

$D_{L_{CO}}/\dot{Q}$ and diffusion limitation at rest and on exercise in patients with interstitial fibrosis

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(Accepted 9 September 1990)

Abstract. Pulmonary diffusing capacity for carbon monoxide ($D_{L_{CO}}$) and pulmonary capillary blood flow ($\dot{Q}p$) were measured on exercise in patients with a low $D_{L_{CO}}$ with the aim of predicting, from the overall $D_L/\dot{Q}p$ ratio, diffusion limitation for oxygen and relating it to the fall in arterial oxygen saturation actually observed. Five patients with cryptogenic fibrosing alveolitis ($D_{L_{CO}}$ ranging from 20–54% predicted normal) exercised for 5 min at a work load equal to 60% of their maximum (45 to 90 watts). At 5 min (and previously at rest) they rebreathed rapidly for 15 sec from a 1.0 L bag containing helium (He), sulphur hexafluoride (SF6) and freon-22, 30% oxygen in argon and < 1 ppm ^{11}C-labelled carbon monoxide. Pulmonary capillary blood flow ($\dot{Q}p$) and diffusing capacity ($D_{L_{CO}}$) were measured from flow-weighted breath-by-breath concentrations of freon-22 and ^{11}CO, after correction for gas mixing delays (using He and SF6). Oxygen saturation (Sa_{O_2}) (ear oximetry), $\dot{M}_{O_2}$ and $\dot{M}_{CO_2}$ and cardiac frequency were measured. $P_{A_{O_2}}$ (ideal) was derived and mixed venous O_2 saturation and content were calculated (Fick); Pa_{O_2} and $P\bar{v}_{O_2}$ were derived from standard dissociation curves. For comparison, $D_{L_{CO}}$ and $\dot{Q}p$ were measured in a similar fashion in five normal subjects exercising at 60 watts. Mean $D_{L_{CO}}$ in patients with fibrosis was 9.62 (SD 2.88) $ml \cdot min^{-1}$, $mm\ Hg^{-1}$ on exercise and mean $\dot{Q}p$ was 10.48 (SD 1.79) $L \cdot min^{-1}$ giving mean $D_{L_{CO}}/\dot{Q}$ ratios of 0.92 (SD 0.28). At 60 watts mean $D_{L_{CO}}/\dot{Q}p$ in normal subjects was 2.54 (SD 0.3), 2.76-times greater than in patients. Sa_{O_2}% fell in patients by 3–15% on exercise. Predictions of alveolar-end capillary P_{O_2} gradients from these overall $D_L/\dot{Q}$ gradients showed that diffusion limitation accounted for 99% of the alveolar-arterial P_{O_2} gradient on exercise in fibrosing alveolitis. The analysis in the companion paper (Hempleman and Hughes, 1990) suggests that this simple approach overestimates the contribution of diffusion limitation by about 30%.

Animal, man; Cryptogenic fibrosing alveolitis; Diffusing capacity, for CO; Diffusion, and alveolar gas exchange; Exercise, in patients with interstitial lung disease; Fibrosis, interstitial

The relative roles of diffusion limitation versus ventilation-perfusion mismatching as causes of the arterial oxygen desaturation on exercise in patients with interstitial lung disease have been in dispute for many years. Baldwin *et al.* (1949) and Austrian *et al.* (1951) described a marked reduction in arterial oxygen saturation on exercise compared

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to rest in patients with various forms of interstitial lung fibrosis. The syndrome on exercise of (a) hyperventilation (b) worsening hypoxaemia (c) a low oxygen diffusing capacity ($D_{L_{O_2}}$) and (d) pulmonary hypertension was designated 'alveolar-capillary block' because, in their opinion, gas exchange was compromized chiefly by alveolar-end capillary P_{O_2} disequilibrium (Austrian *et al.*, 1951). Others have disputed the importance of diffusion limitation as a cause of hypoxaemia in these patients (Finley *et al.*, 1962). Recent estimates of $\dot{V}_A/\dot{Q}$ inhomogeneity using the multiple inert gas elimination technique (MIGET) have concluded that $\dot{V}_A/\dot{Q}$ contributes by far the largest portion (73–81%) of the alveolar-arterial P_{O_2} gradient on exercise in interstitial lung disease (Wagner *et al.*, 1976; Jernudd-Wilhelmsson *et al.*, 1986; Eklund *et al.*, 1989).

A generally accepted model (see Otis, 1987) for capillary-alveolar P_{O_2} equilibrium proposes the dimensionless ratio $D_L/\beta\dot{Q}$ as the crucial parameter determining the extent of diffusion limitation, D_L being the diffusing capacity for O_2, β being the effective solubility of oxygen in blood (or the tangent to the ODC at any P_{O_2}) and $\dot{Q}$ the pulmonary blood flow. Simultaneous measurements of $D_{L_{O_2}}$ (and $D_{L_{CO}}$) and $\dot{Q}$ have been made in normal subjects at rest and on exercise (Meyer *et al.*, 1981), but not in patients suspected of having 'alveolar-capillary' block.

We have measured $D_{L_{CO}}$ and total pulmonary blood flow ($\dot{Q}p$) simultaneously in five patients with interstitial lung disease who showed arterial oxygen desaturation on exercise. We compared the $D_{L_{CO}}/\dot{Q}$ ratios with five normal subjects exercising at the same workload. In the companion paper (Hempleman and Hughes, 1990) we have analysed these data in terms of overall alveolar-arterial pressure and content difference in an inhomogeneous $\dot{V}_A/\dot{Q}$ model in order to predict the contribution of diffusion limitation to the arterial hypoxaemia on exercise in these patients.

Materials and methods

Clinical data for the five patients with cryptogenic fibrosing alveolitis is given in table 1. A further three patients were studied but data for $D_{L_{CO}}$ and $\dot{Q}p$ on exercise were unsatisfactory or unobtainable. The clinical features in all cases were typical of the condition (clubbing, basal crackles on lung auscultation and reticulonodular shadowing in the mid and lower zones of the chest x-ray). Occupational exposure to heavy metals was noted in two cases, [tungsten grinding (no: 3) aluminium polishing (no: 2)], and the rheumatoid factor was positive in no: 3. The diagnosis was confirmed histologically in 4/5 patients by open lung or transbronchial biopsy (table 1). Four of the patients were on immunosuppressive therapy, typically prednisolone 20 mg daily and azathioprine 50–150 mg daily and/or cyclophosphamide 50–150 mg daily.

Five normal subjects (3 male, 2 female, mean age 35 years) with normal lung function acted as controls for the rebreathing measurements of $\dot{Q}p$ and $D_{L_{CO}}$. The measurements were made at rest and two levels of exercise (60 and 120 watts) in an identical manner to those in the patients. In three subjects, the measurements at rest and exercise

TABLE 1

Symptom duration, diagnostic criteria (OLB, open lung biopsy; Tbx, transbronchial lung biopsy; BAL, bronchoalveolar lavage), current treatment (P, Prednisone; Aza, Azathioprine; Cyclo, Cyclophosphamide), haemoglobin concentration, and spirometry in patients with cryptogenic fibrosing alveolitis.

Patient no.	Age	Symptom duration (months)	Diagnostic criteria	Therapy	Hb g/dl	VC %pred	FEV/VC %
1	48	84	Tbx	P:Aza	20.0	51	83
2	61	120	OLB	P:Aza	14.2	70	67
3	69	216	Tbx	Nil	16.4	98	60
4	69	36	OLB	P:Aza:Cyclo	15.0	48	83
5	62	66	BAL	P:Aza:Cyclo	12.7	62	65

were repeated on a different occasion, making a total of eight observations in each situation. Only group data at rest and 60 watts will be shown for the normal subjects, since the individual results and analysis is the subject of another report (H.A. Jones *et al.*, in preparation).

Routine pulmonary function measurements included total lung capacity (body plethysmography) the forced expired volume in 1 second (FEV_1) and slow vital capacity (bellows spirometer, Vitalograph, U.K.). The diffusing capacity for carbon monoxide (DL_{CO}) was estimated by the single breath method (Ogilvie *et al.*, 1957), and corrected for the current blood haemoglobin concentration (Cotes *et al.*, 1972). Normal values for spirometry and lung volumes were taken from Quanjer (1983) and for DL_{CO} from Bradley *et al.* (1979).

Pulmonary gas exchange was measured at rest and after 5 min pedalling on an electronically braked cycle (Model AM368 Elema-Schönander, Stockholm, Sweden) ergometer. In patients, a work load approximately 60% of their maximum was selected. Ventilation, tidal volume and frequency were measured on the inspiratory side of a low resistance valve box (dead space 65 ml) with a gas meter (Parkinson Cowan CD4 Manchester, U.K.) fitted with a potentiometer and output to a direct writing recorder (Mingograf 81, Elema-Schönander, Stockholm, Sweden). Expired gas was sampled on the distal side of a mixing chamber of 6.0 L capacity. Mixed expired gas was analysed for oxygen, CO_2 and nitrogen by a mass spectrometer (Centronic 200 MGA, Croydon, UK) and oxygen consumption ($\dot{M}_{O_2}$) and CO_2 production ($\dot{M}_{CO_2}$) and R calculated. End-tidal P_{CO_2} was measured with an infrared analyser (Capnograph IV, Gould, Ilford, UK) and arterial P_{CO_2} derived according to the formula of Jones *et al.* (1979):

$$Pa_{CO_2} = 5.5 + 0.9\,P_{ET_{CO_2}} - 0.0021\,V_T\ (ml). \quad (1)$$

The physiological dead space fraction (V_D/V_T) and ideal alveolar P_{O_2} were calculated in the conventional manner using the derived value of Pa_{CO_2}. For the measurement of total pulmonary blood flow ($\dot{Q}p$) and DL_{CO}, subjects were switched into a closed circuit

consisting of a 1 L anaesthetic bag filled with approximately 10% each of helium (He), sulphur hexafluoride (SF_6) and freon-22, with 30% oxygen and 40% argon plus less than 1 ppm of ^{11}C-labelled carbon monoxide. ^{11}CO is a positron (β^+) emitting radioisotope with a 20 min half-life produced by the MRC Cyclotron at Hammersmith Hospital by proton irradiation of nitrogen-14. The rebreathing manœuvre consisted of 15 breaths of approximately 1 L each (subjects being encouraged to empty the bag with each breath) at a rate of 1 Hz starting at end tidal expiration. During rebreathing non-radioactive gas concentrations were monitored by mass spectrometry (Centronic 200 MGA) and ^{11}CO by a β^+-detector (Jones *et al.*, 1982). Flow was measured by a pneumotachograph (Fleisch 2) sited between the bottle enclosing the rebreathing bag and a water-filled spirometer which measured the volume of each breath. All signals were interfaced to a microcomputer (Apple II) either via a pulse counter (β^+-detector) or ADC. Flow-weighted mean bag concentrations of each gas were computed throughout each inspiration from flow signals, all sampled at 50 Hz. Flow and β^+-detector signals were delayed to coincide with the mass spectrometer signals, whose delay (measured on each occasion) varied from 200 to 280 msec.

The following equations were used in the calculations of DL_{CO} and $\dot{Q}p$:

$$DL_{CO}\ (ml \cdot min^{-1} \cdot mm\ Hg^{-1}) = \lambda_{CO} \cdot Vs \cdot 60 \cdot 0.826/713 \tag{2}$$

$$\dot{Q}p\ (L \cdot min^{-1}) = \lambda_{Freon}\ (Vs + \alpha Vtiss)/\alpha \tag{3}$$

$$Vtiss\ (ml) = \frac{Vs}{\alpha} \times \frac{1}{\text{freon intercept}} \times \frac{760}{713} \tag{4}$$

where λ is the rate constant (sec^{-1}) of removal of CO or freon from the rebreathing bag, α is the solubility of freon-22 in blood and tissue (Bonde Petersen *et al.*, 1986) and Vs is the gas volume of the system (bag plus lungs). λ was calculated as the fall in breath by breath concentration relative to the insoluble gases, He and SF_6. A further refinement was introduced, using Graham's law, (diffusivity proportional to $1/MW^{-2}$) by which an interpolation was made from the He and SF_6 values to a hypothetical inert insoluble gas with the same molecular weight as ^{11}CO(MW 27) or freon-22 (MW 86) (Jones, 1984). For example, the data points for an insoluble gas with MW 86 lie $(86^{-2}-4^{-2})/(146^{-2}-4^{-2})$ i.e. 0.724 of the distance between the He and SF6 data points; therefore for each breath, the freon-22 concentration is normalised as:

$$[\text{Freon-22}]/(([SF6] - [He] \cdot 0.724) + [He]). \tag{5}$$

The ^{11}CO concentrations were treated similarly. The freon-22 intercept was calculated with a modification of the method of Sackner *et al.* (1975) as the time at which the normalized CO disappearance curve back-extrapolated to unity *i.e.* the moment at which pulmonary gas uptake was poised to start.

Arterial oxygen saturation was measured with a Biox II oximeter (Ohmeda, Harlow,

UK) from an earlobe previously warmed with vasodilator cream. Readings were not accepted until a good flow pulse was obtained. None of the subjects (normals or fibrotics) were current smokers. Arterial P_{O_2} was read off standard dissociation curves for human blood (Severinghaus, 1966). Arterial oxygen content (Ca_{O_2}) ($ml \cdot L^{-1}$) was computed as ($Sa_{O_2} \cdot Hb(gdl^{-1}) \cdot 13.9$) where 13.9 is the oxygen capacity of Hb ($ml \cdot g^{-1} \cdot 10^{-1}$). Since Ca_{O_2}, $\dot{Q}p$ and $\dot{M}_{O_2}$ were known, $C\bar{v}_{O_2}$ was calculated from the Fick equation and $P\bar{v}_{O_2}$ derived from the dissociation curve (a standard P50 was used). Heart rate was measured from an ECG.

Results

Measurements of spirometry (table 1) and routine pulmonary function were typical for patients with chronic interstitial pulmonary fibrosis. DL_{CO} was reduced (38% predicted: range 23–54) somewhat more than DL_{CO}/VA (76% predicted). Pulmonary gas exchange at rest showed $Pa_{O_2} > 70$ mm Hg in 4/5 patients (mean 74.2 mm Hg SEM 7.2) with mean Sa_{O_2}% 93.2 SEM 1.9, partly due to a high resting minute ventilation (13 $L \cdot min^{-1}$ SD 5.1), and hypocapnia (Pa_{CO_2} 33.7 mm Hg SEM 1.6). Their resting ideal alveolar arterial P_{O_2} gradient was considerably increased at 39.6 mm Hg, SEM 7.4, normal values for this age group being 17.4 SD 8.9 mm Hg at rest (Harris *et al.*, 1974) and 12 mm Hg on exercise (Harris et al., 1976). Arterial oxygen desaturation occurred on exercise (table 2) with a mean fall of Sa_{O_2} from resting values of 7.2% (range 3–15%) and an increase in the alveolar-arterial oxygen gradient from 39.6 to 66 mm Hg, both changes being significant on a paired *t*-test. There was no significant change of end-tidal or arterial P_{CO_2} from rest to exercise. Oxygen consumption ($\dot{M}_{O_2}$) was appropriate for their power output (45–90 watts: mean 66) (table 2), except for patient no. 1 where it was low. Minute ventilation (52.5 $L \cdot min^{-1}$ SEM 8.7) and V_D/V_T

TABLE 2

Pulmonary gas exchange on exercise in patients with fibrosing alveolitis.

Patient no.	$\dot{M}_{O_2}$ $L \cdot min^{-1}$	Sa_{O_2} %	Pa_{O_2} mm Hg	Pa_{CO_2} mm Hg	R	$PA_{O_2}-Pa_{O_2}$ mm Hg	V_D/V_T
1	0.68	71	38	31.7	1.24	84	0.36
2	1.08	89	60	34.8	0.97	53	0.44
3	0.88	92	63	29.9	1.22	63	0.4
4	1.52	91	58	34.2	1.21	64	0.5
5	1.26	87	52	32.5	1.21	71	0.47
Mean	1.08	86	54.2	32.6	1.17	67	0.43
SEM	0.15	3.85	4.43	0.9	0.05	5.13	0.025
P (Vs rest)		0.03	0.016	NS	0.02	0.002	

NS, not significant.

TABLE 3

Total pulmonary blood flow ($\dot{Q}p$) and single breath ($D_{L_{CO}}SB$) rebreathing carbon monoxide diffusing capacity ($D_{L_{CO}}RB$) at rest and on exercise (45–90 watts, heart rate (HR) and mixed venous P_{O_2} on exercise in patients with fibrosing alveolitis and normal subjects ($N = 5$) exercising at 60 watts.

Patient no.	$\dot{Q}p$ rest $L \cdot min^{-1}$	$\dot{Q}p$ ex. $L \cdot min^{-1}$	$D_{L_{CO}}SB$ (rest)	$D_{L_{CO}}RB$(rest) $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$	$D_{L_{CO}}RB$(ex)	HR min^{-1}	$P\bar{v}_{O_2}$ mm Hg
1	6.6	7.8	6.6	6.12	5.76	145	23
2	4.5	9.6	8.4	9.8	13	121	19
3	3.5	12.3	9.6	6.9	9.4	111	32
4	3.95	11.2	13.2	9.9	11.8	140	18
5	3.97	11.5	7.8	7.14	8.16	158	17
Mean	4.5	10.45	9.12	7.97	9.62	135	21.8
SEM	0.55	0.8	1.13	0.8	1.3	8.4	2.75
Normal subjects							
Mean	6.64	12.2	–	25.6	32.0	120	
SEM	0.62	0.86	–	1.6	2.2		

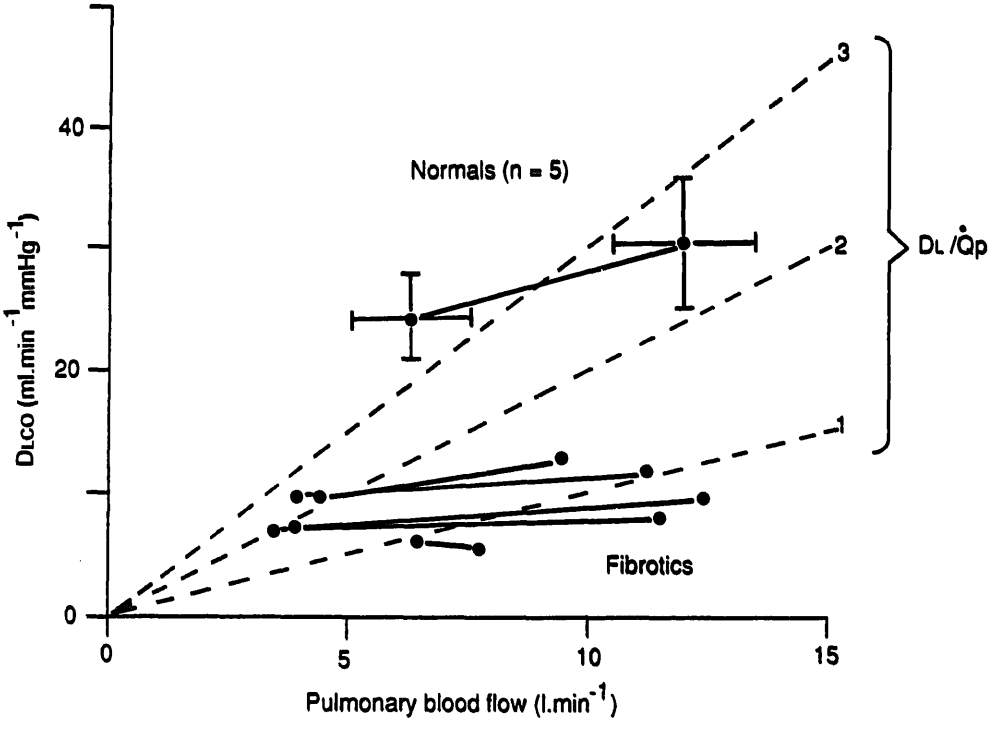

Fig. 1. Carbon monoxide diffusing capacity and pulmonary blood flow, measured simultaneously by rebreathing ^{11}CO and freon-22, for normal subjects at rest and on exercise (60 watts) and patients with fibrosing alveolitis at rest and on exercise (45–90 watts). Isopleths of $D_{L_{CO}}$ ratios are shown.

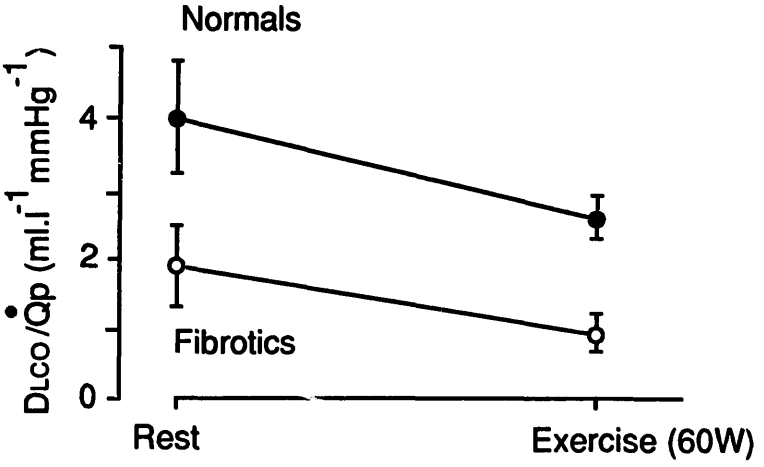

Fig. 2. Mean values (± SD) of $DL_{CO}/\dot{Q}p$ ratios at rest and on exercise in normal subjects and patients with fibrosing alveolitis.

were high on exercise, normal values for this age group at this workload being 23.5 (SD 2.78) $L \cdot min^{-1}$ and <0.2 (Jones, 1988) respectively.

Measurements of pulmonary blood flow and DL_{CO} (single breath and rebreathing techniques) are shown in table 3 and the relationship between them is plotted for the patients individually in fig. 1, contrasted with the mean values (± SD) in normal subjects. The low value of DL_{CO} in the patients and failure to rise much on exercise is evident. The *percentage* increase in DL_{CO} from rest to exercise was not significantly ($P = 0.55$) different (24.4% increase in normal subjects, 19.2% increase in patients). The $DL_{CO}/\dot{Q}$ ratios for both groups are shown in fig. 2. $DL_{CO}/\dot{Q}$ in normal subjects is 3.86 (SD 0.84) at rest, falling to 2.54 (SD 0.3) at 60 watts exercise. In patients, the group mean value at rest was 1.88 (SD 0.59) falling to 0.92 (SD 0.28) on exercise. For both groups the change in $DL_{CO}/\dot{Q}$ ratio from rest to exercise was significant ($P = 0.012$, paired t). The lowest values of exercise $DL_{CO}/\dot{Q}$ were in patients no. 2 (0.74) and no. 3 (0.76). Gas mixing efficiency was assessed during rebreathing as the number of breaths (at a fixed frequency of 60 Hz and fixed VT of 1.0 L) required for 99% helium equilibration ($n = 99$) (Jones *et al.*, 1986a). N99 averaged 8.0 (SD 2.1) at rest and 7.5 (SD 1.8) on exercise for the patients with fibrosis and 3.7 (SD 0.3) and 4.5 (SD 1.5) respectively in normal subjects.

In 3 normal subjects where repeat measurements of DL_{CO} and $\dot{Q}p$ were made on different days, the difference between two measurements as a percentage of the mean value of both never exceeded 20%. Combining the rest and exercise measurements ($n = 6$), the mean difference for DL_{CO} was 10.6%, for $\dot{Q}p$ 8.1% and for the $DL/\dot{Q}$ ratio 6.45%.

Discussion

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DL_{CO} and $\dot{Q}p$. The β^+ scintillation detector for ^{11}CO, the rebreathing circuit and breath-by-breath data for He, SF6 and ^{11}CO have been previously described (Jones

et al., 1982). The mean values for $D_{L_{CO}}$ in nine normal subjects in that paper (25.8 ml · min^{-1} · mm Hg^{-1}) is similar to the mean values for normals at rest in this report (table 3). In the patients the mean difference between $D_{L_{CO}}$ rebreathing at rest using ^{11}CO (table 3) and the standard single breath $D_{L_{CO}}$ was 17.2% (using $D_{L_{CO}}$ (SB) as the standard); in patients 3 and 4, who were both rather overweight, the $D_{L_{CO}}$ (SB) was closer to the exercise $D_{L_{CO}}$ (RB) (2 and 11% respectively), possibly due to shut down of dependent alveolar units during rebreathing at rest. There was no significant difference between $D_{L_{CO}}$ SB at rest and on exercise. The measurement of total pulmonary blood flow using freon-22 and inert gas normalization (with He and SF6) to MW 86 has been compared with simultaneous measurements of cardiac output using indocyanin green (Jones *et al.*, 1986b). In 63 measurements made in 5 anaesthetized dogs the mean difference between the two methods was 0.345 SD 0.25 L · min^{-1}; exclusion of 12 points where gas mixing was extremely slow (n = 99 for He > 15 breaths) reduced the mean difference to 0.052 SD 0.22 L · min^{-1}. The mean n99 for helium in patients with fibrosing alveolitis was only 7.5 (on exercise).

Arterial oxygen saturation and blood gases. Particular care was taken to get a good flow pulse signal on the Biox oximeter; even so the accuracy of pulse oximetry is only ±2% (Nickerson *et al.*, 1988). Arterial blood gases were not sampled (the central purpose of the investigation being the measurements of $D_{L_{CO}}$ and $\dot{Q}$) and we recognise the uncertainty of the estimation of Pa_{O_2} from transcutaneous Sa_{O_2} using a standard ODC, especially when Sa_{O_2} exceeds 90%. Precise measurements of Pa_{O_2} are not crucial to the message of this paper, but in the analysis of pulmonary gas exchange undertaken in the companion paper (Hempleman and Hughes, 1990) a deviation of ±2% of Sa_{O_2} from nominal has been included in the calculations. The computation of Pa_{CO_2} using the formula of Jones *et al.* (1979) is only valid in the absence of airflow obstruction. FEV_1/VC ratios were slightly reduced in patients 3 and 5 (table 1) but their gas mixing efficiency (assessed by n99 for He) did not differ from the other subjects.

TABLE 4

Recent studies of pulmonary gas exchange on exercise in patients with interstitial lung fibrosis (mean values).

Author	*N*	$D_{L_{CO}}$(rest) (% pred)	$\dot{M}_{O_2}$ L · min^{-1}	$\dot{Q}$ L · min^{-1}	Pa_{O_2} mm Hg	A-aP_{O_2} mm Hg	$P\bar{v}_{O_2}$ mm Hg	$D_{L_{O_2}}/\beta\dot{Q}$
Wagner *et al.* (1976)	8	37	0.69	8.55	50.4	-	28.3	-
Jernudd-Wilhelmsson *et al.* (1986)	10	35.7	0.72	8.39	48.9	52.5	-	1.7*
Agusti *et al.* (1987)	15	52	0.91	11.5	59	49	28.6	1.5*
This study	5	37.6	1.08	10.45	54.2	67	21.8	0.36**

* From MIGET analysis (see text). ** From $D_{L_{CO}}/\dot{Q}$ measurements.

Pulmonary gas exchange. Recent studies in patients with interstitial lung fibrosis show quite consistent results (table 4). The patients in this report and that of Agusti *et al.* (1987) were doing more work (higher $\dot{M}_{O_2}$ and $\dot{Q}$). The lower Pa_{O_2} and $P\bar{v}_{O_2}$ and wider A-aP_{O_2} in this study may reflect the lower levels of DL_{CO} compared to Agusti *et al.* (1987).

$DL_{CO}/\dot{Q}$ ratios. From regression equations in the literature (Rampulla *et al.*, 1976), the increase in DL_{CO} for a three-fold increase in cardiac output (from rest to exercise) ranged from 1.4 to 2.0, implying a fall in the $DL_{CO}/\dot{Q}$ ratio in normal subjects on moderate exercise of 33–54%. Meyer *et al.* (1981) reported simultaneous measurements of DL_{CO} and $\dot{Q}$ by rebreathing in six normal subjects. The $DL_{CO}/\dot{Q}$ ratio was 4.5 (rest) falling to 2.75 at 75 watts (40% decrease). The values in this study (fig. 2) were virtually identical to those of Meyer *et al.* (1981) showing a 36% decrease in $DL_{CO}/\dot{Q}$ at 60 watts. There are, surprisingly, no reported measurements of $DL_{CO}/\dot{Q}$ on exercise in patients with fibrosing alveolitis.

Interpretation of $DL_{CO}/\dot{Q}$ ratios. Alveolar-end capillary P_{O_2} equilibration is dependent on the diffusion-perfusion ratio, according to the following exponential diffusion equation for oxygen (Piiper and Scheid, 1981):

$$\frac{P_A - Pc'}{P_A - P\bar{v}} = e^{-DL/(\beta\dot{Q})} \quad (6)$$

This equation predicts that $(P_A - Pc')/(P_A - P\bar{v})$ for oxygen will be 0.006, 0.05, 0.13 and 0.37 at $DL/\beta\dot{Q}$ values of 5, 3, 2 and 1. Therefore a 13% disequilibrium exists at a $DL/\beta\dot{Q}$ ratio of 2. If $P_A - P\bar{v}$ for oxygen were (on exercise) 80 mm Hg, a 10 mm Hg $P_A - Pc'$ gradient would ensue at this level of $D/\beta\dot{Q}$.

There is no simple relationship between $DL_{O_2}/\beta_{O_2} \cdot \dot{Q}$ and $DL_{CO}/\dot{Q}$. Many comparisons of DL_{O_2} and DL_{CO} have been made in 'normal' lungs (animals and humans) with widely diverging results (reviewed by Haab, 1981). The discrepancies can be explained by the relatively greater sensitivity of DL_{O_2} to uneven distribution of $\dot{V}_A/D$ and $\dot{V}_A/\dot{Q}$. If allowance is made for this heterogeneity, a DL_{O_2}/DL_{CO} ratio of 1.2 is generally found (Haab and Geiser, 1986). The most convincing results in humans also find the ratio around 1.2 (on exercise 1.18–1.21) (Meyer *et al.*, 1981). In these experiments normal subjects rebreathed, at rest and on exercise, a hypoxic mixture combining stable isotopes of oxygen and CO (^{18}O and $C^{18}O$) and C_2H_2 (for $\dot{Q}$ measurement). It is a moot point whether this ratio holds in normoxia and in fibrotic lungs; in the accompanying paper (Hempleman and Hughes, 1990) the ratio of DL_{O_2} (calculated) to DL_{CO} (measured) on exercise in the five interstitial fibrous patients was 1.49 (range 1.2–1.81).

The next problem is the measurement of β_{O_2}, the slope of the oxygen dissociation curve (ODC) at any P_{O_2}. Since the ODC is alinear (except in severe alveolar hypoxia) and interacts with P_{CO_2} and pH, β_{O_2} is continuously changing from the venous to the

arterial end of the capillary bed. Therefore, β_{O_2} cannot be measured by experiment unless severe alveolar hypoxia is introduced. This can be done in normal subjects (Piiper and Scheid, 1981) but not in patients with alveolar-capillary block. Hempleman and Gray (1988) have calculated β_{O_2} at different distances along the capillary, at varying alveolar P_{O_2} and $\dot{V}A/\dot{Q}$ ratios. β for O_2 starts at 5–6 $ml \cdot L^{-1} \cdot mm\ Hg^{-1}$ at the venous end of the capillary and falls progressively towards the arterial end. The higher the levels of $\dot{V}A/\dot{Q}$ and PA_{O_2} the sharper the fall with distance along the capillary. Following Hempleman and Hughes (1990), we have assumed a linear ODC and calculated β for O_2 as the slope connecting the arterial and mixed venous points. β_{O_2} at rest in the patients averaged 1.76 $ml \cdot L^{-1} \cdot mm\ Hg^{-1}$ (range 0.91–2.45) increasing to 3.4 (range 2.32–5.56) on exercise. The mean $DL_{O_2}/\beta\dot{Q}$ ratio for patients (assuming $DL_{O_2} = DL_{CO} \times 1.2$) was 1.48 (range 0.96–2.87) at rest and 0.36 (range 0.16–0.6) on exercise. The negative exponential of DL/β_{O_2} (*i.e.* $PA - Pc'/PA - P\bar{v}$) averaged 0.28 (range 0.055–0.5) at rest and 0.67 (range 0.4–0.85) on exercise. Since mean $PA - P\bar{v}$ on exercise in the patients with fibrosing alveolitis was 99.4 mm Hg, $PA - Pc'$ would have been 65 mm Hg (range 53–84). Thus 99% of the $PA - Pa$ gradient on exercise (65/66: see table 2) would seem to be due to alveolar capillary disequilibrium. Insofar as the effects of $\dot{V}A/D$ and $\dot{V}A/\dot{Q}$ inequalities and θ_{O_2}/θ_{CO} uncertainties on DL_{O_2} estimation have been ignored, and a linear ODC assumed, this must be regarded as a worst case estimate (see Hempleman and Hughes, 1990). The corresponding calculations at rest predict 55% (range 32–78) of the $PA - Pc'$ gradient as caused by diffusion limitation. This seems unlikely, and this analysis is criticized in the companion paper.

A different method of estimating $DL/\beta\dot{Q}$ ratios stems from measurement of $\dot{V}A/\dot{Q}$ distribution using the multiple inert gas infusion technique MIGET (Wagner *et al.*, 1986). The difference between the Pa_{O_2} predicted by the inert gases, which are not diffusion limited, and the Pa_{O_2} actually measured is an index of alveolar-capillary disequilibrium i.e. $PA - Pc'$ for oxygen. If $(PA - P\bar{v})_{O_2}$ is known $\varepsilon^{-DL/\beta\dot{Q}}$ can be calculated. In two recent studies in which MIGET analysis was performed on exercise in patients with interstitial lung disease, we calculated a mean $DL/\beta\dot{Q}$ ratio of 1.7 (Jernudd-Wilhelmsson *et al.*, 1986) in one series, and 1.5 (Agusti *et al.*, 1987) in the other (table 4). A $DL/\beta\dot{Q}$ of 1.5 predicts 22% alveolar-capillary disequilibrium or a $PA - Pc'$ of 21.6 mm Hg (33% of the A-a gradient) when applied to our data. The difference between the $DL/\beta\dot{Q}$ ratios calculated from MIGET analysis compared with predictions from $DL_{CO}/\dot{Q}$ ratios (table 4) is discussed in the companion paper (Hempleman and Hughes, 1990) where it appears, from a more critical analysis, that in normoxia the MIGET technique *underestimates* and $DL_{O_2}/\beta\dot{Q}$ analysis *overestimates* the contribution of diffusion limitation on exercise.

References

Agusti, A.G.N., J. Roca, R. Rodriguez-Roisin, J. Gea, A. Xaubet and P.P. Wagner (1987). Role of O_2 diffusion limitation in idiopathic pulmonary fibrosis. *Am. Rev. Respir. Dis.* 135: A307.

Austrian, R., J.H. McClement, A.D. Renzetti, K.W. Donald, R.L. Riley and A. Cournand (1951). Clinical and physiological features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion. *Am. J. Med.* 11: 667–685.

Baldwin, E., A. Cournand and D.W. Richards (1949). Pulmonary insufficiency. II. A study of thirty nine cases of pulmonary fibrosis. *Medicine* 28: 1–25.

Bonde Petersen, F., P. Norsk and Y. Suzuki (1980). A comparison between freon and acetylene rebreathing for measuring cardiac output. *Aviat. Space Environ. Med.* 51: 1214–1221.

Bradley, J., C. Bye, S.P. Hayden and D.T.D. Hughes (1979). Normal values of transfer factor and transfer coefficient in healthy males and females. *Respiration* 38: 221–226.

Cotes, J.E., J.M. Dabbs, P.C. Elwood, A.M. Hall, A. McDonald and M.J. Saunders (1972). Iron-deficiency anaemia: its effect on transfer factor for the lung (diffusing capacity) and ventilation and cardiac frequency during sub-maximal exercise. *Clin. Sci.* 42: 325–335.

Eklund, A., L. Broman, M. Broman and A. Holmgren (1989). $\dot{V}/\dot{Q}$ and alveolar gas exchange in pulmonary sarcoidosis. *Eur. Respir. J.* 2: 135–144.

Finley, T.N., E.W. Swenson and J.H. Comroe (1962). The cause of arterial hypoxemia at rest in patients with 'alveolar-capillary block syndrome'. *J. Clin. Invest.* 41: 618–622.

Haab, P. (1981). Estimation of diffusion limitation in inhomogeneous lung. In: Gas Exchange Function of Normal and Diseased Lungs. Prog. Resp. Res. Vol. 16, edited by J. Piiper and P. Scheid. Karger, Basel, pp. 214–219.

Haab, P. and J. Geiser (1986). Relationship between O_2 and CO diffusing capacities. In: Pulmonary Gas Exchange. Prog. Resp. Res. Vol. 21, edited by M. Meyer and J. Piiper. Karger, Basel, pp. 56–59.

Harris, E.A., A.M. Kenyon, H.D. Nisbet, E.R. Seelye and R.M.L. Whitlock (1974). The normal alveolar-arterial oxygen-tension gradient in man. *Clin. Sci. Mol. Med.* 46: 89–104.

Harris, E.A., E.R. Seelye and R.M.L. Whitlock (1976). Gas exchange during exercise in healthy people. II Venous admixture. *Clin. Sci. Mol. Med.* 51: 335–344.

Hempleman, S.C. and A.T. Gray (1988). Estimating steady state DL_{O_2} with nonlinear dissociation curves and $\dot{V}A/\dot{Q}$ inequality. *Respir. Physiol.* 73: 279–288.

Hempleman, S.C. and J.M.B. Hughes (1990). Analysis of pulmonary gas exchange on exercise in patients with interstitial lung fibrosis. (Companion paper) *Respir. Physiol.* 83: 167–178.

Jernudd-Wilhelmsson, Y., Y. Hornblad and G. Hedenstierna (1986). Ventilation-perfusion relationships in interstitial lung disease. *Eur. J. Respir. Dis.* 68: 39–49.

Jones, H.A., J.C. Clark, E.E. Davies, R.E. Forster and J.M.B. Hughes (1982). Rate of uptake of carbon monoxide at different inspired concentrations in humans. *J. Appl. Physiol. Respir. Environ. Exerc. Physiol.* 52: 109–113.

Jones, H.A. (1984). A rebreathing method for the study of pulmonary gas mixing and transfer. Ph. D. Thesis. University of London.

Jones, H.A., E.E. Davies and J.M.B. Hughes (1986a). Modification of pulmonary gas mixing by postural changes. *J. Appl. Physiol.* 61: 75–80.

Jones, H.A., S. Lakshminarayan, J.M. Becket and J.M.B. Hughes (1986b). Cardiac output: comparison of soluble gas rebreathing and dye dilution in anaesthetized dogs. *Clin. Sci.* 72 (Suppl. 16) 388.

Jones, N.L., P.G. Robertson and J.W. Kane (1979). Estimation of arterial P_{CO_2} in exercising adults. *J. Appl. Physiol.* 47: 954–960.

Jones, N.L. (1988). Clinical exercise testing. 3rd Edition. W.B. Saunders, pp. 299–307.

Meyer, M., P. Scheid, G. Riepl, H.J. Wagner and J. Piiper (1981). Pulmonary diffusing capacities for O_2 and CO measured by a rebreathing technique. *J. Appl. Physiol.* 51: 1643–1650.

Nickerson, B.G., C. Sarkisian and K. Tremper (1988). Bias and precision of pulse oximeters and arterial oximeters. *Chest* 93: 515–517.

Ogilvie, C.M., R.E. Forster, W.S. Blakemore and J.W. Morton (1957). A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J. Clin. Invest.* 36: 1–17.

Otis, A.B. (1987). The Respiratory System. In: Handbook of Physiology. Section 3, Vol. iv. Gas Exchange, edited by L.E. Farhi and S.M. Tenney. Bethesda, Am. Physiol. Soc. pp. 1–12.

Piiper, J. and P. Scheid (1981). Model for capillary-alveolar equilibration with special reference to O_2 uptake in hypoxia. *Respir. Physiol.* 46: 193–208.

Quanjer, Ph. H. (1983). Standardized lung function testing. Report of working party for European Community for Coal and Steel. *Bull. Europ. Physiopath. Respir.* 19 (Suppl. 5) 7–10.

Rampulla, C., C. Marconi, G. Beulcke and S. Amaducci (1976). Correlation between lung transfer factor ventilation and cardiac output during exercise. *Respiration* 33: 405–415.

Sackner, M. A., D. Greeneltch, M. S. Heiman, S. Epstein and N. Atkins (1975). Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume, and cardiac output measured by a rebreathing technique. *Am. Rev. Respir. Dis.* 111: 157–165.

Severinghaus, J. W. (1966). Blood gas calculator. *J. Appl. Physiol.* 21: 1108–1116.

Wagner, P. D., D. R. Dantzker, R. Dueck, J. L. Depolo, K. Wasserman and J. B. West (1976). Distribution of ventilation-perfusion ratios in patients with interstitial lung disease. *Chest* 69: 256–257.

Wagner, P. D., G. E. Gale, R. E. Moon, J. R. Torre-Bueno, B. W. Stolp and H. A. Saltzman (1986). Pulmonary gas exchange in humans exercising at sea level and simulated altitude. *J. Appl. Physiol.* 61: 260–270.