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Estimating exercise DL_{O_2} and diffusion limitation in patients with interstitial fibrosis

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Abstract. Inert gas elimination studies in interstitial fibrosis ascribe all of the resting and most (58–83%) of the exercise (A-a)P_{O_2} difference to ventilation-perfusion inequality. The previous paper (Hughes, J.M.B., D.N.A. Lockwood, H.A. Jones and R.J. Clark, *Respir. Physiol.*, 1990) suggests from estimates of global $DL_{O_2}/\dot{Q}\beta$ ratios a larger role for diffusion limitation on exercise. Gas exchange data from that paper was analyzed at rest and on exercise for five patients with interstitial fibrosis. Hypoxemia at rest was attributed to $\dot{V}_A/\dot{Q}$ inequality which was quantified using a log-normal lung model. DL_{O_2} was calculated by Bohr integration. The base 10 LogSD$\dot{Q}$ at rest averaged 0.5 ± 0.1 (SEM). On the assumption that $\dot{V}_A/\dot{Q}$ inequality remained unchanged on exercise, DL_{O_2} (exercise) was estimated to be 14.3 ± 1.9 ml · min^{-1} · Torr^{-1}. At that level of DL_{O_2}, diffusion limitation accounted for 36% ± 8(SEM)% of the total (A-a)P_{O_2} difference using the log-normal $\dot{V}_A/\dot{Q}$ model. But estimates of $DL_{O_2}/\dot{Q}\beta$ assuming a homogeneous lung, ascribed 96% of the (A-a)P_{O_2} gradient on exercise to diffusion limitation. This discrepancy was shown to be related to the shape of the oxygen equilibrium curve and high alveolar P_{O_2} values. On the other hand, analysis in terms of oxygen contents showed that 68 ± 5% of the (A-a) *content* difference was accounted for by diffusion limitation. This differs substantially from estimates based on partial pressure alone.

Alveolar-arterial P_{O_2} difference; Diffusing capacity, for O_2; Diffusion, and alveolar gas exchange; Hypoxemia, at rest, on exercise

In a companion paper Hughes and coworkers (1990) noted that two different methods for assessing the relative importance of diffusion limitation in exercising fibrotic patients give dissimilar results. The multiple inert gas elimination technique (MIGET) consistently finds $\dot{V}_A/\dot{Q}$ inequality responsible for most of the (A-a)P_{O_2} in these patients. In contrast, analysis of the diffusive to perfusive conduction ratios $DL_{O_2}/\dot{Q}\beta_{O_2}$) indicates that diffusion limitation predominates. In this paper we propose an explanation for this disagreement. We used data from Hughes *et al.* (1990) and a log-normal $\dot{V}_A/\dot{Q}$ model to investigate the partitioning of (A-a)O_2 difference into diffusion limitation and

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$\dot{V}_A/\dot{Q}$ heterogeneity effects. We also used a Bohr integration technique to estimate DL_{O_2}, the perfusive to diffusive conductance ratio, and the diffusion limitation factor.

Methods

The data of Hughes *et al.* (1990) are summarized in table 1. They measured total pulmonary blood flow ($\dot{Q}T$), $\dot{V}T$, fR, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, transcutaneous Sa_{O_2}, $P_{E'CO_2}$, Hb, and DL_{CO} during rest and exercise in 5 patients with fibrotic lung disease. $\dot{Q}T$ and DL_{CO} were measured with a rebreathing technique. From this data we estimated Pa_{CO_2} from $P_{E'CO_2}$, and Pa_{O_2} from Sa_{O_2}. Ca_{O_2} and Ca_{CO_2} were calculated from Pa_{O_2} and Pa_{CO_2}. $C\bar{v}_{O_2}$ and $C\bar{v}_{CO_2}$ were calculated by the Fick Principle, and converted to $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ using Kelman's (1966, 1967) algorithms.

The mathematical model. We added diffusion to the $\dot{V}_A/\dot{Q}$ model of West and Wagner (1977) as previously described (Hempleman and Gray, 1988). Briefly, O_2 and CO_2 carriage and interactions in the blood were modelled with Kelman's routines. Alveolar-capillary O_2 and CO_2 diffusion was modelled using a forward Bohr integration procedure, with diffusing capacity distributed among $\dot{V}_A/\dot{Q}$ compartments in proportion to blood flow. Ten $\dot{V}_A/\dot{Q}$ compartments were used to simulate ventilation-perfusion distribution effects. Blood flow was distributed in a Gaussian fashion among compartments with logarithmically spaced $\dot{V}_A/\dot{Q}$ ratios. The amount of $\dot{V}_A/\dot{Q}$ inequality modelled was quantitated by the base 10 logarithmic standard deviation of the blood flow distribution, 'LogSDQ' (West and Wagner, 1977). The analysis was like that of Hempleman and Gray (1988), differing in that the amount of $\dot{V}_A/\dot{Q}$ inequality was estimated from resting hypoxemia, rather than measured by inert gas retention and excretion.

To model resting conditions for each patient, DL_{O_2} was set to infinity (*i.e.* complete compartmental blood-gas equilibration), and the LogSDQ of the $\dot{V}_A/\dot{Q}$ distribution was increased from zero until modelled Pa_{O_2} agreed with observed Pa_{O_2} (± 0.3 Torr). $\dot{V}A$ was adjusted to maintain $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, R and Pa_{CO_2} at observed values.

To model exercising conditions for each patient, the LogSDQ was assumed unchanged from the resting value. DL_{O_2} was decreased from infinity until modelled Pa_{O_2} agreed with observed Pa_{O_2} (± 0.3 Torr). VA was adjusted to maintain $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, R and Pa_{CO_2} at observed values.

The technique for calculating exercise DL_{O_2} in the $\dot{V}_A/\dot{Q}$ model is illustrated graphically in fig. 1 using data from patient 3. LogSDQ levels of 0.0 (homogeneous), 0.45 (the value calculated from resting data), and 0.60 are shown for comparison. As DL_{O_2} is increased from zero, modelled Pa_{O_2} and Ca_{O_2} values increase from the mixed venous point. Initially the different LogSDQ curves overlie one another, showing that oxygen exchange is predominantly affected by diffusing capacity rather than $\dot{V}_A/\dot{Q}$ inequality at very low DL_{O_2} values. The LogSDQ curves diverge as DL_{O_2} is increased further, and the interaction between $\dot{V}_A/\dot{Q}$ inequality and DL_{O_2} can be clearly seen. At high values

TABLE 1

From Hughes *et al.* (1990)									Calculated							
Patient	Condition	$D_{L_{CO}}$ ml/min/Torr	Hb g%	$\dot{V}_{O_2}$ L/m	$\dot{Q}$ L/m	R	Pa_{CO_2} Torr	Pa_{O_2} Torr	Ca_{O_2} vol%	Ca_{CO_2} vol%	Pv_{O_2} Torr	Pv_{CO_2} Torr	Cv_{O_2} vol%	Cv_{CO_2} vol%	PA_{O_2} Torr	CA_{O_2} vol%
1	Rest	6.1	20.0	0.12	6.6	0.94	33.0	54	25.0	41.2	46.2	35.9	23.2	43.0		
	Exercise	5.8	20.0	0.68	7.8	1.24	31.7	38	21.0	42.0	26.5	55.1	12.4	52.7	124	27.9
2	Rest	9.8	14.2	0.26	4.5	0.97	37.5	79	19.5	46.3	39.4	49.0	13.8	51.9		
	Exercise	13.0	14.2	1.08	9.6	0.97	39.5	60	18.1	47.5	23.3	62.9	6.9	58.3	113	19.7
3	Rest	6.9	16.4	0.46	3.5	1.00	29.0	74	22.1	41.4	24.2	54.8	9.0	54.6		
	Exercise	9.4	16.4	0.88	12.3	1.20	31.0	63	21.5	42.5	35.2	49.0	14.4	51.0	126	22.9
4	Rest	9.9	15.0	0.24	4.0	0.92	37.0	72	20.0	45.8	37.3	47.9	14.0	51.3		
	Exercise	11.8	15.0	1.52	11.2	1.21	34.0	58	19.2	44.9	20.6	72.9	5.6	61.3	127	21.0
5	Rest	7.1	12.7	0.36	4.0	1.00	32.0	72	17.0	45.2	26.2	49.6	8.0	54.3		
	Exercise	8.2	12.7	1.26	11.5	1.20	32.0	52	15.8	45.6	19.8	60.7	4.9	58.7	126	17.8

of DL_{O_2}, diffusion equilibration is complete in all $\dot{V}A/\dot{Q}$ compartments, and differences in Pa_{O_2} and Ca_{O_2} calculated for different LogSDQ values are due only to $\dot{V}A/\dot{Q}$ inequality.

The horizontal dotted lines in fig. 1 mark the Pa_{O_2} and Ca_{O_2} values observed during exercise. In each panel the intersection of the LogSDQ = 0.45 curve (the LogSDQ value calculated at rest) and the dotted line gives the DL_{O_2} estimate. In this exercising patient, and in each of the other four studied, the estimated LogSDQ and DL_{O_2} values were in the region where both diffusing capacity and $\dot{V}A/\dot{Q}$ inequality affect overall gas exchange.

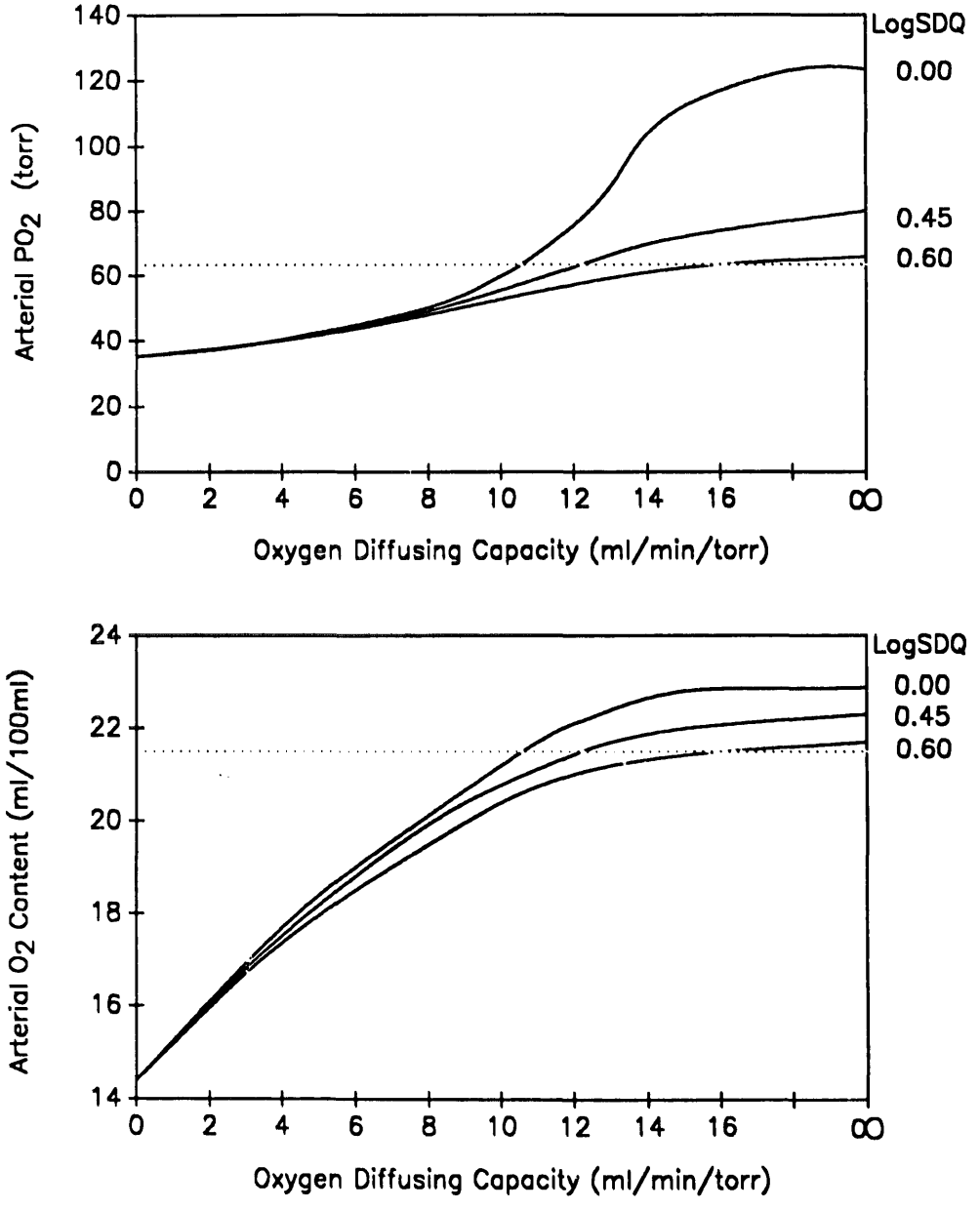

Fig. 1. Calculated exercise Pa_{O_2} and Ca_{O_2} values for subject 3 as a function of DL_{O_2} at different levels of $\dot{V}A/\dot{Q}$ inequality (solid lines). Dotted line marks observed arterial blood values.

Partition of the (A-a)O_2 difference into $\dot{V}_A/\dot{Q}$ inequality and diffusion limitation effects. The difference between calculated ideal alveolar P_{O_2} and measured arterial P_{O_2} has been used to estimate overall impairment of pulmonary O_2 exchange (Cotes, 1965). To understand the mechanism of the difference, the (A-a)P_{O_2} may be subdivided further into a $\dot{V}_A/\dot{Q}$ inequality component (or alternatively, shunt) and a diffusion limitation component. This is commonly done in studies using MIGET, the multiple inert gas elimination technique (Wagner, 1976; Torre-Bueno *et al.*, 1985; Hammond *et al.*, 1986). The (A-a)P_{O_2} is partitioned as follows:

$$(P_{A_{O_2}} - Pa_{O_2}) = (P_{A_{O_2}} - Pa_{O_2}[\dot{V}_A/\dot{Q}]) + (Pa_{O_2}[\dot{V}_A/\dot{Q}] - Pa_{O_2}) \quad (1)$$

total | $\dot{V}_A/\dot{Q}$ inequality component | diffusion limitation component.

$P_{A_{O_2}}$ is the calculated ideal alveolar P_{O_2}. Pa_{O_2} is the measured arterial P_{O_2}. $Pa_{O_2}[V_A/Q]$ is an 'as if' arterial P_{O_2} predicted from the given amount of $\dot{V}_A/\dot{Q}$ inequality but with no diffusion impairment.

$\dot{V}_A/\dot{Q}$ inequality and diffusion impairment both result in Pa_{O_2} values less than the ideal alveolar $P_{A_{O_2}}$. This reduction of arterial Pa_{O_2} may be thought of in terms of a reduction of $\dot{V}_{O_2}$ compared to ideal conditions (*i.e.* the ideal $\dot{V}_{O_2}$ that would be achieved for the *same conditions* if the lung had no $\dot{V}_A/\dot{Q}$ inequality, and complete diffusion equilibration). Unfortunately, the partition of (A-a)P_{O_2} is not a quantitative index of the effect of $\dot{V}_A/\dot{Q}$ and diffusion limitations on $\dot{V}_{O_2}$. The reason for this is the non-linear relationship between blood O_2 tension and blood O_2 content described by the blood oxygen equilibration curve (OEC). To investigate the effect of diffusion and $\dot{V}_A/\dot{Q}$ limitations on $\dot{V}_{O_2}$, we expressed eq. (1) in terms of blood oxygen content. Kelman routines were used to calculate blood O_2 contents from ideal alveolar P_{O_2}, $Pa_{O_2}[V_A/Q]$, and Pa_{O_2}. These were called Ca_{O_2}, $Ca_{O_2}[V_A/Q]$ and Ca_{O_2}, respectively. Ca_{O_2} reflects the maximum possible arterial O_2 content (and thus $\dot{V}_{O_2}$) and corresponds to the condition of no $\dot{V}_A/\dot{Q}$ mismatch or diffusion impairment. The content version of eq. (1) is:

$$(Ca_{O_2} - Ca_{O_2}) = (Ca_{O_2} - Ca_{O_2}[\dot{V}_A/\dot{Q}]) + (Ca_{O_2}[\dot{V}_A/\dot{Q}] - Ca_{O_2}) \quad (2)$$

total | $\dot{V}_A/\dot{Q}$ inequality component | diffusion limitation component.

Estimates of diffusion limitation from $D/\dot{Q}\beta$ ratios. The methods just described estimate the relative importance of $\dot{V}_A/\dot{Q}$ inequality and diffusion limitation effects on the (A-a) O_2 difference. Another way to estimate the importance of diffusion limitation is to consider its effect on the overall ($A-\bar{v}$) O_2 difference across the lung (Hughes *et al.*, 1990). The method of Scheid and Piiper (1989) was used to calculate the diffusion limitation factor, L_{Diff}, from the diffusive-perfusive conductance ratio: $DL_{O_2}/\dot{Q}\beta_{O_2}$. We used our calculated DL_{O_2} values and the measured values of pulmonary blood flow. A linear O_2 dissociation curve (slope = β_{O_2}) connecting the arterial and venous points was

explicitly assumed:

$$L_{Diff} = \exp(-DL_{O_2}/\dot{Q}\beta_{O_2}). \quad (3)$$

L_{Diff} calculated from the $DL_{O_2}/\dot{Q}\beta_{O_2}$ ratio can then be used to estimate the effects of diffusion limitation on the (A-v)O_2 difference across the lung:

$$\text{where } L_{Diff} = \frac{(PA_{O_2} - Pc'_{O_2})}{(PA_{O_2} - P\bar{v}_{O_2})}. \quad (4)$$

An L_{Diff} value of 1.0 indicates complete diffusion limitation, whereas an L_{Diff} value of 0.0 indicates absence of diffusion limitation.

Results

Calculated log-normal $\dot{V}_A/\dot{Q}$ inequality from resting data. All five patients were hypoxemic at rest (table 1). Explaining this hypoxemia in terms of $\dot{V}_A/\dot{Q}$ inequality required an average base 10 LogSDQ of 0.5 (table 2). This represents more $\dot{V}_A/\dot{Q}$ inequality than is normally seen in healthy subjects, but is consistent with previous studies of fibrotic patients (Wagner, 1976; Jernudd-Wilhelmsson *et al.*, 1986; Agusti *et al.*, 1987).

Calculated exercise DL_{O_2} values. All five patients became more hypoxemic with exercise. The $\dot{V}_A/\dot{Q}$ dispersion calculated at rest could not account for the observed amount of hypoxemia in any of the patients (fig. 2). Using the compartmental Bohr integration

TABLE 2

Subject	Log-normal $\dot{V}_A/\dot{Q}$ model					
	Exercise DL_{O_2} (ml/min/Torr) (Bohr)	LogSDQ (base 10)	$\frac{Pa[VQ]-Pa}{PA-Pa}$ (% due to diffusion limitation)	$\frac{Ca[VQ]-Ca}{CA-Ca}$ (% due to diffusion limitation)	$\frac{DL_{O_2}}{\dot{Q}\beta_{O_2}}$	L_{Diff}
1	8.5	0.96	10.5	51.7	0.14	0.87
2	15.7	0.23	57.7	79.6	0.55	0.58
3	12.2	0.45	42.1	69.9	0.38	0.68
4	20.0	0.43	31.2	63.1	0.50	0.61
5	14.9	0.45	38.7	74.6	0.38	0.68
Mean	14.3	0.50	36.0	67.8	0.39	0.68
SEM	1.9	0.12	7.7	4.9	0.07	0.05

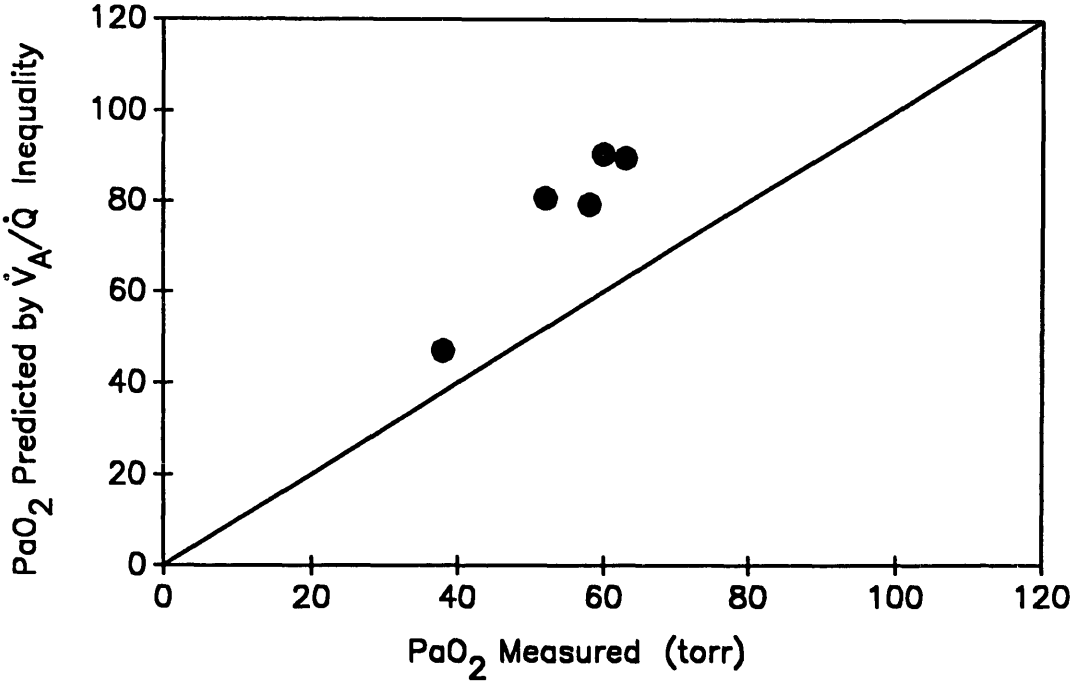

Fig. 2. Comparison of exercise Pa_{O_2} values calculated from the estimated amount of $\dot{V}A/\dot{Q}$ inequality with those observed. Systematically elevation of points above greater Pa_{O_2} values predicted by $\dot{V}A/\dot{Q}$ inequality alone indicate presence of exercise diffusion limitation for O_2.

procedure to explain the remainder of the hypoxemia resulted in DL_{O_2} estimates averaging 14.3 ± 1.9 ml $O_2 \cdot min \cdot Torr^{-1}$ (table 2). These exercise DL_{O_2} values agreed closely with rebreathing DL_{CO} measurements (table 1) in patients 1, 2 and 3 (DL_{O_2}/DL_{CO} ranging from 1.2 to 1.46), but were somewhat larger in patients 4 and 5 (1.69 and 1.81). The average $D/\dot{Q}\beta$ ratio from these DL_{O_2} estimates was 0.39 ± 0.07, and the average L_{Diff} was 0.68 ± 0.05, which represents a considerable amount of diffusion limitation.

Partitioning the exercise (A-a)O_2 difference. Table 2 shows that on average diffusion limitation was responsible for 36% of the (A-a)P_{O_2} difference during exercise, and for 68% of the (A-a)O_2 content difference. The difference between these two partitioning methods was unexpectedly large, and its mechanism and physiological relevance is analyzed below.

Discussion

Critique of method. DL_{O_2} was estimated from a multicompartmental $\dot{V}A/\dot{Q}$ model using a forward Bohr integration procedure which has been described previously (Hempleman and Gray, 1988). Since the data we analyzed did not include measurements of $\dot{V}A/\dot{Q}$ inequality, we estimated $\dot{V}A/\dot{Q}$ inequality by assuming it was the sole source of resting hypoxemia. Our rationale for this comes from three previous studies of fibrotic patients

which used the multiple inert gas elimination technique (MIGET) to measure $\dot{V}_A/\dot{Q}$ distributions. Wagner (1976) and Jernudd-Wilhelmsson *et al.* (1986) reported that all resting hypoxemia was due to $\dot{V}_A/\dot{Q}$ inequality. Agusti and cowokers (1987) found that most resting hypoxemia was due to $\dot{V}_A/\dot{Q}$ inequality, with some diffusion limitation at rest. All three MIGET studies reported little or no change in $\dot{V}_A/\dot{Q}$ inequality between rest and exercise.

Besides relying on these previous studies, we tested our assumption that $\dot{V}_A/\dot{Q}$ inequality was the sole source of resting hypoxemia by considering the other extreme: could resting hypoxemia be due simply to diffusion limitation? We used Bohr integration to calculate the amount of hypoxemia expected at rest if there were no $\dot{V}_A/\dot{Q}$ inequality and resting DL_{O_2} was equal to 1.2 times resting DL_{CO} (*i.e.* our best estimate of resting DL_{O_2}). Under these conditions we calculated that there would be diffusion equilibration at rest for subjects 2–5. This indicates that the large observed $(A\text{-}a)P_{O_2}$ at rest is most likely due to $\dot{V}_A/\dot{Q}$ inequality as we assumed. For subject 1 we calculated a 10 Torr $(A\text{-}a)P_{O_2}$ difference with the resting DL_{O_2} value, suggesting the possibility of some resting diffusion limitation. If this is the case, then in subject 1 we may have slightly overestimated both the $\dot{V}_A/\dot{Q}$ inequality and the exercise DL_{O_2} value.

Sensitivity of estimated DL_{O_2} to uncertainties in Sa_{O_2}. The Pa_{O_2} data from Hughes *et al.* (1990) were based on transcutaneous pulse oximetry measurements, a technique known to have an accuracy of about $\pm 2\%$ (Mackenzie, 1985; Nickerson *et al.*, 1988). To investigate the effect of this uncertainty, we recalculated Pa_{O_2} values for Sa_{O_2} values $\pm 2\%$ of the measured value, and then determined DL_{O_2} as described previously. Resulting low and high DL_{O_2} values in ml/min/Torr for patients 1–5 were (8.4–8.7), (15.0–16.8), (11.2–14.0), (18.8–23.2) and (14.3–15.4), respectively. We concluded that DL_{O_2} estimates remained pathologically low despite the range of uncertainty of Sa_{O_2} associated with pulse oximetry.

Sensitivity of estimated DL_{O_2} to uncertainties in $\dot{V}_A/\dot{Q}$ inequality. Out of necessity we estimated rather than measured $\dot{V}_A/\dot{Q}$ inequality (LogSDQ). Since we were uncertain how much this could affect the determination of DL_{O_2}, we repeated the DL_{O_2} calculations for each patient at several different values of LogSDQ. The results are shown in fig. 3. The points on the left mark DL_{O_2} values assuming LogSDQ = 0.0. The points on the right mark DL_{O_2} assuming resting values of LogSDQ. DL_{O_2} increased with $\dot{V}_A/\dot{Q}$ dispersion as expected. However, the changes in DL_{O_2} over this range of LogSDQ were modest, suggesting that estimated DL_{O_2} in these fibrotic patients is not greatly affected by small uncertainties in LogSDQ.

Comparison of DL_{O_2} and DL_{CO} estimates. Heterogeneities of D, $\dot{Q}$, and $\dot{V}$ within the lung can affect the measurement of DL_{O_2} and DL_{CO} differently. Accounting for $\dot{V}_A/\dot{Q}$ heterogeneity with the log-normal $\dot{V}_A/\dot{Q}$ model probably improved our Bohr integral estimates of DL_{O_2} and helped to explain the close agreement we saw with DL_{CO} values. Geiser and coworkers (1983) studying healthy dogs reported a similar close relationship

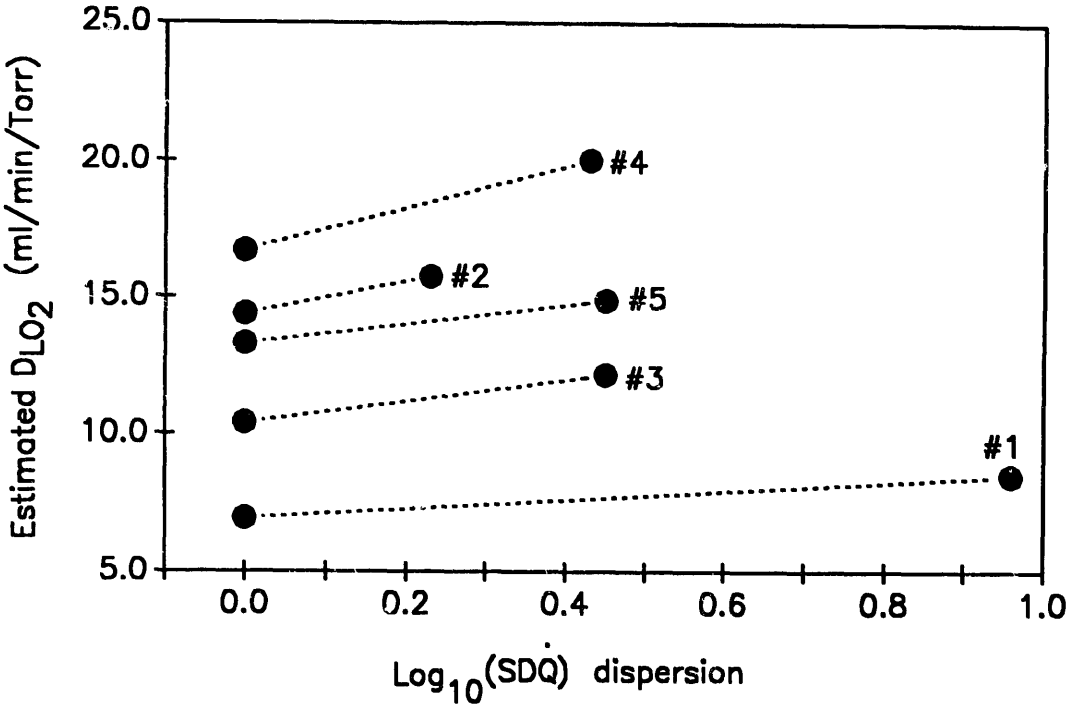

Fig. 3. Sensitivity of exercise D_{LO_2} values determined by Bohr integration in the multicompartmental lung model to varying amounts of $\dot{V}_A/\dot{Q}$ inequality (base 10 LogSDQ). Numbered curves identify subjects. Points at right mark LogSDQ values estimated from resting data. Points at left mark LogSDQ = 0 (no $\dot{V}_A/\dot{Q}$ inequality). D_{LO_2} estimates increased modestly with increasing LogSDQ over this range of $\dot{V}_A/\dot{Q}$ inequality (see text).

between D_{LO_2} and D_{LCO} when they employed a log-normal $\dot{V}_A/\dot{Q}$ model. In any case, D_{LO_2} estimates in the exercising fibrotics are markedly lower than D_{LO_2} estimates from healthy exercising humans (Meyer *et al.*, 1981, Hempleman and Gray, 1988), suggesting the possibility of substantial diffusion limitation in these patients.

Comparison of exercise (A-a)P_{O_2} partitioning to previous studies. Diffusion limitation accounted for an average of 36% of the exercise (A-a)P_{O_2} in our analysis. This value falls among MIGET estimates of 17% reported by Wagner (1976), 30% by Jernudd-Wilhelmsson and coworkers (1986) and 42% reported by Agusti and coworkers (1987) for fibrotic patients during exercise. Variation here could be related to differences in the type and severity of fibrotic disease present in the patients studied, as well as differences in methodology. Nevertheless, a salient feature of all of these multicompartmental $\dot{V}_A/\dot{Q}$ studies is the conclusion that diffusion limitation accounts for less than half of the total (A-a) P_{O_2} in exercising fibrotic patients. As discussed below, we think this measurement underestimates the impairment of pulmonary oxygen exchange by diffusion limitation.

Critique of the partitioning of (A-a)O_2 difference into $\dot{V}_A/\dot{Q}$ distribution and diffusion limitation components. We used two methods: one based on P_{O_2}, and one based on O_2 content. Interestingly, the results of these two methods disagreed dramatically on

the relative contributions of diffusion limitation and $\dot{V}_A/\dot{Q}$ inequality to the overall (A-a)O_2 difference. On average, we calculated that 36% of the (A-a) P_{O_2} difference was due to diffusion limitation, while 68% of the (A-a)O_2 content difference was due to diffusion limitation. To explain this disagreement, we propose that the *order* in which the (A-a)P_{O_2} is partitioned into $\dot{V}_A/\dot{Q}$ inequality and diffusion limitation using the $\dot{V}_A/\dot{Q}$ model is critically important. We also propose that this ordering effect is not a factor in the partitioning of the (A-a)O_2 content difference.

When partitioning the (A-a)P_{O_2} by eq. 1, $\dot{V}_A/\dot{Q}$ inequality is conceptually responsible for the decrement in P_{O_2} from $P_{A_{O_2}}$ to $Pa_{O_2}[\dot{V}_A/\dot{Q}]$. This step tends to be large in fibrosis due to elevated ideal alveolar P_{O_2} values (table 1), but it may reflect relatively little O_2 content change because the OEC is nearly flat in this region. The second P_{O_2} decrement, from $Pa_{O_2}[\dot{V}_A/\dot{Q}]$ to measured Pa_{O_2}, is ascribed to diffusion limitation, and it occurs on a steeper part of the OEC where P_{O_2} changes less for a given O_2 content change. Therefore, even though diffusion limitation may account for a significant decrease in arterial content (and potential $\dot{V}_{O_2}$), this may not be apparent from partitioning of the (A-a)P_{O_2}.

To test this explanation, we tried representing $\dot{V}_A/\dot{Q}$ inequality as an equivalent shunt (venous admixture), combined with an alveolar compartment (Riley and Cournand, 1951; Cotes, 1965). The shunt fraction was estimated from resting data. With this simple two compartment model, the *order* in which the $\dot{V}_A/\dot{Q}$ inequality (*i.e.* shunt) and diffusion limitation effects are subtracted from the ideal alveolar P_{O_2} is *reversed* compared with the multicompartmental $\dot{V}_A/\dot{Q}$ model:

$$(P_{A_{O_2}} - Pa_{O_2}) = (P_{A_{O_2}} - Pc'_{O_2}) + (Pc'_{O_2} - Pa_{O_2}) \quad (5)$$

total — Diffusion limitation component — Shunt component.

Here, diffusion limitation is held responsible for the first (large) drop in P_{O_2} from ideal alveolar levels to end capillary levels (Pc'_{O_2}), and venous admixture is held responsible for the final decrement to the arterial P_{O_2} level. Using data from patient 3 as a test case, the shunt model indicated that 91% of the (A-a) P_{O_2} difference during exercise was due to diffusion limitation. This is a much larger figure than the 42% calculated for patient 3 using the multicompartmental $\dot{V}_A/\dot{Q}$ model (eq. 1, table 2). Interestingly, when we expressed eq. 5 in terms of O_2 content, the shunt model showed that 73% of the (A-a)O_2 content difference in patient 3 was due to diffusion limitation, which closely approximates the 70% value calculated from the 10 compartment $\dot{V}_A/\dot{Q}$ model using (A-a)O_2 content partitioning (eq. 2, table 2).

To summarize, the partition of (A-a)P_{O_2} in fibrosis is very dependent on how $\dot{V}_A/\dot{Q}$ inequality is expressed (whether as shunt or as multiple $\dot{V}_A/\dot{Q}$ compartments), due to influences of the blood oxygen equilibrium curve. On the other hand, the partition of (A-a) O_2 content into diffusion limitation and $\dot{V}_A/\dot{Q}$ inequality components is relatively insensitive to model choice. In addition, the partition of (A-a)O_2 content is a direct

quantitation of the reduction (from ideal values) of O_2 content and $\dot{V}_{O_2}$ due to diffusion impairment, and thus is a more realistic assessment of O_2 exchange limitation than are P_{O_2} differences. We suggest that previous studies using MIGET and (A-a)P_{O_2} differences underestimated the predominant effect of O_2 diffusion limitation in exercising fibrotic patients.

Estimation of overall diffusion limitation from $D/\dot{Q}\beta$ ratios. By using Bohr integration in the heterogeneous $\dot{V}_A/\dot{Q}$ model, we were able to estimate DL_{O_2}, and thus the $DL_{O_2}/\dot{Q}\beta_{O_2}$ ratio. Our average calculated $DL_{O_2}/\dot{Q}\beta_{O_2}$ ratio of 0.39 and L_{Diff} of 0.68 and (table 2) indicate substantial diffusion limitation. These calculations assume that the linear slope of the OEC calculated between Pa_{O_2} and $P\bar{v}_{O_2}$ extends unchanged to $P_{A_{O_2}}$. With this in mind, the L_{Diff} of 0.68 means that if diffusion limitation were removed, Pa_{O_2} would equilibrate with $P_{A_{O_2}}$, and $\dot{V}_{O_2}$ for the same input conditions would approach an ideal value that is 1.0/(1.0–0.68) or 3.1-times the observed value. Clearly, the *in vivo* OEC in these patients flattens considerably when approaching the alveolar point, so that calculated $\dot{V}_{O_2}$ limitation attributed to diffusion limitation by L_{Diff} is overestimated by this technique.

Using L_{Diff}, one can also make backwards calculations of the expected $(P_A\text{-}Pc')/(P_A\text{-}P\bar{v})$ ratio due to diffusion limitation, and compare it to the measured value of $(P_A\text{-}Pa)/(P_A\text{-}P\bar{v})$, as described in the companion paper (Hughes *et al.*, 1990). For example, the mean $(P_{A_{O_2}}\text{-}P\bar{v}_{O_2})$ during exercise was 98 Torr (table 1). Using this value and a $DL_{O_2}/\dot{Q}\beta_{O_2}$ ratio of 0.39 in eq. 4 predicts a $(P_{A_{O_2}}\text{-}Pc'_{O_2})$ of 66 Torr. The observed mean $(P_{A_{O_2}}\text{-}Pa_{O_2})$ was 69 Torr, which suggests that 96% (66/69) of the observed P_A-Pa gradient on exercise was due to diffusion limitation and 4% (3/69) was due to $\dot{V}_A/\dot{Q}$ mismatch.

This calculation of $(P_A\text{-}Pc')/(P_A\text{-}P\bar{v})$ is in many ways analogous to the (A-a)P_{O_2} partition using the shunt/ideal alveolar model discussed earlier (eq. 5). The first P_{O_2} drop from ideal alveolar levels is attributed to diffusion limitation, and *in vivo* the drop is large because of the highly curved OEC in this region. Therefore, the large P_{O_2} difference between $P_{A_{O_2}}$ and Pc'_{O_2} does not represent an equally large difference in O_2 content, and the effect of diffusion limitation on potential O_2 uptake is overestimated by this method.

In summary, we have compared several analytical methods for estimating the diffusion limitation in exercising patients with fibrosis. Because ventilation and alveolar P_{O_2} are extremely high in this disease, quite large (A-a)P_{O_2} differences may exist with very small effects on O_2 content and potential O_2 uptake. We conclude that attempts to partition the (A-a)P_{O_2} into diffusion limitation and $\dot{V}_A/\dot{Q}$ inequality components under these conditions are very sensitive to the order in which the partitioning is done. Multicompartmental $\dot{V}_A/\dot{Q}$ models (including MIGET) ascribe the first part of the drop in (A-a)P_{O_2} to $\dot{V}_A/\dot{Q}$ inequality, and thus tend to exaggerate the importance of $\dot{V}_A/\dot{Q}$ inequality. Models that represent $\dot{V}_A/\dot{Q}$ inequality as shunt, and also model analysis of $DL_{O_2}/\dot{Q}\beta_{O_2}$ ratios, ascribe the first part of the difference in (A-a)P_{O_2} to diffusion

impairment, and thus tend to exaggerate the importance of diffusion limitation. We propose analysis of (A-a)O_2 content differences to overcome this problem. Partitioning of the (A-a)O_2 content gives a direct quantitation of the effect of diffusion impairment and $\dot{V}_A/\dot{Q}$ inequality on O_2 uptake (*i.e.* their limitation), and appears relatively independent of calculation order and type of model chosen.

References

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

Cotes, J.E. (1965). *Lung Function.* Blackwell, Oxford, 216 pp.

Geiser, J., H. Schibli and P. Haab (1983). Simultaneous O_2 and CO diffusing capacity estimates from assumed log-normal $\dot{V}_A$, $\dot{Q}$ and DL distributions. *Respir. Physiol.* 52: 53–67.

Hammond, M.D., G.E. Gale, K.S. Kapitan, A. Ries and P.D. Wagner (1986). Pulmonary gas exchange in humans during normobaric exercise. *J. Appl. Physiol.* 61: 1749–1757.

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.

Hughes, J.M.B., D.N.A. Lockwood, H.A. Jones and R.J. Clark (1990). $DL_{CO}/\dot{Q}$ and diffusion limitation at rest and on exercise in patients with interstitial fibrosis. *Respir. Physiol.*, 83: 155–166.

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

Kelman, G.R. (1966). Digital computer subroutine for the conversion of oxygen tension into saturation. *J. Appl. Physiol.* 21: 1375–1376.

Kelman, G.R. (1967). Digital computer procedure for the conversion of P_{CO_2} into CO_2 content. *Respir. Physiol.* 3: 111–115.

Mackenzie, N. (1985). Comparison of a pulse oximeter with an ear oximeter and an *in-vitro* oximeter. *J. Clin. Mon.* 1(3): 156–160.

Meyer, M., P. Scheid, G. Riedl, 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.

Riley, R.L. and A. Cournand (1951). Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. *J. Appl. Physiol.* 4: 77–101.

Scheid, P. and J. Piiper (1989). Blood gas equilibration in lungs and pulmonary diffusing capacity. In: Respiratory Physiology, An Analytical Approach, edited by H.K. Chang and M. Paiva. Dekker, New York, pp. 453–498.

Torre-Bueno, J.R., P.D. Wagner, H.A. Saltzman, G.E. Gale and R.E. Moon (1985). Diffusion limitation in normal humans during exercise at sea level and simulated altitude. *J. Appl. Physiol.* 58(3): 989–995.

Wagner, P.D. (1976). Ventilation-perfusion inequality and gas exchange during exercise in lung disease. In.: *Muscular Exercise and the Lung*, edited by J.A. Dempsey and C.E. Reed. Univ. Wisconsin Press, Madison, pp. 345–356.

West, J.B. and P.D. Wagner (1977). Pulmonary Gas Exchange. In: *Bioengineering Aspects of the Lung*, edited by J.B. West, Dekker, New York, pp. 361–457.