Respiration Physiology (1987) **69**, 129–147
Elsevier

RSP 01292

Oxygen diffusing capacity estimates derived from measured $\dot{V}_A/\dot{Q}$ distributions in man

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(Accepted for publication 3 March, 1987)

Abstract. Data from eighteen subjects, studied in hypoxia (minimum $P_{I_{O_2}} = 80$ Torr) both at rest and during exercise, were analyzed using computer models which estimate O_2 diffusing capacity from measured $\dot{V}_A/\dot{Q}$ distributions (obtained using the multiple inert gas elimination technique 'MIGET') and measured O_2 exchange. Two of these models assigned the distribution of the diffusing capacity (D) in proportion to either the perfusion ($D_{L_{O_2}}$-Qwt) or ventilation ($D_{L_{O_2}}$-Vwt) distributions from MIGET, and thus modeled the effects of $\dot{V}_A/\dot{Q}$ and $D/\dot{Q}\beta$ (where $\dot{Q}\beta$ is the perfusive conductance) inequalities respectively. The third model ($D_{L_{O_2}}$-3C) assigned all the diffusing capacity to a single homogeneous compartment. At rest $D_{L_{O_2}}$ was 41.1 ± 4.8, 41.1 ± 5.4 and 30.2 ± 2.1 ml · min^{-1} · Torr^{-1} for the Qwt, Vwt and 3C models respectively. These rose to 93.7 ± 2.6, 109.3 ± 4.5 and 81.1 ± 1.9 ml · min^{-1} · Torr^{-1} respectively at maximal exercise, all significantly different from rest ($P < 0.001$ for each). The effects of measured $\dot{V}_A/\dot{Q}$ and theoretical $D/\dot{Q}\beta$ inhomogeneities on diffusing capacity estimates were significant even in normal lungs. Both types of inequality caused an appreciable underestimation of $D_{L_{O_2}}$. These multi-compartment model estimates, using real data, are consistent with published theoretical predictions of the effects of $\dot{V}$, $\dot{Q}$ and D inequalities. The results during exercise come close to morphometric predictions of maximal oxygen diffusing capacity in man.

Exercise; Hypoxia; Inert gases; Lung models; Pulmonary gas exchange

Physiologic estimates of pulmonary diffusing capacity are usually calculated from one compartment mathematical models assuming $\dot{V}_A/\dot{Q}$ homogeneity, or from simple two or three compartment models of $\dot{V}_A/\dot{Q}$ inequality based on CO_2 exchange (Riley and Cournand, 1949). When $\dot{V}_A/\dot{Q}$ inhomogeneity is present, these simplifying assumptions result in an underestimation of the true lung diffusing capacity (Chinet *et al.*, 1971), a fact which must be considered when interpreting diffusing capacity measurements. It has been recognized that physiologic measurements of $D_{L_{O_2}}$ and $D_{L_{CO}}$ are usually

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smaller than morphometric $D_{L_{O_2}}$ and $D_{L_{CO}}$ estimates (Crapo and Crapo, 1983). At least some of this difference might be attributed to the simplifying assumption of $\dot{V}_A/\dot{Q}$ homogeneity. Thus, a method which included the effect of $\dot{V}_A/\dot{Q}$ inequality in the physiologic measurement of diffusing capacity would be a step toward resolving this discrepancy, and would be of interest both to clinicians and physiologists. The multiple inert gas elimination technique (Wagner *et al.*, 1974a,b) can provide the needed independent estimate of the distribution of $\dot{V}_A/\dot{Q}$ ratios in the lung; this distribution can then be applied to physiologic measurements of O_2 uptake, allowing an estimate of the diffusing capacity for oxygen which includes the effect of $\dot{V}_A/\dot{Q}$ inequality.

Our primary goal here was to use data from the multiple inert gas elimination technique (MIGET) in conjunction with respiratory gas measurements to estimate $D_{L_{O_2}}$ in man. Furthermore, we wanted to investigate the relative effects of $D/\dot{Q}$ and $\dot{V}_A/\dot{Q}$ inequalities on the estimation of diffusing capacity ($D_{L_{O_2}}$) by fitting the data to three different models: (1) $D_{L_{O_2}}$-Qwt, a model where D is distributed in proportion to the measured perfusion distribution from the multiple inert gas elimination technique (MIGET), and thus corrects for $\dot{V}_A/\dot{Q}$ inequality; (2) $D_{L_{O_2}}$-Vwt, a model where D is distributed in proportion to the alveolar ventilation distribution from MIGET, and thus allows for $\dot{V}_A/\dot{Q}$ inequality and also tests the effect of $D/\dot{Q}\beta$ inequality; and (3) $D_{L_{O_2}}$-3C, a model where D is assigned to a single ideal compartment which receives all of the non-shunt bloodflow and non-dead space ventilation (as determined by MIGET), and thus is analogous to the three compartment model of Riley and Cournand (1949). Together, these three models allow comparison of the effects of $\dot{V}_A/\dot{Q}$ inequality and $D/\dot{Q}\beta$ inequality on estimates of diffusing capacity. Correcting for the effects of these inequalities should provide an improved physiologic estimate of maximal oxygen diffusing capacity in man.

Methods

General

A total of 133 gas exchange data sets, from 18 healthy male subjects studied previously in hypoxia at rest and during exercise, were analyzed using the computer algorithms described below. The methods for the gas exchange experiments have been reported in detail elsewhere (Gale *et al.*, 1985; Hammond *et al.*, 1986a,b; Wagner *et al.*, 1986) and thus will be reviewed only briefly here.

Gas exchange experiments, outline

Subjects were seated comfortably on a bicycle ergometer and breathed through a mouthpiece which diverted expired gas to a heated mixing box. In ten subjects, the data were collected during normobaric hypoxia while breathing 11% oxygen ($P_{I_{O_2}}$ = 79 Torr) (Hammond *et al.*, 1986a). In eight subjects, the data was collected at simulated altitudes up to 15000 feet in a hypobaric chamber (maximum altitude = 4570 m, minimum P_B = 429 Torr, $F_{I_{O_2}}$ = 0.21, $P_{I_{O_2}}$ = 80 Torr) (Wagner *et al.*,

1986). Inspired gas thus came either from the ambient air (in the chamber experiments) or from a meteorological balloon (in the normobaric experiments). Minute ventilation, cardiac output, simultaneous arterial blood, mixed expired respiratory and inert gas samples, and all ancillary measurements were taken at rest and several workloads (light exercise = 50–75 W, moderate exercise = 100–150 W, heavy exercise = 200+ W). All data were collected under steady state conditions defined by constancy (to $\pm 5\%$) of: minute ventilation ($\dot{V}_E$), respiratory rate, heart rate, and continuously monitored mixed expired respiratory gas tensions. In general, sampling was begun 5–7 min into a given run and was completed within 2 min. Subjects rested between each run for a minimum of 15 min or until heart rate recovered to within 15% of baseline. All instruments were recalibrated between each run while the subjects rested.

Inert gas analysis. Six inert gases (SF_6, ethane, cyclopropane, enflurane, ether and acetone) were dissolved in 5% dextrose, as described previously (Wagner *et al.*, 1974a,b), and infused into a peripheral vein at a constant rate during each exercise period. Simultaneous arterial blood and expired inert gas samples were collected in glass syringes at each exercise level. Mixed venous inert gas levels were calculated from the arterial and expired samples using the Fick relationship and the measured cardiac output and minute ventilation in the normobaric experiments; in the hypobaric experiments these mixed venous values were directly measured. All were analyzed by gas chromatography (Wagner, 1974b). Blood/gas partition coefficients of the six gases were measured in duplicate for each individual. Retention ($Pa/P\bar{v}$) and excretion ($P_E/P\bar{v}$) values for all six gases were used to estimate the $\dot{V}_A/\dot{Q}$ distribution as previously described (Wagner *et al.*, 1974a; Evans and Wagner, 1977).

Cardiac output determinations. This was done using green dye dilution in the normobaric experiments, as described previously (Hammond *et al.*, 1986a). In the hypobaric experiments, a pulmonary artery catheter was in place and cardiac output was determined from inert gas data using the Fick principle (Wagner *et al.*, 1986).

Computational methods

Input values for the DL_{O_2} predictions. These included: (1) measured $\dot{Q}$, $\dot{V}$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, Hb, Hct, body temperature, Pa_{O_2}, pH, base excess/deficit, PI_{O_2}, PI_{CO_2}, and P_B; (2) assumed P_{50} (26.8); (3) $\dot{V}_A/\dot{Q}$ distribution from the inert gas data; and (4) mixed venous P_{O_2} and P_{CO_2} calculated by the Fick relationship in normobaric experiments (from measured $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, arterial blood gas contents, and cardiac output); in the hypobaric experiments mixed venous P_{O_2} and P_{CO_2} were measured directly.

Modeling alveolar-capillary P_{O_2} disequilibrium. By mass balance, Pa_{O_2} and Pa_{CO_2} can be predicted from measured compartmental $\dot{V}_A/\dot{Q}$ distributions if mixed venous P_{O_2} and P_{CO_2}, inspired P_{O_2} and P_{CO_2}, and blood O_2 and CO_2 dissociation relationships are known. This requires graphical solution of the blood and gas convection equations to

produce a 'P_{O_2}–P_{CO_2} diagram' for the lung (Rahn and Fenn, 1955) or computerized numerical solution of the same equations (West, 1969). Both modes of solution normally assume complete blood–gas diffusion equilibration.

In this analysis, the numerical model of $\dot{V}A/\dot{Q}$ inequality was modified to include the effect of diffusion limitation for oxygen in subjects breathing hypoxic gas mixtures. The basic method is similar to the one developed by Chinet *et al.* (1971) and used by Geiser *et al.* (1983). Rather than assuming complete equilibration between pulmonary capillary blood and alveolar gas in each $\dot{V}A/\dot{Q}$ compartment, compartmental blood–gas P_{O_2} equilibration was described numerically using the monoexponential alveolar diffusion equation of Piiper (1969):

$$(PAj - Pc'j) = (PAj - P\bar{v})\exp(-Dj/\dot{Q}j\beta) \quad (1)$$

where $P\bar{v}$ is mixed venous P_{O_2}, PAj is alveolar P_{O_2} in the jth compartment, Pc_j is the end-pulmonary capillary P_{O_2} in the jth compartment, Dj is the compartmental O_2 diffusing capacity, $\dot{Q}j$ is compartmental blood flow and beta (β) is the blood capacitance coefficient for O_2 (assumed to be constant in hypoxia).

$$\beta = \frac{(Ca_{O_2} - C\bar{v}_{O_2})}{(Pa_{O_2} - P\bar{v}_{O_2})} \quad (2)$$

Complete CO_2 equilibration between pulmonary capillary blood and alveolar gas was assumed. Except for the inclusion of eq. (1) in the $\dot{V}A/\dot{Q}$ model, our computer algorithms for compartmental and whole-lung gas exchange were as described by West (1969), and Evans and Wagner (1977).

Modeling the distribution of $D/Q\beta$ ratios. The multiple inert gas elimination technique defines the distribution of alveolar ventilation and perfusion with respect to compartmental $\dot{V}A/\dot{Q}$ ratios within the lung, but it does not define the distribution of diffusing capacity. An assumption about the distribution of D to $\dot{Q}$ within the $\dot{V}A/\dot{Q}$ compartments is thus required. Three models of D distribution were used: two (DL_{O_2}-Qwt and DL_{O_2}-Vwt) were linked to the measured $\dot{V}A/\dot{Q}$ distribution (fig. 1), the third (DL_{O_2}-3C) involved no assumptions about the distribution of D, and ignored $\dot{V}A/\dot{Q}$ inequality.

Model I (DL_{O_2}-Qwt) has Dj distributed in proportion to $\dot{Q}j$ (eq. (3a)) giving a constant $D/\dot{Q}\beta$ ratio in all $\dot{V}A/\dot{Q}$ compartments as shown in eq. (3b):

$$Dj = \frac{DL_{O_2}\,\dot{Q}j}{(\dot{Q}t - \dot{Q}s)} \quad (3a)$$

$$Dj/\dot{Q}_j\beta = \frac{DL_{O_2}}{(\dot{Q}t - \dot{Q}s)\cdot\beta} \quad (3b)$$

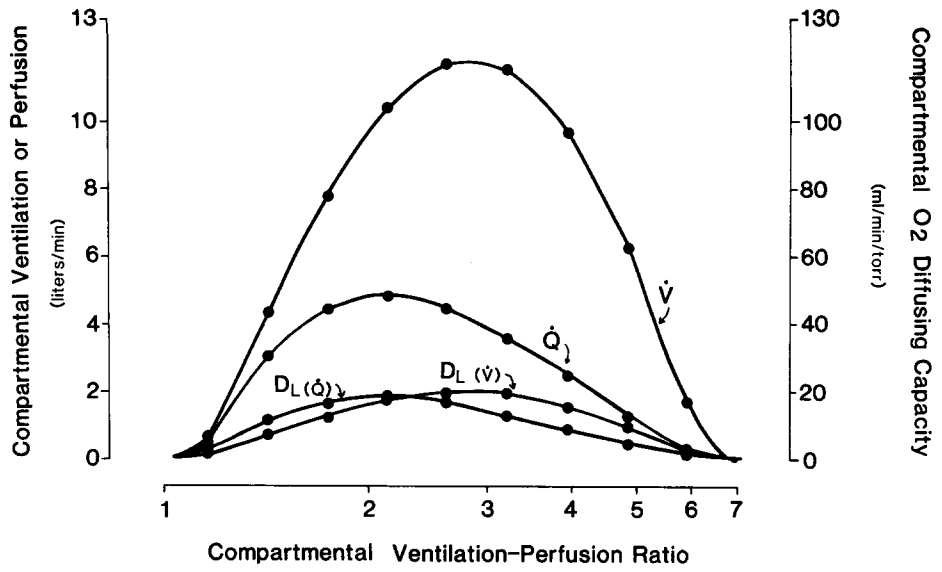

Fig. 1. An example of the modeled distribution of D in: (1) the perfusion weighted model (labeled DL-Q) and (2) the ventilation weighted model (labeled DLV). The distribution of ventilation ($\dot{V}$) and bloodflow ($\dot{Q}$) are shown in the two upper curves. Note how the assignment of D produces a constant $D/\dot{Q}$ ratio for each compartment in the perfusion weighted model, and variable $D/\dot{Q}$ ratios for each compartment in the ventilation weighted model.

where $\dot{Q}t$ is cardiac output and $\dot{Q}s$ is shunt blood flow, both determined by the multiple inert gas elimination technique.

The total lung diffusing capacity for Model I is:

$$DL_{O_2} = \sum_j Dj \tag{4}$$

This model allows $\dot{V}A/\dot{Q}$ inequality but has no regional mismatch between the diffusive and perfusive conductances (*cf.* Piiper, 1969).

Model II (DL_{O_2}-Vwt) had Dj distributed in proportion to $\dot{V}A_j$, giving a constant $D/\dot{V}A$ ratio in all $\dot{V}A/\dot{Q}$ compartments (eq. (5a)) but different $D/\dot{Q}\beta$ ratios as shown in eq. (5b):

$$Dj = \frac{DL_{O_2}\,\dot{V}A_j}{(\dot{V}t - \dot{V}d)} \tag{5a}$$

$$D_j/\dot{Q}_j\beta = \frac{DL_{O_2}\,\dot{V}A_j}{(\dot{V}t - \dot{V}d)\cdot \dot{Q}_j\beta} \tag{5b}$$

where $\dot{V}t$ is total (expired) ventilation and $\dot{V}d$ is deadspace ventilation, measured by MIGET. Although the Dj distribution is ventilation weighted in this model, oxygen exchange between the alveolus and pulmonary capillary is still modeled by a balance

between diffusive and perfusive conductances (eq. (1)). The total lung diffusing capacity in Model II is thus calculated as before using eq. (4). This model introduces a degree of $D/\dot{Q}\beta$ inequality that is proportional to the degree of $\dot{V}A/\dot{Q}$ inequality measured by the inert gas elimination technique, and thus investigates the effect of mismatch between the compartmental diffusive and perfusive conductances on estimates of DL_{O_2}.

Model III (DL_{O_2}-3C) is a simple three compartment analysis that minimizes assumptions about the $D/\dot{Q}\beta$ distribution within the lung. Shunt blood flow (measured by the inert gas technique) was assigned to one compartment, deadspace ventilation (from the inert gas technique) was assigned to a second compartment, and the remaining non-shunt bloodflow and non-deadspace ventilation were assigned to the third compartment. Since gas exchange in this model occurs only in the third ideal 'alveolar' compartment, this compartment is allotted the entire lung diffusing capacity. Estimates of DL_{O_2} based upon this 3 compartment model do not involve assumptions about the distribution of compartmental $D/\dot{Q}\beta$ relative to $\dot{V}A/\dot{Q}$, and ignore the effect of $\dot{V}A/\dot{Q}$ inequality on O_2 and CO_2 exchange.

Estimating DL_{O_2} from the three models. Figure 2 summarizes the method used to determine DL_{O_2} for each model. Initially a 50 compartment $\dot{V}A/\dot{Q}$ distribution was defined from the inert gas retention and excretion data. A first simulation of O_2 and CO_2 exchange was then made with DL_{O_2} set to infinity (complete blood–gas equilibration in all compartments). The Pa_{O_2} predicted by this first simulation was compared to the measured Pa_{O_2}; a simulation Pa_{O_2} greater than one Torr above the measured value was interpreted as evidence for O_2 diffusion limitation lowering the Pa_{O_2} below that predicted by $\dot{V}A/\dot{Q}$ inequality alone. Data sets which demonstrated diffusion limitation by this criterion were then analyzed using the three models described above. The DL_{O_2} required to predict the measured Pa_{O_2} was determined numerically for each model using a two-dimensional Newton–Raphson iteration. Program output for each model included: (1) compartmental values for diffusing capacity, ventilation and bloodflow; (2) compartmental alveolar P_{O_2} and end-capillary P_{O_2} and O_2 content; (3) mixed arterial and alveolar O_2 and CO_2 tensions and arterial O_2 and CO_2 content; (4) DL_{O_2}.

Statistical treatment. All data are expressed as mean ± SEM and have been grouped in ranges of $\dot{V}_{O_2}$ for simplicity. Comparisons between group means are by Student's unpaired *t*-test.

Results

$\dot{V}A/\dot{Q}$ inequality. Respiratory and inert gas exchange results have been presented in detail elsewhere (Hammond *et al.*, 1986a; Wagner *et al.*, 1986). In summary, $\dot{V}A/\dot{Q}$ inequality increased with exercise at each workload during hypoxia regardless of whether the hypoxia was produced in a chamber at reduced ambient pressure, or at sea level while breathing hypoxic gas mixtures. In both instances, the increase in $\dot{V}A/\dot{Q}$

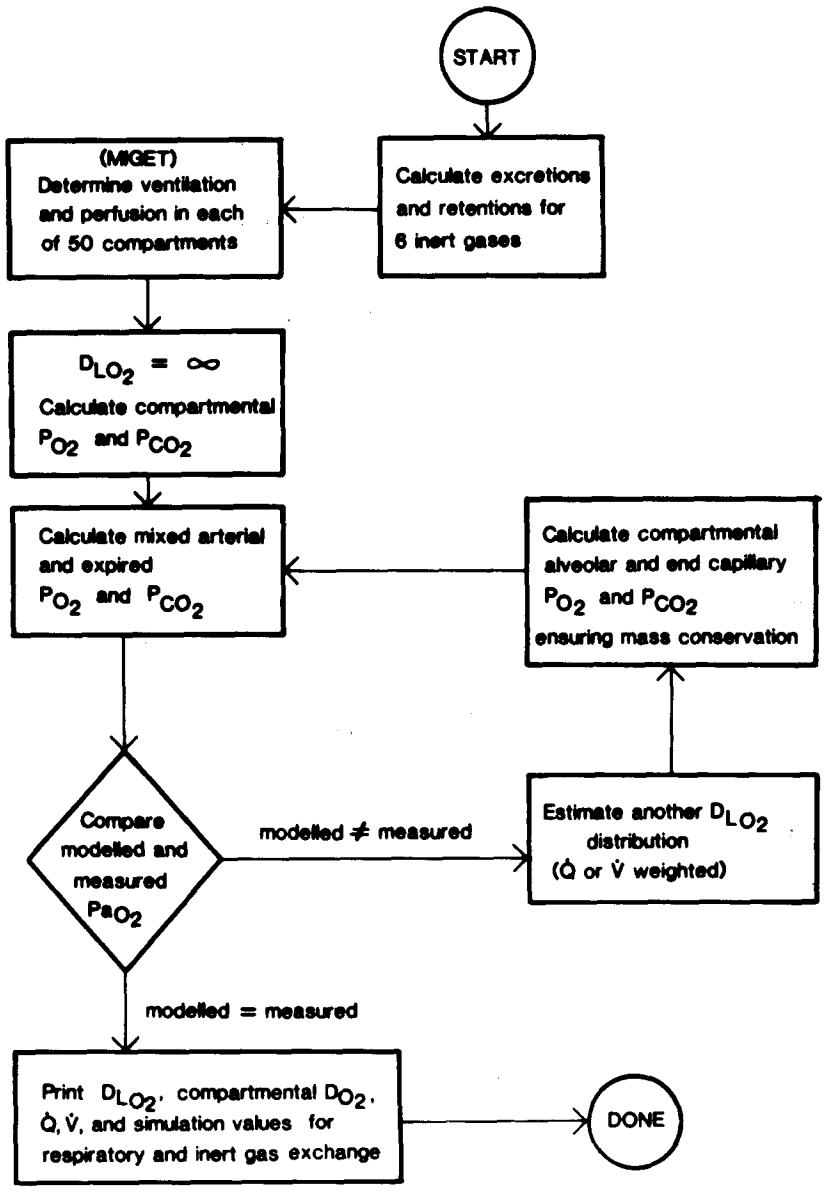

Fig. 2. Flow diagram of computational methods used.

inequality was proportional to $\dot{V}_{O_2}$ with a positive slope for the log standard deviation of the perfusion distribution (LogSDQ) of 0.09 unit per liter $\dot{V}_{O_2}$. This increase was sufficient to cause a significant fall in Pa_{O_2}, but could not explain the entire increase seen in A-aD_{O_2}. This was interpreted as evidence for oxygen diffusion limitation (Hammond *et al.*, 1986a; Wagner *et al.*, 1986). For these subjects 133 data sets were

available during hypoxia. Of these, 11 of 36 (30.5%) at rest and 95 of 97 (97.9%) during exercise demonstrated diffusion limitation (by the criterion described in Methods) and were thus subject to further analysis.

Ventilation, cardiac output and respiratory gas exchange. For the current analysis, all data have been grouped according to workload and oxygen consumption in the following ranges: rest ($\dot{V}_{O_2} < 0.5$ L · min^{-1}); light exercise ($\dot{V}_{O_2}$ 0.5–1.5 L · min^{-1}); moderate exercise ($\dot{V}_{O_2}$ 1.5–2.0 L · min^{-1}), and heavy exercise ($\dot{V}_{O_2} > 2.0$ L · min^{-1}). The number of data sets available (A) and used (n) in this analysis at each workload are shown in table 1. The mean values ± SEM for $\dot{V}_{O_2}$, $\dot{Q}$, Pa_{O_2} and $P\bar{v}_{O_2}$ for each of these workloads are also presented in table 1. Assuming a linear oxygen dissociation curve in hypoxia, the mean effective capacitance coefficient for oxygen (β) can be calculated at each workload, as discussed in Methods; this value is presented in table 1.

Estimates of diffusing capacity. The calculated effective diffusing capacities (mean ± SEM) for each model at each level of oxygen consumption are presented in table 2. Calculated DL_{O_2} increased significantly with increasing workload in all three models: mean resting DL_{O_2} estimates ranged from 30.2 ml · min^{-1} · Torr^{-1} for DL_{O_2}-3C to 41.1 ml · min^{-1} · Torr^{-1} for DL_{O_2}-Qwt and DL_{O_2}-Vwt. At maximal exercise mean DL_{O_2} estimates were 81.1 ml · min^{-1} · Torr^{-1} for DL_{O_2}-3C, 93.7 ml · min^{-1} · Torr^{-1} for DL_{O_2}-Qwt and 109.3 ml · min^{-1} · Torr^{-1} for DL_{O_2}-Vwt, all highly significantly different from the corresponding resting values ($P < 0.001$ for each model). To show intrasubject trends a line plot with results of the DL_{O_2}-Qwt calculations for each subject against $\dot{V}_{O_2}$ is shown in fig. 3.

DL_{O_2} estimates from the three models were systematically related to each other, with

TABLE 1

Ventilation, cardiac output and respiratory gas exchange

Workload:	Rest	Light	Moderate	Heavy
$\dot{V}_{O_2}$ (range):	<0.5	0.5–1.5	1.5–2.0	>2.0
A:	36	23	31	43
n:	11	21	31	43
$\dot{V}_{O_2}$	315.0 ± 11.4	1234.0 ± 30.3	1761.0 ± 30.4	2528.0 ± 64.3
$\dot{Q}$	9.3 ± 0.4	17.0 ± 0.6	18.8 ± 0.4	22.6 ± 0.5
Pa_{O_2}	34.6 ± 0.5	38.6 ± 1.6	36.1 ± 1.2	38.7 ± 0.9
$P\bar{v}_{O_2}$	26.3 ± 0.4	20.5 ± 0.7	16.5 ± 0.7	15.3 ± 0.7
BETA O_2	0.41 ± 0.01	0.42 ± 0.01	0.49 ± 0.01	0.49 ± 0.01

A = number of data sets at each workload
n = number of data sets with diffusion limitation sufficient to allow the current analysis (see text)
$\dot{V}_{O_2}$ = oxygen consumption (ml · min^{-1})
$\dot{Q}$ = cardiac output (L · min^{-1})
BETA O_2 = effective O_2 capacitance coefficient (ml · 100 ml^{-1} · Torr^{-1})

TABLE 2

Estimates of diffusing capacity

Workload:	Rest	Light	Moderate	Heavy
V_{O_2} (range):	<0.5	0.5–1.5	1.5–2.0	>2.0
n:	11	21	31	43
DL_{O_2}-(Qwt)	41.1 ± 4.8	79.3[a] ± 4.9	91.3[a] ± 7.2	93.7[a,b] ± 2.6
DL_{O_2}-(Vwt)	41.1 ± 5.4	85.0[a] ± 5.6	97.3[a] ± 7.5	109.3[a,c] ± 4.5
DL_{O_2}-(3C)	30.2 ± 2.1	61.7[a] ± 3.2	76.9[a] ± 4.6	81.1[a,c] ± 1.9
DL(V)/DL(Q)	0.98 ± 0.01	1.07[a] ± 0.02	1.06[a] ± 0.01	1.15[a] ± 0.02
DL(3C)/DL(Q)	0.78 ± 0.05	0.79 ± 0.02	0.86 ± 0.01	0.87 ± 0.01

n = number of data sets included in analysis.
$DL_{O_2}(Q)$ = perfusion weighted oxygen diffusing capacity ($ml \cdot min^{-1} \cdot Torr^{-1}$).
$DL_{O_2}(V)$ = ventilation weighted oxygen diffusing capacity ($ml \cdot min^{-1} \cdot Torr^{-1}$).
$DL_{O_2}(3C)$ = 3 compartment oxygen diffusing capacity ($ml \cdot min^{-1} \cdot Torr^{-1}$).
DL(V)/DL(Q) = ratio of ventilation to perfusion weighted model.
DL(3C)/DL(Q) = ratio of 3 compartment to perfusion weighted model.
[a] Significantly different from baseline resting value ($P < 0.001$).
[b] Significantly different from light exercise ($P < 0.02$).
[c] Significantly different from light exercise ($P < 0.001$).

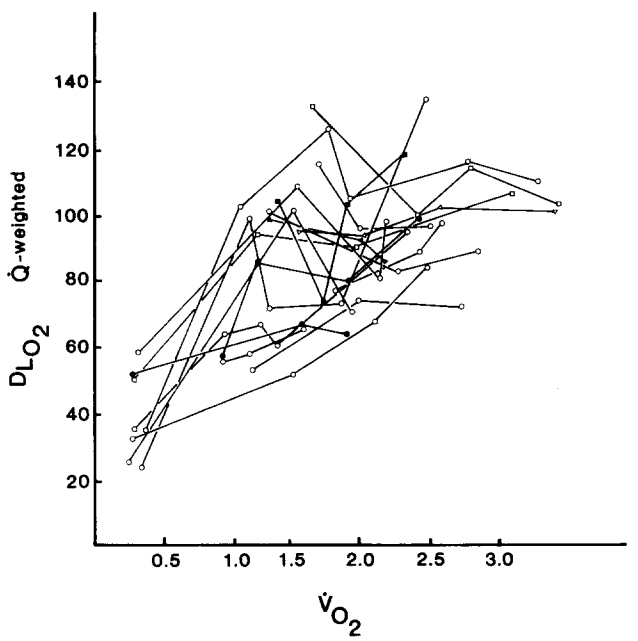

Fig. 3. Line plot of individual data for DL_{O_2}-Qwt ($ml \cdot min^{-1} \cdot Torr^{-1}$) *vs* $\dot{V}_{O_2}$ ($L \cdot min^{-1}$).

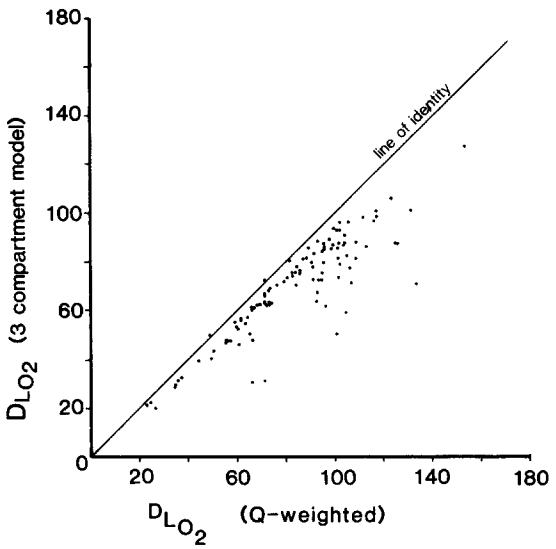

Fig. 4. DL_{O_2}-3C *vs* DL_{O_2}-Qwt. Note that most points lie below the line of identity indicating a systematic 'underestimation' of DL_{O_2} by the three compartment model *vs* the perfusion weighted model.

DL_{O_2}-3C representing a lower bound and DL_{O_2}-Vwt representing an upper bound of our calculated values. We have chosen to use the DL_{O_2}-Qwt model as the standard for comparison because in that model D is distributed in proportion to compartmental perfusion, which is likely most representative of the situation in the real lung. To compare the various models we have summarized the ratios (DL_{O_2}-3C)/(DL_{O_2}-Qwt) and (DL_{O_2}-Vwt)/(DL_{O_2}-Qwt) in table 2. These ratios show the extent of over- or underestimation of DL_{O_2} given by the three compartment (3C) and ventilation weighted (Vwt) models respectively when the perfusion weighted (Qwt) model is used as the standard of reference. The individual data points used to derive these ratios are plotted against each other in figs. 4 and 5 respectively. Assuming the Qwt model gives the best estimate of DL_{O_2}, the degree of 'underestimation' of DL_{O_2} by model DL_{O_2}-3C relative to DL_{O_2}-Qwt decreased with increasing $\dot{V}_{O_2}$. The 'overestimation' of DL_{O_2} by the ventilation weighted model (DL_{O_2}-Vwt) relative to the perfusion weighted model (DL_{O_2}-Qwt) increased with $\dot{V}_{O_2}$.

The relationship between DL_{O_2}-Qwt and cardiac output is shown in fig. 6. Although a clear relationship between the two is evident, it is not well fit to a linear regression (DL_{O_2}-Qwt = 2.17 $\dot{Q}$ + 45.6, R = 0.384). This is equally true for the other two models. There was no significant difference for any of the models between light ($\dot{V}_{O_2}$ = 0.5–1.5 L · min^{-1}) and moderate ($\dot{V}_{O_2}$ = 1.5–2.0 L · min^{-1}) exercise, or between moderate and heavy ($\dot{V}_{O_2}$ > 2.0 L · min^{-1}) exercise. The difference between light and heavy exercise was significant in each case (DL_{O_2}-Qwt, $P < 0.02$; DL_{O_2}-3C, $P < 0.001$).

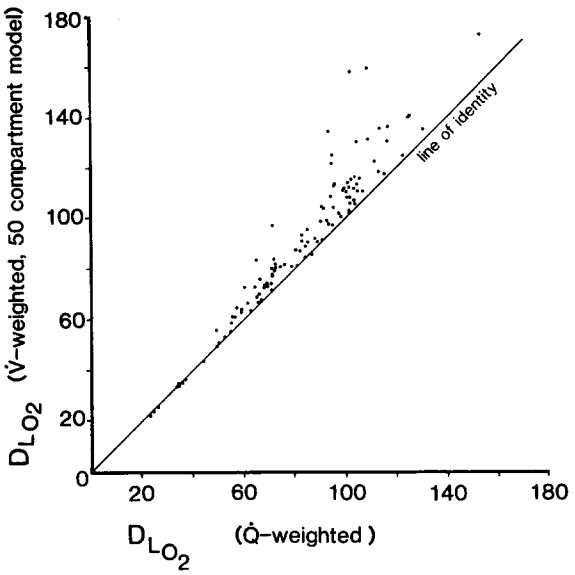

Fig. 5. DL_{O_2}-Vwt *vs* DL_{O_2}-Qwt. Note that most points lie above the line of identity, indicating a systematically higher estimate of DL_{O_2} by the ventilation weighted model *vs* the perfusion weighted model.

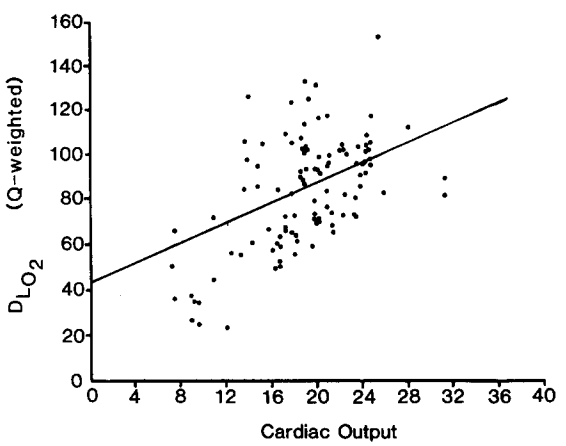

Fig. 6. Scatter plot of individual data points for DL_{O_2}-Qwt ($ml \cdot min^{-1} \cdot Torr^{-1}$) plotted against cardiac output ($L \cdot min^{-1}$). Regression line as indicated in text.

Discussion

Real data for both oxygen and inert gas exchange have been used to formulate three models for estimating pulmonary oxygen diffusing capacity in normal man, both at rest and during exercise. Points now to be considered include: (1) a critique of the models used; (2) the relative effects of $\dot{V}_A/\dot{Q}$ and $D/\dot{Q}\beta$ inequalities on DL_{O_2} estimates implied

by these models; (3) the relationship between exercise, cardiac output, and these DL_{O_2} estimates; and (4) a comparison between these estimates and morphometric predictions of DL_{O_2} obtained by others in healthy lung tissue.

Critique of the computational method

Constant blood O_2 capacitance coefficient. This simplifying assumption is commonly made during simulation of O_2 exchange in hypoxia. However, the oxygen dissociation curve (ODC) is not strictly linear in hypoxia; it has a slight concavity over the hypoxic range from P_{50} to the arterial point (the range where most O_2 exchange occurs at rest and in light exercise). The net effect of this concavity is to maintain the blood P_{O_2} at a lower level for a given O_2 content; this effectively reduces the mean capillary P_{O_2} and thereby increases the mean driving tension for diffusion of O_2 into the blood (Wagner, 1977). In the presence of ODC concavity assuming a constant β_{O_2} would result in a higher mean capillary P_{O_2}, and therefore would increase the calculated DL_{O_2} relative to the actual DL_{O_2}. The opposite argument holds for O_2 exchange occurring below the P_{50} on the convex part of the ODC (*e.g.* for low $P\bar{v}_{O_2}$ values during exercise). With the hypoxic inspired gas tensions breathed by our subjects (PI_{O_2} = 80 Torr), ODC curvature effects should have been held to a minimum.

Assumption of the same β_{O_2} in each compartment overlooks the effect of regional $\dot{V}_A/\dot{Q}$ inequality on the compartmental P_{CO_2}. Compartments with high $\dot{V}_A/\dot{Q}$ would have a lower P_{CO_2} and greater alkaline Bohr shift, which would increase effective β_{O_2} and decrease the compartmental $D/\dot{Q}\beta$ ratio below the modeled value. Low $\dot{V}_A/\dot{Q}$ compartments would have the opposite effect. Thus, $D/\dot{Q}\beta$ inequality can exist even if the $D/\dot{Q}$ ratios of all compartments are equal. Although the net result of assuming the same β_{O_2} in each compartment would be an error in the estimation of true diffusing capacity, the $\dot{V}_A/\dot{Q}$ inequality in these normal subjects would in fact produce a narrow range of β_{O_2} values, and thus relatively little error.

Assumption of CO_2 equilibration between alveolar gas and end-capillary blood. As formulated, our model does not include the potential effect of CO_2 disequilibrium. In normal subjects, the effect of CO_2 disequilibrium should be relatively insignificant; Wagner and West (1972) have shown in a theoretical paper that with a normal membrane diffusing capacity the CO_2 gradient should amount to no more than 1–2 Torr over the range of $\dot{V}_A/\dot{Q}$ ratios we have studied. However, to address this issue and to examine the potential effects of the assumptions already discussed above, we did further calculations using a Bohr integration in place of the monoexponential diffusion expression. This approach allowed for O_2 and CO_2 interactions and eliminated the assumptions discussed above. Unfortunately, the computing time was prohibitively long to allow this approach to be used to analyze all of the data; thus, we confined this analysis to the Qwt model, choosing one-half of the available data sets at random. The net effect was an average 14% lower calculated DL_{O_2}–Qwt when using the Bohr

integration versus the monoexponential expression. This effect was greatest when there was more blood flow to units with relatively high $\dot{V}_A/\dot{Q}$ ratios and where O_2 exchange begins to occur on the flat part of the oxygen dissociation curve (*e.g.* with wide $\dot{V}_A/\dot{Q}$ distributions during exercise). Compartmental gas exchange would be similarly affected in the other two models (Vwt and 3C) and therefore a similar positive bias on the calculated DL_{O_2} would be found. Thus, using a Bohr integration would not alter the general conclusions we have drawn from the data because all three models would be affected similarly and the relative differences between them would not change.

DL_{O_2}-Qwt and DL_{O_2}-Vwt estimates are both based on D distributions derived from the same measured $\dot{V}_A/\dot{Q}$ distribution. There is no simple method for measuring actual $D/\dot{Q}\beta$ distributions in the lung although attempts have been made using radioactive tracer gases (Pande and Hughes, 1983). Our models are an effort to investigate the effect of $\dot{V}_A/\dot{Q}$ inequality on DL_{O_2} estimates in man assuming simple homogeneous and inhomogeneous distributions of $D/\dot{Q}\beta$. Actual $D/\dot{Q}\beta$ distributions within the lung are undoubtedly more complicated than this, and may not be tightly linked to either ventilation or perfusion. Theoretical analysis of the effect of independent $D/\dot{Q}\beta$ and $\dot{V}_A/\dot{Q}$ distributions on gas exchange remains an area for future investigation. It is, however, generally thought that variations in local bloodflow ($\dot{Q}$) affect diffusing capacity by recruitment and distention of pulmonary capillaries. We, therefore, used the DL_{O_2}-Qwt model (which distributes D proportional to $\dot{Q}$) as a basis for comparison when examining the DL_{O_2}-Vwt and DL_{O_2}-3C models.

Resting values are at the limit of the resolution of our methodology. At the levels of hypoxemia seen in this study, there is minimal diffusion limitation for oxygen at rest. Using our algorithm, DL_{O_2} can only be calculated when there is a positive difference between the predicted and measured Pa_{O_2} values. We have used 1 Torr as a cut-off value here because as the P_{O_2} difference decreases below this value O_2 exchange becomes predominantly perfusion- rather than diffusion-limited. Calculation of DL_{O_2} under perfusion-limited conditions is inappropriate and, we found, sensitive to small errors in blood gas measurements. Also, because diffusion limitation is barely measureable at rest in these individuals, only 30% of our resting data sets met the criterion of a 1 Torr difference between measured and predicted Pa_{O_2}. Thus, the mean values presented during rest may well represent a lower limit for DL_{O_2} at rest in our subjects and the true mean value might be somewhat higher. However, using this approach has resulted in DL_{O_2} values which are consistent with previous estimates, and does provide a resting value for comparison with exercise. Furthermore, the calculated exercising DL_{O_2} values for those subjects with a definable resting DL_{O_2} were not different from the exercise DL_{O_2} values of the group as a whole, supporting the contention that the reported resting values would also be representative of the entire group.

Possible effects of changes in lung volume are ignored. It is known that conventional methods used to measure diffusing capacity are sensitive to the lung volume at which

this is measured. This is particularly true for single breath tests using carbon monoxide to measure diffusing capacity. No data on absolute lung volume were available to us in this study and no assumptions regarding lung volume were made because the algorithm does not use this variable. During exercise the large increases in tidal volume certainly mean that our steady state measurements were made over a wide range of dynamically changing lung volumes; however, it is unlikely that significant gas trapping occurred. Therefore, we do not think the changes in lung volume can explain the increase in DL_{O_2} we measured during exercise, but rather believe that this represents a true increase in D due to recruitment of the pulmonary vasculature secondary to increased flow and increased pulmonary vascular pressure.

Post-pulmonary shunt is assumed to be negligible. The methodology we have used assumes that all of the mixed alveolar to arterial oxygen tension difference ($A\text{-}aD_{O_2}$) that cannot be explained by measured $\dot{V}A/\dot{Q}$ inequality is due to diffusion limitation. In the strictest sense this cannot be true because post-pulmonary shunts, through thebesian veins and bronchial-arterial-to-pulmonary-venous anastomoses, can also produce a fall in mixed arterial O_2 tension, and these potential shunts are not measured using the inert gas method. We have previously argued that the practical effect of post-pulmonary shunts is negligible (Hammond *et al.*, 1986a; Wagner *et al.*, 1986). This conclusion is based on data obtained breathing 100% oxygen at altitude, where the effect of post-pulmonary shunt could explain only a small portion of the $A\text{-}aD_{O_2}$ not due to $\dot{V}A/\dot{Q}$ inequality. The following points provide further support for the argument that post-pulmonary shunt in humans is relatively small: (1) the thebesian venous system in man is poorly developed in the left ventricle; (2) although the mixed venous P_{O_2} falls during exercise, it is unlikely that the bronchial venous P_{O_2} decreases by the same amount, because this would imply a significant increase in bronchial tissue oxygen consumption (proportional to that of exercising muscle); (3) there is increasing evidence that O_2 and CO_2 exchange occurs between airway gas and the bronchial circulation, and therefore this 'shunted' blood may be less desaturated than mixed venous blood. If our assumption regarding these shunts proves to be incorrect, the effect of ignoring post-pulmonary shunts would be to underestimate oxygen diffusing capacity in the lung.

The role of $\dot{V}A/\dot{Q}$ and D inequalities

The importance of $\dot{V}A/\dot{Q}$ inequality in the measurement of D has long been recognized. Methods such as rapid-rebreathing DL_{CO} and DL_{O_2} (Meyer *et al.*, 1981) reduce the effect of ventilatory inequality in the lung, but perfusion inequality cannot be similarly handled. Single breath or multi-breath analysis of DL_{O_2} or DL_{CO} using two or three compartments rely on a rough estimate of $\dot{V}A/\dot{Q}$ inequality determined from CO_2 exchange (which is assumed to be limited only by $\dot{V}A/\dot{Q}$ inequality). Such methods are complicated by problems in quantitating the perfusive shunt under experimental conditions and by underestimation of $\dot{V}A/\dot{Q}$ inequality by the simple models. Only recently, with the introduction of MIGET, has it been possible to independently

estimate the distribution of $\dot{V}_A/\dot{Q}$ ratios in the lung and thus address directly the effect of $\dot{V}_A/\dot{Q}$ inequality on $D_{L_{O_2}}$. Interestingly, the underestimation of $D_{L_{O_2}}$ and $D_{L_{CO}}$ by simple models was thought to be smaller during exercise, based on data from topographical isotope $\dot{V}_A/\dot{Q}$ studies which suggested that $\dot{V}_A/\dot{Q}$ relationships became more uniform during exercise (Bake *et al.*, 1968; Harf *et al.*, 1978). However, recent data obtained using MIGET show that functional $\dot{V}_A/\dot{Q}$ inequality in fact increases during both normoxic and hypoxic exercise (Gale *et al.*, 1985; Hammond *et al.*, 1986a,b; Wagner *et al.*, 1986), and thus may contribute to an even greater underestimation of D by simple models during exercise.

In a theoretical study, Chinet *et al.* (1971) used an approach similar to ours to examine the effects of inhomogeneities of $\dot{V}_A/\dot{Q}$ and D on steady state O_2 and CO diffusing capacity estimates. They showed that any inhomogeneity of these parameters caused an underestimation of $D_{L_{O_2}}$ which was accentuated by increases in inhomogeneity or in the absolute value of D. The underestimation of $D_{L_{O_2}}$ was less when D was distributed with respect to $\dot{V}_A$ rather than $\dot{Q}$. Our real data is consistent with these theoretical predictions: not only do the multi-compartment models predict higher $D_{L_{O_2}}$ values than a simpler three compartment model, but also the $D_{L_{O_2}}$-Vwt/$D_{L_{O_2}}$-Qwt ratio increased with increases in inhomogeneity and $\dot{V}_{O_2}$ during hypoxic exercise.

Geiser *et al.* (1983) have done an analysis similar to ours on data obtained in dogs using the $(A\text{-}a)P_{CO_2}$ difference to derive an index of $\dot{V}_A/\dot{Q}$ inequality in a fifteen compartment model. They again found that this approach resulted in an improved estimate of true D, and were able to compute $D_{L_{O_2}}/D_{L_{CO}}$ ratios which were consistent with the characteristics of diffusion and of chemical association of O_2 and CO in tissue and blood. The 'corrected' $D_{L_{O_2}}$ estimates computed in their multi-compartment models were nearly twice those measured by two conventional methods (using either mean or 'ideal' values for P_A tension in simple homogeneous models). Thus, their ratio of conventional to 'corrected' $D_{L_{O_2}}$ was roughly 0.5; this is considerably lower than our $D_{L_{O_2}}$-3C/$D_{L_{O_2}}$-Qwt ratio, which ranged from 0.78 ± 0.05 at rest to 0.87 ± 0.01 during maximal hypoxic exercise.

Our $D_{L_{O_2}}$-Qwt model allows for the effect of $\dot{V}_A/\dot{Q}$ inhomogeneity, but assumes uniform $D/\dot{Q}\beta$ ratios throughout the lung. If this model were taken as the basis for comparison to the results of Geiser *et al.* (1983), two conclusions could be drawn. (1) Even our simple three compartment model ($D_{L_{O_2}}$-3C, defined by inert gas shunt and deadspace) may offer an improvement over conventional estimates of $D_{L_{O_2}}$, presumably because this model more closely approximates the true mean $\dot{V}_A/\dot{Q}$ ratio and $P_{A_{O_2}}$ in the perfused and ventilated compartment than do other simpler models based solely on CO_2 exchange. (2) Ignoring $\dot{V}_A/\dot{Q}$ inhomogeneity causes significant underestimation of $D_{L_{O_2}}$ in the normal lung, even if shunt and deadspace are known. The $D_{L_{O_2}}$-3C/$D_{L_{O_2}}$-Qwt ratios indicate that this underestimation is roughly 22% at rest and 13% during maximal hypoxic exercise.

Our approach also allows the effect of $D/\dot{Q}\beta$ inequality to be examined indirectly by comparing the results derived from our ventilation and perfusion weighted models. The ventilation weighted model ($D_{L_{O_2}}$-Vwt) assigns the distribution of the diffusing capacity

in proportion to the compartmental ventilations estimated from MIGET. Since the MIGET model contains $\dot{V}_A/\dot{Q}$ inequalities, an inhomogeneous distribution of D to $\dot{Q}$ results from this assignment of D, as shown in fig. 1. It is important to emphasize that this does not represent an actual measurement of $D/\dot{Q}\beta$ ratios in the lung, but is simply a convenient way to model such effects. Comparing the ventilation weighted model to the perfusion weighted model shows that the effect of a relatively small degree of $D/\dot{Q}\beta$ inequality could be significant, even in the normal lung. The overall ratio of DL_{O_2}-Vwt to DL_{O_2}-Qwt of 1.15 seen during heavy exercise indicates that ignoring the effect of $D/\dot{Q}\beta$ inequalities could produce underestimation errors of roughly equal magnitude (15%) to those which result when $\dot{V}_A/\dot{Q}$ inequality is ignored. These errors would be additive when conventional methods are used to measure DL_{O_2}.

We have made no estimates of DL_{CO} here, but should emphasize that DL_{CO} and DL_{O_2} may behave quite differently in the presence of inequalities. Chinet *et al.* (1983) have shown that DL_{CO} is less sensitive to $D/\dot{Q}\beta$ inequalities than DL_{O_2} because the perfusive conductance for CO is so high, however, CO is more sensitive to the effect of $\dot{V}_A/D$ inequalities than O_2 in simple models where 'ideal' alveolar P_{CO} is used in the computation. Thus in the presence of $\dot{V}_A/D$ inhomogeneity an actual overestimation of the true DL_{CO} may occur – exactly the opposite to what occurs for DL_{O_2}.

DL_{O_2} during exercise

Meyer *et al.* (1981) have reported simultaneous measurements of DL_{CO} and DL_{O_2} in normal subjects using the rapid rebreathing method at rest and four levels of light exercise. Their mean 'resting' value of 47.0 ± 2 for DL_{O_2} was similar to our mean DL_{O_2}-Qwt value of 41.1 ± 4.8. Although cardiac ouputs were similar in these cases, these rapid rebreathing measurements cannot be considered truly 'at rest' given the high minute ventilations ($100\ L \cdot min^{-1}$) necessary to perform the technique. This may explain the slightly higher results found at rest with that method. Also, as mentioned earlier, our resting results may be lower than the true mean values due to the requirement of a predicted minus measured Pa_{O_2} gradient of at least 1 Torr to calculate DL_{O_2}. During light exercise (75 W, $\dot{Q} = 14.6\ L \cdot min^{-1}$, $\dot{V}_{O_2} = 1.4\ L \cdot min^{-1}$) the rebreathing method gave a DL_{O_2} of 64.0 ± 13.0, this was again similar to our DL_{O_2}-Qwt result of 79.3 ± 4.9 at light exercise (75 W, $\dot{Q} = 17.0\ L \cdot min^{-1}$, $V_{O_2} = 1.2\ L \cdot min^{-1}$).

Our results at higher workloads and higher $\dot{V}_{O_2}$ values continue to increase to a maximum of 93.7 ± 2.6 for DL_{O_2}-Qwt and 109.3 ± 4.5 for DL_{O_2}-Vwt at the highest workload. These values are both somewhat higher than Meyer *et al.* There are several possible explanations for this difference. First, our maximum cardiac outputs are higher (mean $22.6\ L \cdot min^{-1}$) *vs* $16.6\ L \cdot min^{-1}$ for Meyer *et al.* (1981), and it is possible that their subjects had not fully recruited the pulmonary vasculature; at equivalent cardiac outputs, the two approaches are quite consistent with each other. Second, although the rebreathing method reduces the effect of $\dot{V}_A/\dot{Q}$ inequality, it cannot eliminate it completely and therefore will still tend to underestimate the true diffusing capacity. Third, the assumption of a constant capacitance coefficient (β) in our algorithm does introduce a small positive bias into the data as shown by the re-analysis using a Bohr

integration procedure described above. Finally, as already mentioned, the 'resting' measurements made using the rebreathing technique may be slightly high; this would tend to mask any subsequent increase in $D_{L_{O_2}}$ during exercise and produce a reduced slope of $D_{L_{O_2}}$ *vs* $\dot{V}_{O_2}$.

The increase in $D_{L_{O_2}}$ during exercise has been attributed to distention and recruitment of pulmonary capillaries as pulmonary arterial pressure rises. Of interest in our data is the relationship between $D_{L_{O_2}}$ and $\dot{Q}$, which suggests that $D_{L_{O_2}}$ may approach a plateau with respect to cardiac output at values above two to three times the resting cardiac output. One explanation for this is that the early rapid increase is predominately due to vascular recruitment; this may be essentially complete when cardiac output reaches two to three times the resting value with relatively little increase in pulmonary arterial pressure being required. The subsequent slower rise in $D_{L_{O_2}}$ is consistent with ongoing distention of the capillary bed as vascular pressure slowly rises further. This analysis is consistent with both topographical (Bake *et al.*, 1968) and inert gas results (Hammond *et al.*, 1986a,b; Wagner *et al.*, 1986): recruitment, particularly in the upper zones, could produce the improved topographical distribution of perfusion seen with isotopes during moderate exercise; any mechanical inhomogeneity in the lung could cause functional $\dot{V}_A/\dot{Q}$ inequality by altering the extent of regional capillary distention, and thus perfusion.

Comparison to morphometry

Morphometric measurements from Weibel (1984) predict a maximal Dm of 560 ml · min^{-1} · Torr^{-1}, and a maximal $D_{L_{O_2}}$ of approximately 135 ml · min^{-1} · Torr^{-1} in normal man assuming: (1) a mean reaction rate (theta) of 0.85 ml · ml^{-1} · min^{-1} · Torr^{-1} for O_2 in whole blood and (2) a pulmonary capillary volume of 200 ml. Most resting measurements of $D_{L_{O_2}}$ are substantially below this maximal predicted value and thus estimates of maximal $D_{L_{O_2}}$ have been attempted during exercise. These measurements in exercising man have produced a broad range of results from as low as 40 ml · min^{-1} · Torr^{-1} using isotopic O_2 methods to as high as 100 ml · min^{-1} · Torr^{-1} using rebreathing methods, as outlined in a recent review by Piiper and Scheid (1980). The corresponding mean maximum $D_{L_{CO}}$ (over 27 references cited in that review) was 40 ± 15 ml · min^{-1} · Torr^{-1}. Thus, although it is generally agreed that D increases during exercise, the amount of this increase remains open to question as does the absolute maximum value for $D_{L_{O_2}}$ in man.

Our maximal uncorrected $D_{L_{O_2}}$ values (mean $D_{L_{O_2}}$-3C = 81.1 ± 1.9 ml · min^{-1} · Torr^{-1}) fall roughly in the middle of the range of previously reported measurements. The absolute values we have derived when including the effects of $\dot{V}_A/\dot{Q}$ inequality ($D_{L_{O_2}}$-Qwt mean = 93.7 ± 2.6 ml · min^{-1} · Torr^{-1}), although still somewhat below the theoretical maximum predicted from morphometry, are in closer agreement than conventional methods. When the effects of $D/\dot{Q}\beta$ inhomogeneity are modeled, the results are closer still (mean maximal $D_{L_{O_2}}$-Vwt = 109.3 ± 4.5 ml · min^{-1} · Torr^{-1}). These latter two estimates are both significantly greater than the 3 compartment model ($P < 0.05$ for each). Thus, even in the normal human lung, both $\dot{V}_A/\dot{Q}$ inequality and

potential $D/\dot{Q}\beta$ inequalities have significant effects on the estimation of true D. When these inhomogeneities are considered, the resulting physiologic measurements more closely reflect actual lung morphometry.

We would expect the underestimation of $D_{L_{O_2}}$ by classical methods to be much more pronounced as the degree of $\dot{V}_A/\dot{Q}$ inequality increases in diseased lungs. The log standard deviation of the perfusion distribution (Log_{SDQ}) may be used as an index of overall $\dot{V}_A/\dot{Q}$ inequality; a typical value of this index in normal subjects during heavy exercise is 0.6. In contrast to this, a patient with moderately severe chronic airflow obstruction may have a Log_{SDQ} of 1.5 or greater; D will be substantially underestimated if this degree of $\dot{V}_A/\dot{Q}$ inequality is not considered, as is the case when using conventional methods to measure diffusing capacity. The errors which result could have clinical significance.

Summary. Three models to estimate $D_{L_{O_2}}$ were formulated from measured inert gas retention and excretion data and oxygen exchange. These models were used to investigate the effects of $\dot{V}_A/\dot{Q}$ and $D/\dot{Q}\beta$ inhomogeneity on the measurement of $D_{L_{O_2}}$ in man in hypoxia. The results indicate that both types of inhomogeneity will produce significant underestimation of $D_{L_{O_2}}$ in normal lungs and can be expected to become more important in diseased lungs with greater inequalities. The data suggest that the increase may not be linear, but rather tends to plateau at higher cardiac outputs. The maximal $D_{L_{O_2}}$ values predicted by these multi-compartment models are in closer agreement with morphometric predictions than conventional methods using simpler homogeneous models.

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