Importance of adjusting carbon monoxide diffusing capacity ($D_L{CO}$) and carbon monoxide transfer coefficient ($K{CO}$) for alveolar volume

D. C. JOHNSON

Department of Medicine (Pulmonary and Critical Care Unit), Massachusetts General Hospital and Harvard Medical School, Boston, MA, U.S.A.

The volume dependence of single breath carbon monoxide diffusing capacity ($D_L{CO}$) and carbon monoxide transfer coefficient ($K{CO}$) was determined in 24 healthy subjects. The change in $D_L{CO}$ [fraction of $D_L{CO}$ measured at total lung capacity (TLC)] to change in alveolar volume [fraction of alveolar volume ($V_A$) at TLC] closely fitted a simple linear regression and matched a theoretical model. As $V_A$ decreased, $D_L{CO}$ fell linearly and $K{CO}$ increased as expected from the relation of $D_L{CO}$ to $V_A$. The equations for adjustment of predicted $D_L{CO}$ and $K{CO}$ for alveolar volume are:

$$D_L{CO}/D_L{CO}_{TLC} = 0.58 + 0.042V_A/V_A_{TLC}$$

$$K{CO}/K_{CO}_{TLC} = 0.42 + 0.58/(V_A/V_A_{TLC})$$

$D_L{CO}$ and $K{CO}$ were evaluated in 2313 patients. Subgroups of patients with asthma, emphysema, extrapulmonary lung disease, interstitial lung disease and lung resection were identified. Unadjusted $D_L{CO}$ and $K{CO}$ percent predicted values showed large differences and much variability, so can be misleading. As expected, $K{CO}$ and $D_L{CO}$ percent predicted values adjusted for alveolar volume were nearly identical. Subgroups have characteristic patterns of $V_A$ and unadjusted and adjusted $D_L{CO}$ and $K{CO}$. Changes in $D_L{CO}$ and $K{CO}$ with alveolar volume are relevant for accurate interpretation of diffusion in patients with low lung volumes. Adjusting predicted $D_L{CO}$ and $K{CO}$ for alveolar volume provides a better assessment of lung function.

Key words: asthma; $D_L{CO}$; $D_L{CO}/V_A$; emphysema; interstitial lung disease; $K{CO}$; lung volume; normals; sarcoidosis.

Introduction

Carbon monoxide diffusing capacity ($D_L{CO}$) has been shown to be a sensitive indicator of gas exchange, being abnormal in patients with interstitial lung disease, pulmonary vascular lung disease and emphysema. The single breath technique also determines the volume ($V_A$) of helium distribution. The ratio $D_L{CO}/V_A$, or $K{CO}$, measures diffusing capacity per litre alveolar volume. Uptake of CO can be affected by factors other than intrinsic lung disease. Anemia lowers $D_L{CO}$ (1,2,3). Exercise increases $D_L{CO}$ (4,5). Pulmonary hemorrhage can elevate $D_L{CO}$ (6).

Predicted $D_L{CO}$ values are traditionally adjusted for age, height, sex and race. In an attempt to have $D_L{CO}$ % predicted provide information about lung function independent of hemoglobin. The American Thoracic Society (7) recommends that $D_L{CO}$ values be adjusted for hemoglobin. Another factor which influences both $D_L{CO}$ and $K{CO}$ is lung volume. However, the ATS has not recommended that predicted $D_L{CO}$ or $K{CO}$ be adjusted for lung volume. There is much confusion over how to adjust predicted values of $D_L{CO}$ and $K{CO}$ for lung volume, with investigators using widely varying methods (8,9,10). This has contributed to confusion and controversy about how to interpret $D_L{CO}$ and $K{CO}$ as measures of lung function.

This study was designed to show how lung volume affects $D_L{CO}$ and $K{CO}$ in healthy subjects, propose a method for
adjusting predicted $D_{L}CO$ and KCO values for alveolar volume, and then apply this to a broad patient population. Subgroups of patients were identified to determine if patterns of $D_{L}CO$, KCO and VA exist for particular pulmonary conditions.

## Methods

### NOMENCLATURE

Alveolar volume, or $VA$, is the volume of distribution of helium, expressed in body temperature and pressure saturated (BTPS) units, from a single-breath $D_{L}CO$ test. KCO equals $D_{L}CO/VA$. Predicted or percent predicted $D_{L}CO$ and KCO unadjusted for alveolar volume indicate the predicted or percent of predicted values measured at TLC. Predicted or percent predicted $D_{L}CO$ and KCO adjusted for alveolar volume indicate the predicted or percent of predicted values adjusted for the subject’s VA. $D_{L}CO$ and KCO adjusted for alveolar volume can also be called $D_{L}CO$ and KCO adjusted for VA.

### PREDICTED VALUES

Prediction equations were used for forced expiratory volume in 1 sec (FEV$_1$), FEV$_1$/vital capacity (VC), VC (11), TLC (12) and $D_{L}CO$ (13). While there is no consensus on how to adjust predicted values for ethnic differences (14), predicted values for FEV$_1$, VC, TLC, $D_{L}CO$ and VA were reduced by 10% for blacks. If the hemoglobin was known, the predicted $D_{L}CO$ was adjusted (1). Predicted VA was calculated from equations for TLC (12) from which predicted dead space was subtracted. The predicted dead space (ml BTPS) equals 1-32 Height (cm) +0.86 Age (years) -110, which is based on an equation of Harris et al. (15). The predicted KCO equals predicted $D_{L}CO$/predicted VA. The predicted $D_{L}CO$ and KCO adjusted for alveolar volume use the regression equations determined in this study of healthy subjects to adjust the predicted value for the patient’s VA.

Alternative methods to calculate predicted KCO used equations derived from single breath $D_{L}CO$ measurements for alveolar volume and for KCO. Miller et al. (13) provides equations for single breath TLC and single breath $D_{L}CO$/TLC among non-smokers. These were adjusted for dead space to yield predicted KCO equals predicted $D_{L}CO$/predicted VA (with $VA$=single breath; TLC=dead space); and to yield predicted KCO equals predicted $D_{L}CO$/TLC * TLC/VA.

### $D_{L}CO$ test

The subjects took a deep breath in, expired to residual volume, inspired rapidly a gas mixture containing approximately 0.3% CO, 10% He, 21% O$_2$, balance N$_2$, held their breath for about 9 sec and then expired rapidly. Maneuvers were performed using a P.K. Morgan Transfertest (Morgan Medical Ltd., Rainham, U.K.). Alveolar samples were collected after the washout volume was discarded. To ensure sufficient alveolar sample for measurements, the alveolar sample was 0.9 l for expected inspired volumes $>$1.5 l, 0.6 l for volumes 1-2-1.5 l and 0.5 l for volumes $<$1.2 l. The washout was 0.9 l for expected inspired volumes $>$2-1 l, 0.5 l for volumes 1.7-2-1 l and 0.3 l for volumes $<$1.7 l. The interval between consecutive measurements was at least 5 min. Helium and CO were measured in the inspired gas and alveolar sample. Inspired volume was measured from a paper kymograph with 50 ml resolution.

### CALCULATION OF VI, VA, $D_{L}CO$ AND KCO

Inspired volume ($VI$), alveolar volume ($VA$), diffusing capacity ($D_{L}CO$) and KCO ($D_{L}CO/VA$), were calculated from the inspired volume (atmospheric pressure temperature dry (APTD), room temperature, barometric pressure and inspired and alveolar sample concentrations of He and CO using estimated values for dead space and for alveolar $PCO_2$ (7). CO backpressure was ignored in the calculation of $D_{L}CO$.

### NORMAL SUBJECTS

In 24 healthy non-smokers, values of $VA$, $D_{L}CO$ and KCO at functional residual capacity (FRC), total lung capacity (TLC) and two intermediate volumes were determined after informed consent. Subjects were required to have no known respiratory or cardiac disease, and have FEV$_1$, FVC, TLC and $D_{L}CO$ values above 75% predicted. The group consisted of 13 males and 11 females with ages ranging from 24-66 years ($40 \pm 12$) (mean $\pm$sd).

### Procedure in study of normals

Spirometry (FEV$_1$, FVC) and expiratory reserve volume were measured using a P.K. Morgan rolling seal spirometer. The best FEV$_1$ and FVC were chosen from three efforts, and the average expiratory reserve volume (ERV) of two tests was used. Functional residual capacity (FRC) was determined by plethysmography. $D_{L}CO$ and KCO were determined at lung volumes near FRC, FRC +1/3 inspiratory capacity (IC), FRC +2/3 IC, and TLC. The subjects aimed for the targeted volume by observing a digital display of volume inspired. The order of the testing was selected randomly without repeats from the 24 possible test sequences. After completing these four maneuvers, a final $D_{L}CO$ test was performed at TLC.

### Eect of lung volume on $D_{L}CO$ and KCO

The average of the two measurements at TLC provided $D_{L}CO_{tlc}$, $VA_{tlc}$ and KCO. The $D_{L}CO$, $VA$ and KCO measured at the three other lung volumes for each subject were expressed as a fraction of the TLC value.
**Model of dependence of $D_{1,CO}$ and $KCO$ on $VA$**

A model to predict the dependence of $D_{1,CO}$ and $KCO$ on $VA$ is to use the relationship $1/D_{1,CO}=1/Dm+1/\theta Vc$, where $\theta$ equals the rate of CO uptake by blood, $Dm$ equals the membrane conductance component of $D_{1,CO}$, and $Vc$ equals the pulmonary capillary blood volume. This relates diffusion to the components of membrane diffusion and pulmonary blood volume. Solving the equation $1/D_{1,CO}=1/DM+1/\theta Vc$, yields $D_{1,CO}=Dm*\theta Vc/(\theta Vc+Dm)$. If $\theta Vc$ stays constant as lung volume changes (16), and $Dm$ increases by $kVA^{3/3}$, then the relationship becomes $D_{1,CO}=Dm VA^{2/3}\theta Vc/(\theta Vc+Dm VA^{2/3})$.

**PATIENTS**

All patients studied in the pulmonary function laboratory at a large teaching hospital who had both spirometry and $D_{1,CO}$ results on our on-line data base were included. Two thousand three hundred and thirteen patients were identified. The most recent $D_{1,CO}$ for each patient was analyzed, along with spirometry and plethysmography results from the same day. Most patients had two or three $D_{1,CO}$ measurements. Mean $D_{1,CO}$ and $VA$ values were used.

Subsets of patients were determined by pulmonary function test (PFT) criteria, and by a recorded diagnosis of sarcoidosis. PFT criteria for obstruction were $FEV_1<60\%$ predicted and $FVC/VC<70\%$ predicted. Criteria for elevated lung volumes was $TLC>105\%$ predicted, or if plethysmography was not done $VA>80\%$ predicted. Restriction was present if $TLC<80\%$ predicted, or if plethysmography was not done $VA<75\%$ predicted.

Normal diffusion for alveolar volume was defined as $D_{1,CO}>80\%$ predicted for alveolar volume, while low diffusion for alveolar volume was $D_{1,CO}<75\%$ predicted for alveolar volume.

PFT criteria were used to identify patients with probable emphysema, asthma, interstitial lung disease and extrapulmonary cause for low lung volume. Emphysema was identified as obstruction, elevated lung volumes and low diffusion for alveolar volume. Interstitial lung disease was identified as low VC without obstruction ($VC<85\%$ predicted and $FEV_1/VC>90\%$ predicted), restriction and low diffusion for alveolar volume. Asthma was identified as obstruction, elevated lung volumes and normal diffusion for alveolar volume. Extrapulmonary cause for low lung volume was identified as low lung volume ($VA<70\%$ predicted and $TLC<80\%$ predicted if done), low vital capacity (<70% predicted) and normal diffusion for alveolar volume.

Patients with both preoperative and postoperative $D_{1,CO}$ tests who has lung resections from 7/94 to 4/97 were identified. The group included one segmental resection, one pneumonectomy and seven lobectomy patients.

**STATISTICS**

Linear regression analysis was performed on $D_{1,CO}/D_{1,COtlc}$ vs. $VA/VAtlc$, on $KCO/KCOtlc$ vs. $VA/VAtlc$ and on $KCO/KCOtlc$ vs. $1/(VA/VAtlc)$. To determine whether age influenced the effect of lung volume on $D_{1,CO}$ and $KCO$, linear regression analyses were also performed on the younger 12 subjects (age 30±2.8) and older 12 subjects (age 51±7.0). Student’s $t$-test was used to compare the first and second measurements of $D_{1,CO}$ or of $KCO$ at TLC. Mean, standard deviation and confidence interval analysis was performed on the differences between $KCO$ and $D_{1,CO}$ values. Values are reported as mean ± SD.

**Results**

**HEALTHY SUBJECTS**

As lung volume decreased $D_{1,CO}$ fell and $KCO$ increased in each of the 24 subjects. $D_{1,CO}$ varied linearly with $VA$ (Fig. 1). The relationship between $KCO$ and $VA$ was well explained by a linear change in $KCO$ vs. $1/VA$ (which results in a curvilinear change in $KCO$ vs. $VA$). The regression equations and 95% confidence intervals for the slopes were $D_{1,CO}/D_{1,COtlc}=0.58±0.42 \quad VA/VAtlc$ ($R^2=0.70$, CI 0.37 to 0.47 and $KCO/KCOtlc=0.43±0.37/ (VA/VAtlc)$ ($R^2=0.92$, CI 0.53 to 0.61).

The 12 younger subjects had different regression coefficients than did the older subjects. For the younger subjects, $D_{1,CO}/D_{1,COtlc}=0.64±0.37 \quad VA/VAtlc$ and $KCO/KCOtlc=0.39±0.62/(VA/VAtlc)$. For the 12 older subjects, $D_{1,CO}/D_{1,COtlc}=0.51±0.50 \quad VA/VAtlc$ and $KCO/KCOtlc=0.52±0.49/(VA/VAtlc)$. The results from these equations are within 0.02 of those for the equations for the entire group over the range of $VA/VAtlc$ from 0.8–1.1, and within 0.03 of those for $VA/VAtlc$ from 0.7–1.2.

![Fig. 1 $D_{1,CO}$ and $KCO$ vs. $VA$ in 24 normal subjects expressed as fraction of value measured at TLC. Linear regression equations are $D_{1,CO}/D_{1,COtlc}=0.58±0.42 \quad VA/VAtlc$; and $KCO/KCOtlc=0.43±0.57 \quad (VA/VAtlc)$. (For abbreviations see text.)](image-url)
As expected, the slope and intercept for $D_1\text{CO}$ vs. $VA$ were nearly identical to the intercept and slope for $KCO$ vs. $VA$. Using the intercept and slope from the $D_1\text{CO}$ vs. $VA$ for the slope and intercept of $KCO$ vs. $VA/LCO$ yields the equation $KCO/LCO = -0.42 + 0.58(VA/LCO)$. This equation is within 1% of that determined by regression over the range of $VA/LCO$ from 0–1.5, equals 1 at $VA/LCO = 1$, and results in $KCO$ percent predicted for alveolar volume $= D_1\text{CO}$ percent predicted for alveolar volume.

There were no significant differences between the first and second measurements of $D_1\text{CO}$ or of $KCO$ at TLC (ratios of second/first values of 1.00±0.05 for both), indicating no effect of increasing CO backpressure. There was good agreement between lung volume determined by helium dilution during $D_1\text{CO}$ testing and by plethysmography, with $VA/LCO = 96.2±6.4\%$. The ratio of $VA$ by single breath helium dilution to $VA$ by plethysmography (TLC=estimated dead space) was $98.7±6.5\%$. The inspired volume with maximal inspiration during $D_1\text{CO}$ testing was near that of the largest VC by spirometry, with $V/I/VC = 95.5±6.7\%$.

**MODEL**

The dependence of $D_1\text{CO}$ and $KCO$ on $VA$ can be described using a model which assumes that the membrane component of diffusion changes with lung volume while the blood component of diffusion does not change. Figure 2 compares the equations $D_1\text{CO}/D_1\text{CO}LCO = -0.58 + 0.42 VA/LCO$ and $KCO/KCO LCO = -0.42 + 0.58(VA/LCO)$ to those expected for different exponents for $VA$, and typical values for $Dm$ of 50 and $\theta Vc$ of 80 at a TLC of 51. For the model with $Dm$ proportional to $VA^{-2/3}$, the empiric equation and the model for both $D_1\text{CO}/D_1\text{CO}LCO$ and $KCO/KCO LCO$ are within 0.03 of each other over the range of $VA/LCO$ from 0–1.2. Varying the $VA$ from 4–61 or the $\theta Vc$ from 70–90 changes the results by a few percent over this range.

**PATIENTS**

Of the 2313 patients who underwent single breath $D_1\text{CO}$ testing, 2224 (96%) also had spirometry and 1964 (85%) had plethysmography on the same day. Twelve hundred and eighty-five (56%) were male, 137 (6%) black and the group’s age was 55.2±16.2 years (range 12–97 years; 15 under age 18; 85 over age 79).

There was much variation between $KCO$ and $D_1\text{CO}$ percent predicted values unadjusted for alveolar volume (Fig. 3). $D_1\text{CO}$ was lower than $KCO$ by 12.9±17.8%. Thirteen hundred and sixteen patients (57%) had a discrepancy between $KCO$ and $D_1\text{CO}$ of more than 10%, 718 (31%) a discrepancy over 20% and 371 (16%) a discrepancy over 30%. Similar results were found using other sets of prediction equations. $D_1\text{CO}$ was lower than $KCO$ by 15.7±18.7% using single breath equations for $VA$, and by 11.8%±17.8% using single breath equations for $D_1\text{CO}/VA$. As expected, adjusting $D_1\text{CO}$ and $KCO$ predicted values for alveolar volume yielded nearly identical percent predicted $D_1\text{CO}$ and $KCO$ values ($KCO–D_1\text{CO}=0.03±0.15\%$).

Adjusting for alveolar volume increases $D_1\text{CO}$ percent predicted values (Fig. 4). The unadjusted $D_1\text{CO}$ is lower

![Fig. 2. Estimated $D_1\text{CO}$ and $KCO$ as fraction of value at TLC. The dark solid line represents the equation $D_1\text{CO}/D_1\text{CO}LCO = -0.58 + 0.42 VA/LCO$. The thin solid line uses the equation $D_1\text{CO} = Dm VA^{-2/3} \theta Vc/(\theta Vc + Dm VA^{-2/3})$, which assumes that $\theta Vc$ stays constant and $Dm$ increases by $VA^{-2/3}$. The dashed line uses the equation $D_1\text{CO} = Dm VA \theta Vc/(\theta Vc + Dm VA)$, which assumes that $\theta Vc$ stays constant and $Dm$ increases proportionate to $VA$. Values for $VA/LCO$ of 51, $Dm$ of 50 and $\theta Vc$ of 80 are used. The range of $VA/LCO$ from 0–1.2, the values for the first two equations are within 0.03 of each other. (For abbreviations see text.)

![Fig. 3. $KCO$ and $D_1\text{CO}$ unadjusted for alveolar volume percent predicted values ($KCO$ vs. $D_1\text{CO}$) in 2313 patients. $KCO–D_1\text{CO}=12.9±17.8\%$ (mean±sd). (For abbreviations see text.)](image-url)
There is some overlap between probable emphysema and probable interstitial lung disease (ILD) patients, but most emphysema patients had lower unadjusted KCO due to larger VA. While the selection criteria specified that none of the ILD group had KCO adjusted for alveolar volume >80%. 52% of the ILD group had unadjusted KCO >80% and 13% had unadjusted KCO >100%. For emphysema patients, none (by selection criteria) had adjusted KCO >80% and only 5% had unadjusted KCO >80%.

The 122 patients with recorded diagnoses of sarcoidosis had KCO and DlCO values which overlapped those of the ILD group and extended into the normal range. Half of sarcoidosis patients had unadjusted DlCO >80%. While 75% had unadjusted KCO >80%, 60% had KCO adjusted for alveolar volume >80%.

Lung resection patients had percent predicted results (preoperative, postoperative) of FEV1 (79%, 62%), VC (85%, 63%), TLC (109%, 87%), unadjusted DlCO (82%, 61%), unadjusted KCO (88%, 92%), F'A (94%, 68%), DlCO adjusted for alveolar volume (85%, 69%) and KCO adjusted for alveolar volume (84%, 69%).

Comparison to spirometry and lung volume results provides quality control checks on the DlCO results. The inspired volume (VI) should be very similar to the vital capacity. The VI of healthy subjects was 94±6% of VC. For the entire patient group, VI was 91±13% of VC. If VI matches VC, the DlCO test was performed at TLC. If VI is smaller than VC, the test was performed below TLC if the patient inspired from residual volume (RV).

Another check on the validity of the DlCO test, as well as providing an assessment of lung volume, is to compare VA to TLC. The VA provides the lung volume in which helium is distributed during the DlCO test. Healthy subjects had a VA 96±6% of their TLC determined by plethysmography. The interstitial lung disease group had low lung volumes, but their VA was near their TLC (VA 91±17% of TLC), as expected since there is not much airway obstruction in the ILD group. If moderate to severe obstruction was present. TLC was increased and the VA was lower than TLC, being 58±15% of TLC in the emphysema group and 68±13% of TLC in the asthma

### Table 1. PFT results among subgroups of 2313 patients [percent predicted (%p) values, or percent (%)] among patients with probable diagnoses of emphysema, asthma, interstitial lung disease (ILD) and extrapulmonary restrictive disease by PFT criteria, or reported diagnosis of sarcoidosis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>FEV1 %p</th>
<th>FEV1/VC %p</th>
<th>VC %p</th>
<th>VA %p</th>
<th>TLC %p</th>
<th>VA/TLC %p</th>
<th>VI/VC %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>165</td>
<td>33.1 ± 11.5</td>
<td>53.4 ± 10.6</td>
<td>61.4 ± 15.7</td>
<td>81.3 ± 19.4</td>
<td>135.8 ± 22.2</td>
<td>58.4 ± 14.7</td>
<td>89.5 ± 17.1</td>
</tr>
<tr>
<td>Asthma</td>
<td>22</td>
<td>39.7 ± 8.6</td>
<td>59.9 ± 6.8</td>
<td>66.4 ± 13.1</td>
<td>85.0 ± 13.8</td>
<td>126.7 ± 14.5</td>
<td>66.0 ± 12.5</td>
<td>98.4 ± 15.8</td>
</tr>
<tr>
<td>ILD</td>
<td>175</td>
<td>55.9 ± 15.6</td>
<td>106.3 ± 9.1</td>
<td>52.6 ± 14.1</td>
<td>61.1 ± 13.1</td>
<td>66.7 ± 9.9</td>
<td>89.9 ± 17.4</td>
<td>9.10 ± 13.4</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>36</td>
<td>55.5 ± 13.2</td>
<td>101.2 ± 12.4</td>
<td>54.7 ± 10.7</td>
<td>61.5 ± 7.7</td>
<td>72.3 ± 6.4</td>
<td>85.9 ± 8.8</td>
<td>90.3 ± 13.3</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>122</td>
<td>84.6 ± 19.7</td>
<td>99.0 ± 11.1</td>
<td>85.5 ± 17.3</td>
<td>86.9 ± 16.5</td>
<td>98.6 ± 16.8</td>
<td>86.6 ± 10.6</td>
<td>91.6 ± 8.8</td>
</tr>
<tr>
<td>All</td>
<td>2313</td>
<td>71.1 ± 24.6</td>
<td>93.3 ± 18.4</td>
<td>75.4 ± 20.2</td>
<td>85.6 ± 19.1</td>
<td>104.0 ± 23.2</td>
<td>82.2 ± 21.4</td>
<td>90.9 ± 12.6</td>
</tr>
</tbody>
</table>

VC: vital capacity during spirometry test; VA: alveolar volume by single-breath helium dilution; TLC: total lung capacity by plethysmography; VI: inspired volume during DlCO test. Values are mean ± SD.
D_{1}CO and KCO results among subgroups of 2313 patients [Percent predicted for normal lung volume (unadjusted), percent predicted for the subjects’ alveolar volume (adjusted), and differences between predicted values]

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>$D_{1}$CO unadjusted</th>
<th>KCO unadjusted</th>
<th>$D_{1}$CO adjusted</th>
<th>$D_{1}$CO* (adjusted–unadjusted)</th>
<th>KCO* (adjusted–unadjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema</td>
<td>165</td>
<td>36·6±16·7</td>
<td>46·1±20·9</td>
<td>39·2±17·3</td>
<td>2·8±3·6</td>
<td>−6·7±8·5</td>
</tr>
<tr>
<td>Asthma</td>
<td>22</td>
<td>90·8±12·4</td>
<td>108·3±14·7</td>
<td>95·9±10·8</td>
<td>5·6±5·4</td>
<td>−11·7±11·2</td>
</tr>
<tr>
<td>ILD</td>
<td>175</td>
<td>47·3±12·5</td>
<td>79·2±21·5</td>
<td>54·8±13·8</td>
<td>9·0±3·6</td>
<td>−22·8±11·9</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>36</td>
<td>79·6±7·3</td>
<td>131·0±16·7</td>
<td>92·1±7·7</td>
<td>15·0±3·3</td>
<td>−36·0±13·4</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>122</td>
<td>80·0±19·2</td>
<td>92·9±19·0</td>
<td>84·0±18·3</td>
<td>3·9±5·5</td>
<td>−9·0±10·6</td>
</tr>
<tr>
<td>All</td>
<td>2313</td>
<td>71·6±25·4</td>
<td>84·5±26·9</td>
<td>75·5±25·1</td>
<td>3·7±3·2</td>
<td>−9·1±13·4</td>
</tr>
</tbody>
</table>

Patients with probable diagnoses of emphysema, asthma, interstitial lung disease (ILD) and extrapulmonary restrictive disease by PFT criteria, or reported diagnosis of sarcoidosis. $KCO$ adjusted for alveolar volume values are not shown since they are nearly identical to $D_{1}$CO adjusted for alveolar volume values. *Values for all groups are significantly ($P<0·05$, t-distribution) different from 0. Values are mean ±sd. (For abbreviations see text.)

Discussion

While it is known that lung volume influences $D_{1}$CO and $KCO$ (18,19,20,21,16), there is much confusion about how to adjust predicted values for alveolar volume, how to report them and their clinical significance. Some studies propose making an adjustment for $VA$ of reference prediction equations (22), others propose independent prediction equations based on sex, height, age and $VA$ (23), or both methods (10). This study proposes an easy method to adjust reference $D_{1}$CO and $KCO$ predicted values for alveolar volume, how to report them, and shows that the results have much clinical significance.

Lung volume influences $D_{1}$CO and $KCO$ ($D_{1}$CO/$VA$), with reductions in $D_{1}$CO and increases in $KCO$ at smaller lung volumes in healthy subjects. There are linear relationships between $D_{1}$CO and $VA$ and between $KCO$ and $1/VA$. To adjust predicted $D_{1}$CO at TLC to the patient’s alveolar volume, the factor 0·58+0·42 $VA$/VAtlc was determined by regression analysis. To adjust predicted $KCO$ at TLC the factor 0·42+0·58($VA$/VAtlc) is recommended. With these factors and prediction equations for $VA$ and for $D_{1}$CO used to calculate predicted $D_{1}$CO/$VA$, the percent predicted $D_{1}$CO for alveolar volume and $KCO$ for alveolar volume will be equal. The reductions in $D_{1}$CO and increases in $KCO$ in the healthy subjects occur with incomplete alveolar expansion.

Table 3. Pattern of $D_{1}$CO percent predicted parameters among groups of patients with lung resection, or probable diagnoses of emphysema, asthma, interstitial lung disease (ILD), and extrapulmonary lung disease

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>$D_{1}$CO</th>
<th>KCO</th>
<th>$D_{1}$CO</th>
<th>KCO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(for normal $VA$)</td>
<td>(for patient’s $VA$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema</td>
<td>normal</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Asthma</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>ILD</td>
<td>low</td>
<td>low</td>
<td>below 100%</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>low</td>
<td>low</td>
<td>elevated</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Lung resection</td>
<td>low</td>
<td>low</td>
<td>normal</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

$D_{1}$CO and $KCO$ for normal $VA$ use predicted values unadjusted for alveolar volume. $D_{1}$CO and $KCO$ for the patient’s $VA$ adjust for alveolar volume. Patients with probable diagnoses were selected by PFT criteria from among 2313 patients. (For abbreviations see text.)
Krogh factor (16), the ‘normalization ratio’ (25), KCO and diffusion coefficient (26). KCO is recommended as a shorter term for $D_L CO/VA$.

This study found that the effect of lung volume on $D_L CO$ was modest, with a 24% fall in $VA$ needed to produce a 10% fall in $D_L CO$. The effect on KCO is larger, with a 24% fall in $VA$ causing a 20% increase in KCO. Thus unadjusted prediction equations underestimate a patient’s $D_L CO$ (% predicted) and over-estimate a patient’s KCO (% predicted) when the lung volume is below TLC.

The reduction in $D_L CO$ at lower lung volumes is primarily due to lower membrane diffusion with pulmonary capillary blood volume remaining relatively constant (16,27,28). Anatomic studies show that alveolar membrane thickness changes little as lung volume changes (29). The changes in $D_L CO$ with increased inspired volumes do not appear related to changing regional distribution (30). $D_L CO$ and KCO increase immediately after a deep breath compared to after 10 min of tidal breathing (31). There is hysteresis, with $D_L CO$ being higher when a lung volume is reached by exhalation compared to inhalation (21). This may be related to more bulging of capillaries into alveoli on deflation (32).

Lung volume primarily affects the membrane conductance component ($D_m$), with much smaller changes in capillary blood volume ($V_c$) (16,27,28). When the relation of lung volume to the membrane conductance component ($D_m$) of $D_L CO$ was studied, different relations were found, with an exponent between 0.6 and 1.0 for most individuals (16). The linear relationship between $D_L CO$ and $VA$ found in this study matched very closely those predicted from a model in which the membrane conductance component of diffusion varies with surface area.

Stam et al. (10) found an age dependence of the volume dependence of KCO. Younger healthy subjects had a greater rise in KCO as volume decreased than older subjects. This study confirmed these findings, with a steeper slope of KCO vs. $1/VA$ in younger subjects. However, the differences in slopes led to only minor adjustments in $D_L CO$ and KCO equations compared to the equations for the entire group.

The physiological significance of $D_L CO/VA$ has been controversial. $D_L CO/VA$ has been referred to as the ‘$D_L CO$ corrected for lung volume’ (8), implying that KCO provides an assessment of diffusion which is independent of lung volume. However, this is not the case. Just as $D_L CO/ Hb$ does not correct $D_L CO$ for hemoglobin, $D_L CO/VA$ does not correct $D_L CO$ for $VA$.

Since many lung diseases affect both gas exchange and lung volume, prediction equations which assume a normal TLC make it difficult to sort out how much of an abnormality of DLCO is due to gas exchange versus how much is due to low lung volume. Predicted values that account for lung volume should allow better evaluation of gas exchange.

This study found much variation between KCO and $D_L CO$ percent predicted values unadjusted for alveolar volume. KCO was greater than $D_L CO$ for most of the 2313 patients studied (Fig. 3). The majority of patients had a discrepancy between KCO and $D_L CO$ of more than 10%,
nearly a third over 20%, and one sixth a discrepancy over 30%. Much different results were found when $D_1CO$ and $KCO$ predicted values were adjusted to account for alveolar volume, with adjusted $D_1CO$ and $KCO$ nearly identical. Thus $D_1CO$ or $KCO$ adjusted for alveolar volume provide a single measure of diffusion.

Some studies have questioned the validity of $KCO$ to assess disease. Kanengiser et al. (9) concluded that ‘volume ($D_1CO/VA$) relationships are not a measurement of (interstitial lung) disease’. However, since they did not adjust predicted values for alveolar volume, their study shows that $KCO$ values unadjusted for alveolar volume are not very helpful. Others promote $KCO$ as a more sensitive test of diffusion than $D_1CO$ (26,33). Agusti et al. (8) found discrepancies between $D_1CO$ and $KCO$, with a better correlation between $KCO$ and $aaDO_2$ and V/Q mismatch than for $D_1CO$ in patients with interstitial lung disease. Re-analyzing their data using the methods described in this paper yields unadjusted $D_1CO$ of 51±15% and $KCO$ of 99±28%. Adjusting for alveolar volume changes the $D_1CO$ and $KCO$ to 64±18%. Adjusted $D_1CO$ and $KCO$ correlated with their independent measures of gas exchange abnormalities. Only seven of their 15 patients had $KCO$ unadjusted for alveolar volume under 80% predicted, while 13 of 15 patients had $D_1CO$ and $KCO$ adjusted for alveolar volume under 80%.

Frans et al. (22) advocate adjusting $D_1CO$ and $KCO$ for alveolar volume in the presence of restrictive lung disease. They found that for patients with diffuse interstitial lung disease the arterial oxygen tension during exercise correlated very well with $D_1CO$ and $KCO$ adjusted for alveolar volume. Our results for volume dependence of $D_1CO$ in younger adults (age 30±2.8) were nearly identical to that found by Frans et al. (22) in healthy males aged 22–41 years. They found $D_1CO/D_1CO_{Otc}=0.642+0.358$ $VA/VA_{tr}$ vs. this study’s results of $D_1CO/ D_1CO_{Otc}=0.64+0.37$ $VA/VA_{tr}$.

Percent predicted $VA$, unadjusted $D_1CO$ and $KCO$, and $D_1CO$ and $KCO$ adjusted for alveolar volume show characteristic findings depending upon the patient’s disease as determined by PFT criteria (Tables 1, 2 and 3). Therefore, it is very helpful for the clinical to have all these values reported. Our laboratory reports single-breath $D_1CO$ results with both sets of predicted values (Table 4).

Patients with probable emphysema had an elevated TLC, normal or mildly low $VA$ and low unadjusted $D_1CO$ and $KCO$. Their $D_1CO$ adjusted for alveolar volume was slightly higher than unadjusted $D_1CO$ (2.7±3.7%).

Patients with probable interstitial lung disease had low unadjusted $D_1CO$ and a higher unadjusted $KCO$. Their $D_1CO$ adjusted for alveolar volume was higher than unadjusted $D_1CO$ by 9.0±3.6%, and $KCO$ adjusted for alveolar volume much lower (−22.8±11.9%) than unadjusted $KCO$. Most (87%) had an unadjusted $KCO$ below 100%. If unadjusted $KCO$ had been used to assess diffusion, 52% would have been called normal ($KCO>80$%). None had $KCO$ adjusted for alveolar volume $>80$%. Thus adjusted $KCO$ for alveolar volume is more sensitive than unadjusted $KCO$ in detecting interstitial lung disease.

Half the patients with probable extrapulmonary disease had unadjusted $D_1CO$ below 80% and thus could have been misidentified as having abnormal diffusion. Sixty-nine percent had a supernormal (>120%) unadjusted $KCO$. The group’s $D_1CO$ adjusted for alveolar volume was higher than unadjusted $D_1CO$ by 15.0±3.2%, and $KCO$ adjusted for alveolar volume much lower (−36.0±13.4%) than unadjusted $KCO$. These findings are similar to those of patients with scoliosis (34).

Patients after lung resection had low unadjusted $D_1CO$, normal unadjusted $KCO$ values and low adjusted $D_1CO$ and $KCO$ values. Recruitment of pulmonary vasculature in the remaining lung could account for increased unadjusted $KCO$. Since lung resection reduces overall gas exchange, the adjusted $D_1CO$ and $KCO$ decrease.

In summary, it is important to adjust $D_1CO$ and $KCO$ for alveolar volume. $D_1CO$ falls and $KCO$ rises as lung volume becomes smaller in both healthy subjects and models. While unadjusted $D_1CO$ and $KCO$ percent predicted values are often much different, values adjusted for alveolar volume are nearly identical and provide a measure of diffusion that accounts for lung volume. Different pulmonary diseases have characteristic patterns of $VA$ and unadjusted and adjusted $D_1CO$ and $KCO$. Therefore, it is helpful to report both unadjusted and adjusted values. $D_1CO$ and $KCO$ unadjusted for alveolar volume can be misleading in patients with low lung volume. Unadjusted $KCO$ often over-estimates diffu-

### Table 4. Report of $D_1CO$ results from a 27 year old woman with pectus excavatum

<table>
<thead>
<tr>
<th>Diffusion (Single Breath)</th>
<th>Observed</th>
<th>Predicted</th>
<th>% Pred</th>
<th>Predicted</th>
<th>% Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(for normal $VA$)</td>
<td>(for patient’s $VA$)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_1CO$ (ml/min/mm Hg)</td>
<td>23.9</td>
<td>27.5</td>
<td>87</td>
<td>21.8</td>
<td>109</td>
</tr>
<tr>
<td>$KCO$ (ml/min/mm Hg/L)</td>
<td>7.6</td>
<td>4.5</td>
<td>169</td>
<td>7.0</td>
<td>109</td>
</tr>
<tr>
<td>$VA$ (l BTPS of helium dilution)</td>
<td>3.13</td>
<td>6.09</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume Inspired (l BTPS)</td>
<td>1.68</td>
<td>4.49</td>
<td>37</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Predicteds adjusted for hemoglobin. If Hb were normal, DLCO would be 24.1
sion in patients with interstitial lung disease or extra-
pulmonary restriction, while unadjusted \( D_1 \)CO often
underestimates diffusion. Adjusting for alveolar volume
helps determine how much of an abnormality of \( D_1 \)CO is
due to abnormal gas exchange versus due to low lung
volume. \( D_1 \)CO and KCO adjusted for alveolar volume
better assess the lung’s intrinsic ability to perform gas
exchange.

References

1. Clark EH, Woods RL, Hughes JMB. Effect of blood
transfusion on the carbon monoxide transfer factor
727–731.
2. Cotes JE, Dabbs JM, Elwood PC, Hall AM,
McDonald A, Saunders MJ. Iron-deficiency anaemia:
its effect on transfer factor for the lung (diffusing
capacity) and ventilation and cardiac frequency
during sub-maximal exercise. Clin Sci 1972; 42:
325–3285.
3. Marrades RM, Diaz O, Roca J, et al. Adjustment of
\( D_1 \)CO for hemoglobin concentration. Am J Respir
4. Filley GF, MacIntosh DJ, Wright GW. Carbon
monoxide uptake and pulmonary diffusing capacity in
normal subjects at rest and during exercise. J Clin
Invest 1953; 33: 530–539.
5. Hsia CC, McBryar DG, Ramanathan M. Reference
values of pulmonary diffusing capacity during exercise
by a rebreathing technique. Am J Respir Crit Care Med
6. Ewan PW, Jones HA, Rhodes CG, Hughes JMB.
Detection of intrapulmonary hemorrhage with carbon
monoxide diffusing capacity (transfer factor). Recom-
mandations for a standard technique — 1995 update.
8. Agusti AGN, Roca J, Gea J, Wagner PD, Xaubet A,
Rodriguez-Roisin R. Mechanisms of gas-exchange
impairment in idiopathic pulmonary fibrosis. Am Rev
RM. Volume adjustment of mechanics and diffusion in
interstitial lung disease: lack of clinical relevance. Chest
10. Stam H, Hrachovina V, Stijnen T, Versprille A.
Diffusing capacity dependent on lung volume and
age in normal subjects. J Appl Physiol 1994; 76:
2356–2363.
11. Crapo RO, Morris AH, Gardner RM. Reference
spirometric values using techniques and equipment
that meet ATS recommendations. Am Rev Respir Dis
12. Goldman HI, Becklake MR. Respiratory function
Teirstein AS, Selkoff IJ. Single breath diffusing
capacity in a representative sample of the population
of Michigan, a large industrial state. Am Rev Resp Dis
used to predict pulmonary function. Chest 1990; 97:
400–403.
15. Harris EA, Seelye ER, Whitlock RML. Revised
standards for normal resting dead space volume and
16. Stam H, Versprille A, Bogaard JM. The components of
the carbon monoxide diffusing capacity in man
dependent on alveolar volume. Bull Eur Physiopathol
17. Shore SA, Huk O, Mannix S, Martin JG. Effect of
panting frequency on the plethysmographic determina-
tion of thoracic gas volume in chronic obstructive
pulmonary disease. Am Rev Respir Dis 1983; 128:
54–59.
18. McGrath MW, Thomson ML. The effect of age, body
size and lung volume change on alveolar-capillary
permeability and diffusing capacity in man. J Physiol
1959; 146: 572–582.
19. Cadigan JB, Marks A, Elliott MF, Jones RH,
Gaensler EA. An analysis of factors affecting the
measurement of pulmonary diffusing capacity by the
single breath method. J Clin Invest 1961; 40:
1495–1514.
20. Hamer NAJ. Variations in the components of the
diffusing capacity as the lung expands. Clin Sci 1963;
Hysteresis in the relation between diffusing capacity of
the lung and lung volume. J Appl Physiol: Respirat
Environ Exercise Physiol 1980; 49: 566–570.
22. Frans A, Nemery B, Veriter C, Lacquet L, Francis C.
Effect of alveolar volume on the interpretation of single
breath \( D_1 \)CO. Respir Med 1997; 91: 263–273.
23. Chin D, Cotes JE, Flowers R, Marks A-M, Reed
JW. Transfer factor (diffusing capacity) standardized
for alveolar volume: validation, reference values and
applications of a new linear model to replace KCO (TL/
24. Krogh M. The diffusion of gases through the lungs of
25. Crapo RO. Single breath carbon monoxide diffusing
137: 1244.
26. Macnaughton PD, Evans TW. Measurement of lung
volume and \( D_1 \)CO in acute respiratory failure. Am J
Respir Crit Care Med 1994; 150: 770–775.
27. Lipscomb DJ, Patel K, Hughes JMB. Interpretation of
increases in the transfer coefficient for carbon mon-
28. Miller JM, Johnson RL Jr. Effect of lung inflation on
pulmonary diffusing capacity at rest and exercise. J


