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Transfer factor (diffusing capacity) standardized for alveolar volume: validation, reference values and applications of a new linear model to replace *K*CO (*T*L/*V*A)

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Transfer factor (diffusing capacity) standardized for alveolar volume: validation, reference values and applications of a new linear model to replace ***K*****CO** *(TL/VA). D.J. Chinn, J.E. Cotes, R. Flowers, A-M. Marks, J.W. Reed. ©ERS Journals Ltd 1996.*

ABSTRACT: Transfer factor (*T*L) varies with alveolar volume (*V*A), but not in the manner implied by the carbon monoxide transfer coefficient (*K*CO (*T*L/*V*A)). This paper considers two other simple models (one linear and one exponential) which might standardize *T*L for *V*A, and asks the questions: 1) Is either model valid? 2) What are appropriate reference values? and 3) Will the model be useful?

The relationship of *T*L to *V*A within subjects at different depths of inspiration, and between subjects having lungs of different sizes, were measured and compared. The subjects were asymptomatic, nonsmoking, Caucasian adults, including 31 males assessed in the laboratory and 503 male and female participants in population studies.

The linear partial regression coefficients of *T*L on *V*A (L corrected for body temperature, atmospheric pressure and water saturation (BTPS)) standardized for height (H) in metres, were similar within- and between- subjects; the coefficients applied over a wide range of values for *V*A. This was not the case for the exponential model. The resulting reference equations in SI units for males and females were: *T*L = 11.52 H + 2.72 $V_A \cdot H^{-2}$ - 0.051 Age -12.35. RSD 1.17; and *T*L = 4.87 H + 2.29 $V_A \cdot H^{-2}$ - 0.019 Age -3.03. RSD 0.92, respectively. The residual standard deviations (RSD) about the new relationships were less than in other series. The new linear model could account for much of the variation between different published reference values for *T*L; it could be useful clinically, in circumstances when *V*A deviates from the norm. The model does not explain differences in *T*L associated with gender.

Inclusion of $V_A \cdot H^{-2}$ as a covariate in the reference equation for transfer factor, in addition to age and height, improves the accuracy of prediction of normal transfer factor compared with current reference values; its use suggests that some of the differences between published values is due to the volume term. The equations can be used clinically, and eliminate the need for carbon monoxide transfer coefficient.
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When an individual subject performs measurements of transfer factor (*T*L, which is also called diffusing capacity) by the single-breath method, the result is found to vary with the depth of inspiration, and hence with the alveolar volume (*V*A) during breatholding. This was first observed by KROGH [1] who, in 1915, reported that "with increasing lung volumes above mean capacity, the permeability factor *k* (*i.e.* diffusing capacity per unit lung volume) remained practically constant". Based on this observation the carbon monoxide transfer coefficient (*K*CO), hereafter designated *T*L/*V*A, has been equated with transfer factor standardized for alveolar volume. However, subsequent studies, reviewed by STAM and coworkers [2], have shown that between functional residual capacity and total lung capacity, *T*L/*V*A was not constant; instead, it was negatively correlated with alveolar volume. On this account, the usefulness of *T*L/*V*A as a means for standardizing *T*L has been questioned [3, 4].

The Krogh model (*T*L/*V*A) can be represented as *T*L= m*V*A, where m is a constant. It is invalid because m is not independent of *V*A. In this paper, two other simple models are considered, an exponential model of the form $T_L = mV_A^{\delta}$, and a linear model which can be represented as *T*L=m*V*A + c (fig. 1). To be valid, the parameters of the equations should be independent of *V*A within the range covered by inspiratory reserve volume. To be of practical use, the models should apply both to data for individual subjects at different lung volumes, and to data for populations where the alveolar volumes reflect the sizes of the subjects' lungs.

It appears that the exponential model has not been explored previously. Information about the linear model, as applied to data for individuals, was reviewed in 1970; at that time, the average slope of the relationship of *T*L on *V*A (the parameter m) was estimated as 0.86 $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot L^{-1}$ (2.57 $mL \cdot min^{-1} \cdot mmHg^{-1} \cdot L^{-1}$) [3]. Subsequent studies have yielded a similar result [5, 6].

A linear model describing *T*L at total lung capacity (TLC) on age and *V*A was applied to population data by GAENSLER and SMITH [7], and a more sophisticated model,

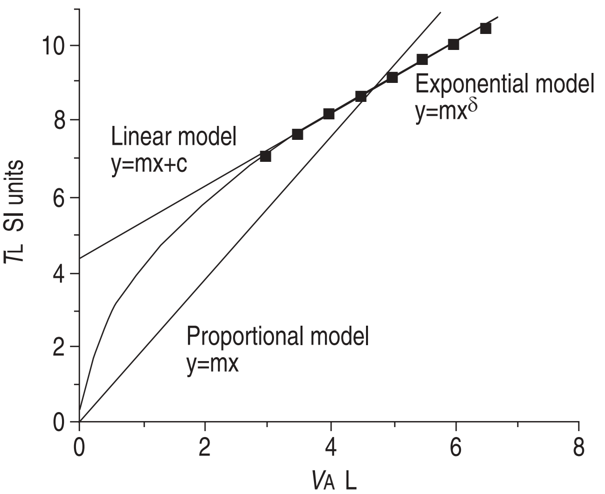

Fig. 1. – Alternative simple models which might describe the relationship of transfer factor (*T*L) to alveolar volume (*V*A); the models are illustrated using idealized data. SI units: mmol·min^{-1}·kPa^{-1}.

which also included the square of *V*A and its interaction with age, was developed by STAM *et al.* [8]. Compared with linear regression equations in current use [3, 9, 10], the former equations explained less of the variance in the data; the latter, whilst of a different format, were successful in describing *T*L at TLC, but less so *T*L at reduced lung volumes. Nevertheless, alveolar volume can vary independent of the diffusion characteristics of lung parenchymal tissue, so that without an allowance for lung volume, a measurement of transfer factor made at a volume above or below the normal maximum can only be interpreted empirically. Failure to make such an allowance can lead to error in diagnosis. For example, in a patient who has a history of exposure to asbestos and an abnormal chest radiograph, a diagnosis of asbestosis might be missed if *T*L/*V*A was considered normal on account of being close to its reference value [11]. Conversely, if the interpretation of *T*L/*V*A was rightly considered to present difficulties, a subject in whom *T*L was reduced by a failure to make a full inspiration during the test could be wrongly diagnosed as having parenchymal disease.

Against this background, the present investigation was set up to answer the following questions: 1) Can one simple model describe the relationship of transfer factor to alveolar volume both for population data, where alveolar volume reflects TLC, and individual data, where alveolar volume reflects the depth of the test inspiration? 2) If this turns out to be the case, what are appropriate reference values? and 3) Can the model be of practical use for interpreting measurements of transfer factor made during the course of occupational, epidemiological and clinical investigations?

Methods

Subjects and study design

Measurements of transfer factor at several alveolar volumes above functional residual capacity (FRC) were obtained on male volunteers comprising students, university staff and shipyard workers [12], here designated Group 1. The males were selected as being asymptomatic nonsmokers. They attended the Respiration and Exercise Laboratory for the study, which included measurement of TLC, its subdivisions, and six measurements of transfer factor. For each of the latter measurements, the inspiration of test gas was made from residual volume (RV). In the first two instances, the inspiration was maximal, hence the measurement was made at or close to TLC; in the other four, which were in random order, the alveolar volume was arranged to lie within the inspiratory reserve volume and to span at least the top 25% of TLC. Data sets were included in the analysis, provided that they met the criteria that at least five of the six individual results were technically satisfactory as defined previously [4] and that the results were internally consistent as judged by a correlation between *T*L and *V*A greater than 0.70 (r^2 >0.49). The latter criterion led to the exclusion of three subjects.

The population data were for asymptomatic adult nonsmokers (ages >20 yrs) from both the shipyard study [12, 13], which took place in north-east England (Group 2), and a previous study of personnel in local government offices, schools and light industry in north-west England (Group 3); the latter group included both male and female subjects [14]. The same methods and compatible items of equipment were used throughout. For the population studies, the measurements were made or supervised by one observer (DJC). Prior to the studies being undertaken, the protocols were submitted to and approved by the relevant Ethics Committees.

Comparisons were made with reference values compiled by the European Coal and Steel Community [10], and selected reference values from the UK and USA [9]. The present results were used to reinterpret the findings of eight technically comparable sets of reference values obtained at sea level for males, and the corresponding series for females, using mean results for age 45 yrs; these were compiled for a recent report [15]. The model was also applied to the results for selected patients assessed in the laboratory, including a patient with asbestos pleural disease, whose chest radiograph was presented previously [16].

Measurements

The subjects completed the Medical Research Council (MRC) Questionnaire on respiratory symptoms (1976), with additional questions about employment and habitual leisure time activity [17].

Stature and body mass, were measured using a stadiometer (Harpenden, Holtain) and beam balance (Avery, GEC). The equipment was calibrated and used in the manner recommended for the International Biological Programme [18]. Dynamic spirometry was performed in quintuplicate, seated, using a dry bellows digital spirometer [19]. The forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were calculated using the conventions recommended by the European Community [20].

The transfer factor of the lung for carbon monoxide (*T*L,CO) was measured in duplicate by the single-breath method, using a Resparameter or transfer test equipment (P.K. Morgan); it was reported in standard international units ($mmol \cdot min^{-1} \cdot kPa^{-1}$), here abbreviated to SI. The alveolar volume used in the calculation (V_A) was that obtained from the dilution in the lung of the helium present in the mixture of test gas; it was expressed in litres at body temperature and pressure, saturated with water vapour (L BTPS). Gas analysis for carbon monoxide was by infrared absorption and for helium by katharometry. Details of the methods used to calibrate equipment, the procedures and the calculations have been given previously [9].

Analysis

For each test, all the results were scrutinized for technical quality by the same observer (DJC). The numerical values were checked again after entry into the mainframe computer. Actual data were analysed, except in the case of equations which might be used for reference values; in these instances, in order to allow for the lung function reaching a plateau in early adult life, the ages of persons aged less than 25 yrs were arbitrarily increased to this level [9, 20]. The increase affected the results for 40 males and 34 females in Group 3, and one male in Group 2. The multiple regression analyses were performed using the Statistical Package for the Social Sciences of the University of Michigan (SPSS^x, release 4.0). Linear terms were used and care was taken to avoid co-linearity between variables. To this end, alveolar volume was standardized for height (H) using the relationship:

$$V_{A,std} = V_A/H^\beta \times (\text{mean height})^\beta \qquad (1)$$

where $V_{A,std}$ in litres is alveolar volume standardized to the mean height of the subjects. The exponent β was estimated from the regression coefficient of ln V_A on ln height. The exponent which best described the relationship of T_L to $V_{A,std}$ (exponent δ) was similarly obtained from the relationship of ln T_L on ln $V_{A,std}$.

Terms were admitted to the multiple regression in a stepwise fashion, in the order which reflected their contributions to the explained variance. Variability about the resulting equation was expressed as the residual standard deviation (RSD) both in absolute units and as a percentage of the mean level (coefficient of variation (CV)). The proportion of variance explained by the regression (r^2) was used for comparisons between equations of the same general form, but not between those where the form differed. The 5% level of probability was accepted as significant. Reference values were both those in current use [9, 15, 21] and values developed for the present Group 2 and Group 3 subjects. Differences from results predicted using a reference equation were expressed in SD units, calculated using the relationship:

$$\text{SD units} = (Y_{obs} - Y_{ref}) \div \text{RSD about the equation} \qquad (2)$$

where Y is the relevant index of lung function. A difference of ≤1.64 SD units and/or the 5% level of probability ($p=0.05$), was accepted as significant.

For analysis of mean results from published studies of reference values, using age 45 yrs and a standard height, the mean alveolar volumes were estimated as mean T_L divided by mean T_L/V_A. This approach was validated using the present results.

Table 1. – Details of subjects in Group 1 (n=31)

Index	Mean±SD	Range
Age yrs	36 (9)	20–52
Height m	1.76 (0.08)	1.64–1.91
Body mass kg	79 (11)	55–103
FEV_1 L	4.3 (0.6)	3.0–5.5
FVC L	5.4 (0.6)	4.1–6.4
T_L SI units†	12.3 (1.6)	8.6–16.0
T_L at minimal volume SI units	10.4 (1.6)	7.2–14.5
V_A L	6.9 (0.8)	5.4–8.4
Minimal V_A L	4.5 (0.7)	3.2–5.8
K_{CO} (T_L/V_A)	1.80 (0.23)	1.38–2.55
TLC L	7.0 (0.8)	5.3–8.7
RV L	1.3 (0.5)	0.5–2.6
FRC L	3.4 (0.7)	2.1–5.0

†: $mmol \cdot min^{-1} \cdot kPa^{-1}$. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; T_L: transfer factor; V_A: alveolar volume; K_{CO}: carbon monoxide transfer coefficient; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity.

Results

Relationship of T_L to V_A within subjects

Data sets from 31 subjects met the criteria for acceptability, and were included in the study. Details of these Group 1 subjects are summarized in table 1.

Linear model. For the Group 1 subjects individually, the relationship of transfer factor to alveolar volume was effectively linear with a mean slope of 0.882 (SD 0.266) SI units·L^{-1}; the values for r^2 were in the range 0.52–0.97. For the subjects collectively, the exponent β, which described the relationship of V_A to height, had a value of 1.4. This quantity was used in Equation (1) to standardize V_A to the mean height for the group (hence $V_{A,std}$). After standardization, the slope of the relationship of T_L to V_A became 0.875 (SD 0.245) SI units·L^{-1}. The 95% confidence interval (95% CI) for the mean slope was 0.785–0.964 SI units·L^{-1} (fig. 2). The slope was independent of height, age and maximal V_A. A value for the exponent β of 2.0, which arose from analysis of the population data (reported below), yielded a similar result.

Exponential model. The exponent δ relating T_L to standardized V_A was on average 0.44 (range 0.21–0.75). Hence, for the 31 subjects, T_L was on average nearly proportional to the square root of V_A ($V_{A,std}^{0.5}$). When this model was applied to the results of individuals, it fitted in 23 instances. In the remainder, there was a significant residual correlation between $T_L/V_A^{0.5}$ and V_A. In seven men the imposed exponent (0.5) was higher than the observed exponent (range 0.21–0.35) and so overcorrected for V_A, whilst in one man it was too low (observed exponent 0.75) and so did not correct sufficiently. Overall, $T_L/V_A^{0.5}$ at the highest alveolar volume (6.98 L) was significantly less than that at the lowest alveolar volume (4.74 L). The respective values were 4.74 and 4.92 SI units per $L^{0.5}$ ($p<0.01$).

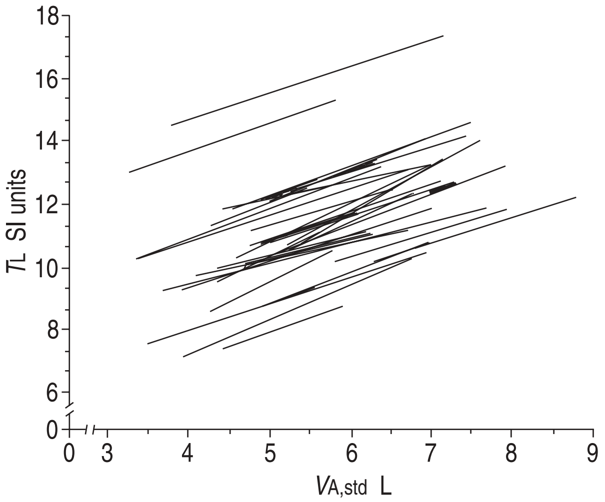

Fig. 2. – Graph illustrating the relationship of transfer factor (*T*L) to alveolar volume standardized for height (*V*A,std) for the subjects individually (n=31). The regression lines span the range of alveolar volumes for each subject. SI units: mmol·min^{-1}·kPa^{-1}.

Relationship of TL to VA between subjects

Subjects. Three hundred and seventy four males and 129 females from the population studies met the predetermined criteria of normality, so their data were used for the construction of reference values. The ages of the shipyard workers (Group 2) were in the range 24–53 yrs, and of the other subjects (Group 3) in the range 20–63 years. Some mean results are given in table 2 and the relationships of indices of lung function to height and age in table 3.

Amongst the males, the mean FEV_1 and FVC adjusted for age and height, and *T*L/*V*A adjusted for age, did not differ between the groups. After adjustment, the mean *V*A for Group 2 exceeded that for Group 3 male subjects by an average of 0.15 L ($p<0.05$); the corresponding difference for *T*L was not significant.

Linear model describing TL. The average value of the exponent β relating *V*A to H was 2.06 (range 1.81–2.29) (table 2); hence, for practical purposes the *V*A varied with the square of the height. In, confirmation of this, *V*A divided by height squared ($V_A \cdot H^{-2}$) was independent of height; it was also independent of age; the index was normally distributed.

Table 2. – Details of subjects, analysed by Group and gender

Index	Group 2		Group 3		Group 3	
Sex	Male		Male		Female	
Subjects n	192		182		129	
Age yrs	34	(7)	35	(11)	34	(11)
Height m	1.75	(0.06)	1.74	(0.06)	1.61	(0.06)
*T*L SI units†	12.0	(1.6)	11.7	(1.6)	8.2	(1.1)
*T*L/*V*A	1.81	(0.21)	1.82	(0.22)	1.79	(0.23)
*V*A,std L	6.7	(0.64)	6.4	(0.59)	4.6	(0.48)
Exponent β	2.29		2.09		1.81	
$V_A \cdot H^{-2}$ L·m^{-2}	2.17	(0.21)	2.12	(0.19)	1.77	(0.19)

Values are presented as mean, and SD in parenthesis. *V*A,std: alveolar volume standardized to the mean height of the subjects.

Table 3. – Conventional regression equations describing ventilatory capacity and transfer factor in terms of height and age

Group	Index	Regres. coeffs Height	Age†	Constant	RSD	r^2
Male	FEV_1	4.63	-0.031	-2.74	0.47	0.46
(n=374)	FVC	6.58	-0.020	-5.41	0.53	0.45
	*T*L	12.3	-0.047	-7.93	1.29	0.34
Female	FEV_1	3.12	-0.029	-0.90	0.37	0.51
(n=129)	FVC	3.86	-0.021	-1.82	0.43	0.39
	*T*L	4.28	-0.024	2.13	1.01	0.13

†: minimal age adjusted to 25 yrs, see methods (Analysis). RSD: residual standard deviation; Regres. coeffs: regression coefficients. Details of the subjects are given in table 2. For further definitions see legend to table 1.

After adjustment for age and height, the partial regression coefficients of transfer factor on height standardized alveolar volume (*V*A,std), using the directly determined exponents (β) were similar for the three subject groups. The regression coefficients for the male and female subjects, respectively 0.880 (SEM 0.097) SI units·L^{-1}, and 0.881 (SEM 0.169) SI units·L^{-1}, did not differ significantly from the corresponding within-subject coefficient reported above (0.875 (SEM 0.044) SI units·L^{-1}). Use of the average exponent (β=2) did not alter this result.

The values for the exponent δ relating *T*L to *V*A were for the male subjects 0.51 and for the females 0.52. The term $V_{A,std}^{0.5}$ together with age, height and $V_A \cdot H^{-2}$ were, therefore, used as reference variables for the description of transfer factor. In the event, the use of $V_{A,std}^{0.5}$ did not improve the relationship compared with using $V_A \cdot H^{-2}$. The equations obtained using the latter reference variable were, in SI units, for males:

$$T_L = 11.52\ H + 2.72\ V_A \cdot H^{-2} - 0.051\ Age - 12.35 \quad (3)$$
$$RSD\ 1.17,\ CV\ 9.9\%,\ r^2=0.46$$

and for females:

$$T_L = 4.87\ H + 2.29\ V_A \cdot H^{-2} - 0.019\ Age - 3.03 \quad (4)$$
$$RSD\ 0.92,\ CV\ 11\%,\ r^2=0.28$$

The reference equations in traditional units for *D*L (mL·min^{-1}·mmHg^{-1}) on height (m), alveolar volume (L BTPS) and age (yrs) are:

$$D_L = 34.3\ H + 8.11\ V_A \cdot H^{-2} - 0.15\ Age - 36.8\ RSD\ 3.49$$

$$D_L = 14.5\ H + 6.82\ V_A \cdot H^{-2} - 0.06\ Age - 9.04\ RSD\ 2.73$$

The inclusion of $V_A \cdot H^{-2}$ (L BTPS·m^{-2}) materially increased the variance in *T*L explained by the regression (increases in r^2 for males and females 0.12 and 0.15, respectively). The inclusion of the new term had little effect on the partial regression coefficients on age and height. In addition, neither this term, nor individual allowance for haemoglobin concentration could account fully for the difference in transfer factor between the sexes.

Exponential model describing TL. For this analysis *T*L/*V*A and $T_L/V_A^{0.5}$ were regressed on age, height, gender and $V_A \cdot H^{-2}$. The resulting equations are given in table 4. In the two sexes separately, the largest single contributor

Table 4. – Regression equations describing *T*L/*V*A and *T*L/*V*A$^{0.5}$

	Coefficient terms Age	Height	*V*A·H^{-2}	Constant	RSD	CV	r^2
*T*L/*V*A (M)	-0.0074	-0.29	-0.429	3.51	0.180	9.9	0.28
*T*L/*V*A$^{0.5}$ (M)	-0.0195	1.906	NS†	1.98	0.456	9.9	0.20
*T*L/*V*A (F)	-0.0045	-1.17	-0.521	4.77	0.200	11	0.26
*T*L/*V*A$^{0.5}$ (F)	-0.0091	NS	NS	4.14	0.424	11	0.04

†: NS, coefficient not significant. CV: coefficient of variation; M: male; F: female. For further definitions see legends to tables 1 and 3.

to the variance in *T*L/*V*A was *V*A; this term, after adjustment for height, accounted for 19 and 15% of the variance in males and females, respectively. However, when the dependent variable was *T*L/*V*A$^{0.5}$, the terms for *V*A or *V*A·H^{-2} were not significant. The next largest contributions to the variance in *T*L/*V*A were made by height in males and age in females, with smaller contributions from the other term. For both dependent variables the regression coefficients on age differed between the sexes ($p<0.05$).

*Interpretation of differences in T*L *between published reference values*

The material comprised mean results from the data sets identified previously (see Subjects), together with exactly comparable information from the present study. For these nine studies in males and, separately, for seven studies in females, the mean transfer factor at 45 yrs of age was significantly correlated with the estimated mean *V*A. In each instance, the slope of the relationship was similar to that found in the present study (figs. 3 and 4).

*Interpretation of clinical results for T*L *in circumstances when V*A *was atypical*

Predominantly restrictive defect (Case No. 1, table 5). In this patient who had extensive asbestos-related calcified pleural plaques, the transfer factor was significantly reduced with respect to the conventional reference value (observed 8.6 SI units; reference 12.2 SI units). Thus, there appeared to be a material transfer defect, and yet *T*L/*V*A was normal. However, the *V*A was also reduced (observed 5.4 L; reference 7.9 L). The situation could be clarified by obtaining the reference value for *T*L at the patient's own *V*A. This was 10.3 SI units, and so by comparison with the appropriate reference value there was a mild transfer defect, and *T*L/*V*A was misleading. However, the main problem was the restrictive defect.

Large TLC associated with emphysema (Case No. 2, table 5). In this patient *T*L/*V*A was reduced by 3.1 SD units, but *T*L was at the lower end of the normal range (*i.e.* ±1.64 SD). However, *V*A was increased (observed 7.99 L; reference 6.25 L). When the transfer factor was calculated using the patient's own *V*A, the extent to which it was reduced became apparent (-3.3 SD units).

Acromegalic lung, without emphysema (Case No. 3, table 5). In this patient *T*L/*V*A was significantly reduced, whilst *T*L was at the upper end of the normal range. However, *V*A was increased (observed 11.7 L; reference 8.5 L). When the transfer factor was compared with the reference value appropriate for the patient's measured *V*A the transfer factor was shown to be completely normal, and the result for *T*L/*V*A misleading.

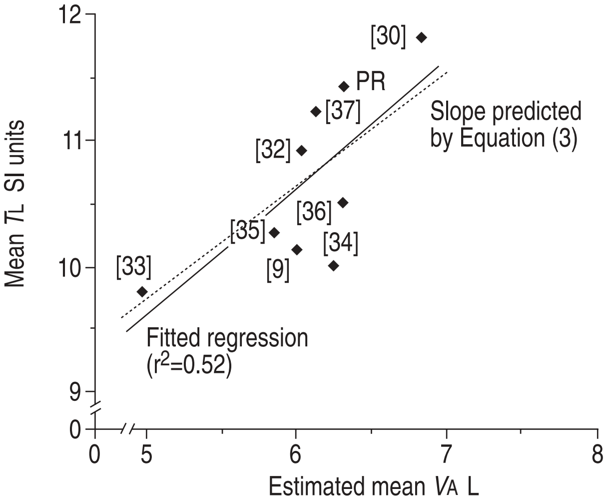

Fig. 3. – Mean transfer factor (*T*L) in males aged 45 yrs, height 1.75 m, reported by different authors, related to the corresponding estimated mean alveolar volume (*V*A) (*T*L÷*T*L/*V*A). The data were those compiled in [15], from sources indicated by the reference numbers. PR is the present result. SI units: mmol·min^{-1}·kPa^{-1}.

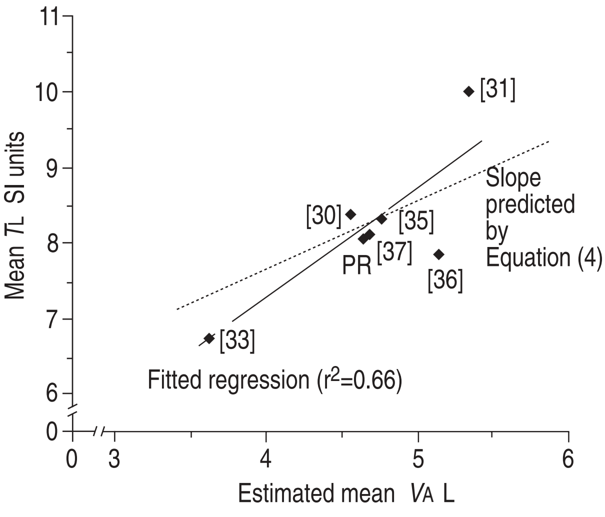

Fig. 4. – Mean transfer factor (*T*L) in females aged 45 yrs, height 1.65 m reported by different authors [15], related to the corresponding estimated mean alveolar volume (*V*A). Further details are given in the legend to figure 3. SI units: mmol·min^{-1}·kPa^{-1}.

Table 5. – Lung function in selected male patients in whom V_A was abnormal

	Case			
Diagnosis	No. 1 Asbestos-related pleural plaques	No. 2 Emphysema	No. 3 Acromegaly	No. 4 COPD
Age yrs	60	71	57	37
Height m	1.87	1.7	1.94	1.69
TLC L observed	5.9	8.02	11.9	6.3
ref. based on H	7.9	6.25	8.5	6.2
V_A L observed	5.4	7.99	11.7	4.77†
T_L SI observed	8.6	7.27	15.3	8.41†
ref. based on Age and H	12.2 (-2.8)	9.6 (-1.8)	13.2 (1.6)	11.1 (-2.1)
ref. based on Age, H and $V_A \cdot H^{-2}$	10.3 (-1.5)	11.1 (-3.3)	15.5 (-0.2)	9.7 (-1.1)
T_L/V_A $SI \cdot L^{-1}$ observed	1.60	0.91	1.31	1.76
ref. based on Age	1.62 (-0.1)	1.54 (-3.1)	1.65 (-1.7)	1.80 (-0.2)

Differences from reference values (in SD units) are presented in parentheses. †: FEV_1/FVC 54%. Reported results are for $V_{A,eff}$ and $T_{L,eff}$. $V_{A,eff}/V_A$ was 0.77, and T_L measured using the multibreath estimate of residual volume was 10.9 SI units. $V_{A,eff}$ and $T_{L,eff}$: alveolar volume and transfer factor, respectively, obtained from the dilution in the lung of the single-breath of helium. COPD: chronic obstructive pulmonary disease; ref: reference. SI: $mmol \cdot min^{-1} \cdot kPa^{-1}$. For further definitions see legend to table 1.

Small single-breath lung volume associated with impaired gas mixing (Case No. 4, table 5). In this patient with chronic obstructive pulmonary disease (COPD) the V_A obtained from the dilution in the lung of the single-breath of helium ($V_{A,eff}$, 4.77 L) was reduced relative to that by the multibreath technique (V_A, 6.2 L). The corresponding transfer factor ($T_{L,eff}$, 8.41 SI units), was similarly reduced relative to T_L measured using the multibreath estimate of RV: the latter was 10.9 SI units, consistent with the reference value. The result for $T_{L,eff}$ might have been interpreted as evidence for a transfer defect, but it was within normal limits when compared with the reference value based on $V_{A,eff}$.

Small lung volume due to submaximal inhalation. Amongst the subjects in group 1, there were 10 in whom the value for T_L at the lowest recorded V_A was significantly below the reference value based on age and height. After the reference values had been adjusted for V_A using $V_A \cdot H^{-2}$, the individual results for T_L were all within the "normal" range (table 6).

Discussion

Are the present data suitable for their purpose?

The lung function of the males and females who participated in the population studies (Groups 2 and 3) expressed relative to age and height, is summarized in tables 3 and 4. The results for females were similar to, and those for males on average 8% higher than, the commonly used reference values [9, 15, 21]. For the subjects seen in the laboratory (Group 1), the average relationship of T_L to V_A (0.875 SI units$\cdot L^{-1}$, coefficient of variation 5%) was almost identical with that extracted previously from the literature (0.865 SI units$\cdot L^{-1}$) [3]. Thus, these data were consistent with others and hence, appropriate, for considering how T_L could best be related to V_A.

Table 6. – Use of new equation to allow for the effects of a submaximal test inspiration (n=10)

Depth of inspiration	V_A L	T_L $mmol \cdot min^{-1} \cdot kPa^{-1}$ Obs	Ref	T_L/V_A $SI \cdot L^{-1}$
Maximal	6.7 (1.5)	11.2	11.8**	1.68
Submaximal	4.0 (0.6)	9.02*	9.6**	2.29*

Values are presented as mean, and SD in parenthesis. *: result significantly different from that at full inspiration (p<0.001); **: reference value, including term for $V_A \cdot H^{-2}$, not different from that observed. For further definitions see legend to table 1.

Is there a case for continuing to use T_L/V_A? The perceived inappropriateness of the allowance for V_A inherent in the proportional model (T_L/V_A) was reinforced by the present analysis; this showed that, for the two sexes separately, V_A was the largest single contributor to the variance in T_L/V_A; the coefficient on V_A in effect corrected the bias introduced by the proportional model. After correction, the next contributor was age but height also made a significant contribution (table 4). Thus, the use of T_L/V_A both introduces a material bias into the data because the model is inappropriate, and entails loss of information because the model ignores height and, hence, the contribution to T_L of body size independent of lung size.

Support for T_L/V_A has come from the view that it can be used for persons of either sex, independent of gender [22, 23]. However, this is not the general experience [9, 15, 21], nor that of the present study. The index has also been considered helpful for interpreting the lung function of patients with emphysema in circumstances when V_A is increased. However, a more accurate allowance for the effects of V_A on T_L can be made using the present model. Indeed, because of its unsatisfactory features and the absence of any unique advantages, the use of T_L/V_A cannot be justified on scientific grounds. The extent of the bias alone is sufficient reason for abandoning the index; the loss of accuracy due to ignoring height is an additional consideration.

Can K_{CO} (T_L/V_A) be improved by using an exponential model? The proportional model can be represented as a special case of an exponential model, in which the exponent of T_L on V_A is unity. This value for the exponent is not compatible with the evidence. However, within subjects assessed at different lung volumes, the average exponent was 0.44, whilst between subjects having lungs of different sizes, the exponent was 0.51. The similarity led to the expectation that $T_L/V_A^{0.5}$ would be independent of V_A both within and between subjects. Between subjects, using the population data, the expectation proved to be correct. Within subjects, using the individual data, it was correct in most, but not all instances. The deviations occurred in individuals having values for the exponent δ at both ends of the observed range. Hence, there was no single value for the exponent that was valid for all subjects, and consequently no ratio of T_L to V_A which would be appropriate for clinical use. $T_L/V_A^{0.5}$ could have a role in population studies, but for this application it has the defect of not including an allowance for that part of the variance in T_L which was related to height. Height did not contribute in the female subjects, but in the males it made a material contribution, equivalent to 40% of that associated with age.

An improved linear model for describing T_L. The present study has followed others in including V_A as a linear reference variable for describing T_L [3, 7, 24]. V_A was included in the form $V_A \cdot H^{-2}$ in order to avoid colinearity resulting from V_A being correlated with height. The exponent of two was determined empirically, and so was appropriate for its purpose. It was the same as that found suitable for standardizing forced expiratory volume for height in adults [25], though not in children [26]. The use of $V_A \cdot H^{-2}$ reduced the within-subject variability, whilst not affecting the apparent linearity of the relationship of T_L to V_A over the present range of volumes. The biological relationship is more complex, since it reflects the underlying relationships to V_A of the components of T_L. For the present method of measurement, these are the diffusing capacity of the alveolar capillary membrane (D_m), the volume of blood in alveolar capillaries (V_c) and the reaction rate of carbon monoxide with partially oxygenated haemoglobin. The reaction rate is independent of V_A, but D_m is nearly proportional to it, whilst for V_c, at most lung volumes, the correlation with V_A is negative [2, 9]. Thus, the linearity of the relationship of T_L to V_A is at best an approximation. However, the present analysis suggested that for measurements made at breathholding volumes within the range covered by the inspiratory reserve volume, the relationship could be treated as linear without introducing a material bias.

GAENSLER and SMITH [7] extended the model to include variation between subjects, by adding a term for age. There is a strong case for also including height which, in the present study contributed more to the variance in T_L than was the case for V_A. However, the inclusion of V_A, in the form $V_A \cdot H^{-2}$, accounted for an additional 12–15% of the variance in T_L. For the present male subjects, this reduced the RSD about the regression from 1.29 SI units without $V_A \cdot H^{-2}$ to 1.17 SI units when this term was included. The new figure represents a material improvement compared with reference equations based on the traditional model (range 1.28–1.94 SI units) [15]. A similar improvement was observed for the female subjects, where the present RSD was 0.92 SI units; the range for the conventional model was 0.94–1.51 [15]. Thus, reference values based on the new model appear to be an improvement on the current ones.

The current reference values relate to measurements made at a normal TLC. However, the population-based partial regression coefficient of T_L on V_A standardized for height (0.88 SI units$\cdot L^{-1}$) also described the relationship of T_L to V_A within subjects. This made it possible to use the reference values both in the conventional way, and for interpreting measurements of T_L in circumstances when the V_A is atypical as a result of disease, deliberate choice, or the operation of environmental factors. That the method was effective was shown by it successfully predicting the transfer factor of 10 individuals in whom the alveolar volume was voluntarily reduced to below the normal range (table 6).

Examples of possible applications of the new relationship

Quality control in the lung function laboratory. The T_L, as reported, is normally the mean of two technically satisfactory measurements, which are required to agree to within 10% [4]. This recommendation implies that any differences are random, yet there is evidence that a part is systematic and related to the depth of the test breath affecting the V_A during breathholding [9]. Such variation can now be allowed for. In addition, the procedure can be used to estimate T_L, or to test the validity of another result if, for any reason, a measurement turns out to have been made at a submaximal lung volume. The effect of the algorithm used for the derivation of alveolar volume (V_A or $V_{A,eff}$) can also be explored; this aspect is considered below.

Population studies. Alveolar volume can vary between populations, for example between the present Group 2 and Group 3 male subjects. In this instance, the population difference in V_A was too small to materially affect T_L. However, the present analysis has demonstrated that variation in V_A is the main cause of differences between published reference values for T_L (figs. 3 and 4). Some of the variation may have been biological, but, to the extent that the origins of the populations overlapped, much of it must have been technical; this indicates a need for a review of the methods used, and possibly for a reanalysis of the results in terms of the new model. A similar reappraisal might also be considered for the results of studies of transfer factor in children, and subjects with large lungs relative to height, including some athletes, deep sea divers and residents at high altitude [9].

Study of differences between ethnic groups. Transfer factor and T_L/V_A can vary with ethnic group, but the differences are often small and due to the combined effects of several factors, of which one is V_A [9]. In the case of persons of West African and South Indian descent, the alveolar volumes are materially less than in Europeans, but the differences in transfer factor are on average small [9, 27]. In this circumstance, a valid allowance for alveolar volume could lead to a better understanding of the ethnic factor, compared with relying on T_L/V_A.

Patients with atypical lung volumes. The transfer factor is sometimes abnormal, wholely or partly as a result of a change in lung volume, for example when there is uncomplicated restrictive disease, or acromegaly. Thus, in patient No. 1, who had asbestos pleural disease, the conventional interpretation was of a very small transfer factor and normal T_L/V_A, in the patient with emphysema of a subnormal T_L and in the patient with acromegaly of an increased T_L but reduced T_L/V_A. After making an appropriate allowance, the acromegalic was shown to have normal lung function. In the patient with emphysema, the extent of the impairment of gas exchange was then shown to be unequivocal, and not dependent on the interpretation of T_L/V_A. The patient with asbestos pleural disease was moved from the ambiguous position of having either normal or grossly abnormal gas transfer, depending on point of view, to the more realistic position of having borderline changes. These improvements in interpretation were made using the present model, which adjusted the reference value to the alveolar volume of the subject. The alternative of adjusting the measured value could also have been carried out. However, whilst this has been shown here to be valid for healthy adults, it may not be valid in disease. There is some evidence that the relationship of T_L to V_A may be independent of the disease process in sarcoidosis [28], but the subject needs to be explored more generally.

The model can also be used to interpret an apparently reduced transfer factor obtained using a single-breath estimate of alveolar volume ($V_{A,eff}$), in a patient in whom $V_{A,eff}$ is low as a consequence of impaired gas mixing (table 5). This approach could be relevant for laboratories where the measurement of transfer factor is no longer based on a multibreath estimate of alveolar volume [4, 9, 29].

In conclusion, a common regression coefficient can be used to describe transfer factor with respect to alveolar volume within and between healthy, adult Caucasians of either gender. The relevant term is the partial regression coefficient of T_L on V_A standardized for height ($V_A \cdot H^{-2}$). The best estimate of the coefficient in male subjects is 2.7 $mmol \cdot min^{-1} \cdot kPa^{-1} \cdot m^{-2}$. It is less in females, so that the new model does not fully account for the gender difference in T_L, and this is also the case after allowing for haemoglobin concentration. Reference values for Caucasians are given in Equations (3) and (4). Different coefficients of T_L on $V_A \cdot H^{-2}$ are likely to be needed for other ethnic groups.

In population studies, the inclusion of the term $V_A \cdot H^{-2}$ materially increases the proportion of variance explained by the regression compared with using age and height alone.

Use of the new model has thrown light on the contribution of differences associated with the measurement of alveolar volume on systematic differences between published reference values for transfer factor. The model provides a physiologically appropriate relationship for indicating the contribution of alveolar volume to an observed result for transfer factor; this can be informative in circumstances when the alveolar volume either differs between populations, or is increased by environmental factors, low as a result of poor subject co-operation, or abnormal because of disease. The use of carbon monoxide transfer coefficient (T_L/V_A) can mislead in these circumstances, as can any other index having the general form T_L/V_A^{δ}.

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