Lung transfer factor and K_{CO} at cardiac frequency 100 beats/min as a guide to impaired function of lung parenchyma

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ABSTRACT Transfer factor (TL) and K_{CO} have been measured by the single breath carbon monoxide method in 39 patients with confirmed or suspected lung disease, mostly of occupational origin, and 37 healthy subjects. TL and K_{CO} at an exercise cardiac frequency of 100 beats/min (TL_{100} and $K_{CO_{100}}$) and the slopes of the regression of exercise transfer factor and K_{CO} on exercise cardiac frequency ($\Delta TL/\Delta fC$ and $\Delta K_{CO}/\Delta fC$) were obtained. The discriminatory performance of these indices in detecting defective gas transfer was compared with that of TL and K_{CO} at rest (TL_{rest} and $K_{CO_{rest}}$). The slope indices did not distinguish between healthy subjects and patients with emphysema or conditions of the lung parenchyma, including asbestosis. The slope indices also failed to distinguish between individuals with normal and abnormal gas transfer at rest. The indices TL_{100} and $K_{CO_{100}}$ contributed additional information not contained in the indices at rest and they merit further study.

Defective lung gas transfer may be diagnosed at rest from measurements of the transfer factor for the lung (TL , also called diffusing capacity). In some circumstances, however, the measured value is less abnormal than might be expected from the appearance of the chest radiograph¹ or is inconsistent with the observed ability to increase oxygen uptake during activity.² Transfer factor increases during exercise³ and recently Ingram and colleagues⁴ suggested using as an index the slope of the regression of exercise K_{CO} (transfer factor/alveolar volume) on cardiac frequency. These authors investigated patients with pulmonary sarcoidosis; the present paper describes the usefulness of the regression slope and position in the assessment of patients with pulmonary emphysema and fibrosis.

Subjects and methods

The subjects were 23 men and 14 women who appeared to be healthy and 39 patients with confirmed or suspected abnormality of the lung. The

healthy subjects were recruited casually. The mean age was 39 (range 21-70) years; they were free of symptoms and had normal spirometric results and transfer factor. Thirty two of the patients had previously attended for physiological assessment in connection with a claim for disablement benefit on account of pneumoconiosis; the remainder were attending a chest clinic. All subjects were genuine volunteers and the study was approved by the local ethical committee. A questionnaire of respiratory symptoms and measurement of ventilatory capacity were completed for all subjects. In addition, the clinical and occupational history, a detailed assessment of respiratory function, and a chest radiograph were available for the patients, who had moderate respiratory disability and no detectable ischaemic heart disease. All patients underwent a standard exercise test before any measurements of gas transfer during exercise were made. The mean age of the patients was 54.3 (range 22-70) years and the ventilatory capacity was on average reduced. Thus in standard deviations (SD units, age, sex, and height corrected—see below) the FEV_1 was -1.96 (range 0.7 to -4.5) and FVC -1.21 (range 1.1 to -4.4) litres. On the basis of all the information available at the start of the study four subjects were diagnosed as having definite and four borderline emphysema,

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seven chronic bronchitis without emphysema, three asthma, 10 asbestosis, five coalworkers' pneumoconiosis, two extrinsic allergic alveolitis, two siderosis, one pulmonary sarcoidosis, and one pleural thickening associated with exposure to asbestos.

Transfer factor and KCO were measured by the single breath carbon monoxide method with a transfer test apparatus (PK Morgan). The gas mixture comprised 0.3% carbon monoxide, 14% helium, and 18% oxygen, the remainder being nitrogen plus rare gases. The method is described elsewhere.⁵ The breath holding time was as near constant as possible for each subject and in the range 5–9 seconds, depending on the ability to hold the breath during exercise. The alveolar volume (V_A) was measured by the dilution in the lung of the helium in the test breath. The effect on TL and KCO of within subject variation in V_A was minimised by standardising the results for each subject to their largest recorded alveolar volume.⁶ Exercise was performed on a cycle ergometer (Siemens) at two or three rates of work, usually 30, 60, and 90 watts. The electrocardiogram was recorded from electrodes in the CM5 configuration⁷ and the cardiac frequency was measured over the 12 seconds before each measurement of transfer factor. This was done at rest and during exercise, initially at a range of times after the start of exercise, and in some normal subjects after the end of exercise. After scrutiny of the results the duration of exercise to the commencement of measurement at each work load was standardised at two minutes. A rest period of four minutes was allowed between measurements.

Results were reported in either absolute units or standard deviations about the reference value for a healthy person of the same age, sex, and stature as the subject—hence SD units. Reference values for TL at rest (TL_{rest}) were taken from a standard source⁵ for classification and from the results for the present healthy subjects for comparison. Transfer factor results that exceeded the lower 95% confidence limit about the reference value (that is, mean -1.64 SD) were considered normal and results below the 95% confidence limit abnormal.⁸ Abnormal groups were further divided into reduced (<-2 SD) and borderline (≥ -2 SD but <-1.64 SD). For each subject the relationships TL and KCO on cardiac frequency (fC) were obtained by linear regression analysis and used to derive indices of slope (for example, $\Delta TL/\Delta fC$) and position, the latter being taken as the value for TL and KCO when the cardiac frequency was 100 beats/min (TL_{100}). Mathematical analysis, including multiple regression analysis, t tests, and paired t tests, were undertaken with the help of an IBM 370 computer and the

Fig 1 Transfer factor (TL) measured with five second breath holding time during (●) and after (○) exercise in one healthy subject. Numbers indicate time in seconds from the end of exercise. The continuous line represents a steady state relationship.

Statistical Package for the Social Sciences of the University of Michigan.⁹ The coefficient of variation was calculated as the standard deviation divided by the mean. The 5% level of probability was accepted as significant.

Results

In the preliminary part of the study we examined TL soon after the subjects had stopped exercise. In four normal subjects we found that TL fell faster than cardiac frequency (fig 1). All of the results presented here are derived from measurements made during exercise. Serial results for two unselected

Fig 2 Serial values for transfer factor (TL) standardised for alveolar volume and cardiac frequency from six individuals with normal (●), borderline (○), and abnormal (□) values at rest (two unselected members of each group). Normal = ≥ -1.64 SD units; borderline = ≥ -2 , <-1.64 SD units; reduced = <-2 SD units compared with published reference values.

Table 1 Comparison of indices of gas transfer in healthy subjects and patients (mean values with standard deviations in parentheses)

Index (see under "Methods")	Healthy	Emphysema (a)	Disease of lung parenchyma (b)	Other lung conditions (c)
Number of subjects	37	8	18	13
TL _{rest} (mmol min ⁻¹ kPa ⁻¹)	10.3 (3.0)	6.1 (2.2)**	6.8 (2.1)**	7.9 (2.6) NS
Kco _{rest} (mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	1.70 (0.3)	9.70 (0.22)**	1.30 (0.3)**	1.40 (0.46)**
TL _{rest} (SD)	-0.02 (0.87)	-2.38 (1.27)**	-1.59 (1.25)**	-0.963 (1.08)**
ΔTL/ΔfC (mmol min ⁻¹ kPa ⁻¹ beat ⁻¹)	0.057 (0.034)	0.06 (0.05) NS	0.06 (0.05) NS	0.06 (0.04) NS
ΔKco/ΔfC (mmol min ⁻¹ kPa ⁻¹ l ⁻¹ beat ⁻¹)	0.01 (0.005)	0.01 (0.01) NS	0.01 (0.01) NS	0.01 (0.01) NS
TL ₁₀₀ (mmol min ⁻¹ kPa ⁻¹)	11.65 (3.7)	7.26 (2.00)**	7.31 (2.26)**	9.37 (2.75)*
TL ₁₀₀ (SD)	-0.02 (0.93)	-2.32 (1.40)**	-1.91 (1.43)**†	-0.789 (1.185)*
Kco ₁₀₀ (mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	1.94 (0.37)	1.15 (0.17)**	1.40 (0.35)**	1.66 (0.45)*
Kco ₁₀₀ (SD)	-0.037 (0.96)	-1.97 (0.69)**	-1.28 (1.08)**	-0.614 (1.2) NS
fC ₃₀ (min ⁻¹)	99.9 (12.5)	101.6 (18.1) NS	107.2 (15.2) NS	90.1 (13.9)*

(a) Definite or probable; (b) asbestosis, coalworkers' pneumoconiosis, extrinsic allergic alveolitis, sarcoidosis; (c) bronchitis, asthma, siderosis. fC₃₀—cardiac frequency at 30 watts; NS—not significant compared with healthy subjects.

*Compared with healthy subjects (two tailed *t* test) *p* < 0.05.

**Compared with healthy subjects (two tailed *t* test) *p* < 0.01.

†Compared with TL_{rest} (SD) (paired *t* test) *p* < 0.05.

SD—standard deviation units from reference values derived from healthy subjects in the present study; NS—not significant.

representatives from each of the groups of subjects with normal, borderline, and reduced transfer factor are given in figure 2. This shows that the relationship of TL to cardiac frequency was consistent within subjects as the results were reasonably linear. The variability of the serial estimates of alveolar volume of all subjects was small (coefficient of variation <2%). The within subject variability of transfer factor based on three way analysis of variance of duplicate results on four subjects, at rest and during exercise, was 4.55%. The between subject variability was significantly larger (*p* < 0.01).

For the present healthy subjects TL_{rest} and the indices of position, TL₁₀₀ and KCO₁₀₀, were related to age and other variables by the following relationships:

$$\text{TL}_{\text{rest}} (\text{mmol min}^{-1} \text{ kPa}^{-1}) = 27.4 \text{ st} - 0.058 \text{ A} - 33.9 (1.63) \quad (1)$$

$$\text{TL}_{100} (\text{mmol min}^{-1} \text{ kPa}^{-1}) = 32.3 \text{ st} - 0.06 \text{ A} - 41.1 (1.849) \quad (2)$$

$$\text{KCO}_{100} (\text{mmol min}^{-1} \text{ kPa}^{-1} \text{ l}^{-1}) = 0.61 \text{ st} - 0.01 \text{ A} - 0.15 \text{ G} + 1.34 (0.343), \quad (3)$$

where st is stature (m), A is age (y), G is gender (1 if female, 0 if male), and SD is in parentheses.

The mean results for the healthy subjects and the patients classified in broad groups are given in table 1. This shows that the slope indices (ΔTL/ΔfC and ΔKCO/ΔfC) did not differentiate between the healthy subjects and the three groups of patients. By contrast, the position indices TL₁₀₀ and KCO₁₀₀ were significantly lower in the patients with emphysema and with disease of the lung parenchyma than in the healthy subjects; for the group with disease of the lung parenchyma the reduction in TL₁₀₀ was greater than that in TL_{rest} (table 1). The slope indices were unhelpful in differentiating those with normal trans-

Table 2 Comparison of indices of gas transfer in individuals with normal and abnormal resting transfer factor* (mean values with standard deviations in parentheses)

Index (see under "Methods")	TL _{rest}	
	Normal	Abnormal
Number of subjects	59	17
TL _{rest} (mmol min ⁻¹ kPa ⁻¹)	9.61 (2.76)	5.11 (0.97)**
Kco _{rest} (mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	1.61 (0.34)	1.04 (0.25)**
TL _{rest} (SD)	-0.32 (0.97)	-2.46 (1.08)**
ΔTL/ΔfC (mmol min ⁻¹ kPa ⁻¹ beat ⁻¹)	0.056 (0.033)	0.057 (0.059) NS
ΔKco/ΔfC (mmol min ⁻¹ kPa ⁻¹ l ⁻¹ beat ⁻¹)	0.010 (0.005)	0.013 (0.010) NS
TL ₁₀₀ (mmol min ⁻¹ kPa ⁻¹)	10.7 (3.20)	6.02 (1.26)**
Kco ₁₀₀ (mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	1.79 (0.39)	1.21 (0.33)**
TL ₁₀₀ (SD)	-0.428 (1.12)	-2.42 (1.33)**
Kco ₁₀₀ (SD)	-0.32 (0.97)	-1.84 (1.05)**
fC ₃₀ (min ⁻¹)	98.7 (15.2)	104.8 (12.8) NS

Normal = more than -1.64 SD compared with published reference values.

***p* < 0.01 (two tailed *t* tests).

SD—standard deviation units from reference values derived from healthy subjects in the present study; NS—not significant.

fer factor at rest from those with abnormal transfer factor at rest (table 2). With 2 SD as a criterion of reduction, TL_{rest} and TL_{100} jointly identified 13 patients with reduced gas transfer. TL_{100} also identified an additional four subjects, of whom two had asbestosis and one had radiographic evidence of pulmonary fibrosis and in one a clinical diagnosis of emphysema had been made.

Discussion

The measurement of transfer factor during exercise resembles ergo-oximetry in testing the processes of gas exchange under conditions of load. It has the practical advantage of being available to most lung function laboratories and the theoretical advantage of possibly being more specific than ergo-oximetry, though this has still to be assessed in practice. The procedure has, however, the disadvantage of requiring breath holding during exercise and this may be beyond the ability of some patients with lung disease. To overcome this difficulty Ingram and colleagues made the measurement of transfer factor immediately after exercise,⁴ but this may not be satisfactory since in four healthy subjects during the subsequent few seconds we have found the transfer factor to fall faster than cardiac frequency; an example is given in figure 1. We therefore made the measurement during exercise but reduced the time of breath holding when this seemed necessary and shortened the period of exercise to two minutes. Because transfer factor and KCO are influenced by alveolar volume⁵ we also standardised our results to each subject's largest recorded volume; this procedure made almost no difference to the results for the healthy subjects (maximal correction 2.9%) but improved the consistency of the results in the patients. With these procedures our results do not confirm for the present subjects the finding of Ingram and colleagues for patients with sarcoidosis that the slope indices ($TL/\Delta fC$ and $\Delta KCO/\Delta fC$) provide an early indication of abnormality. When a reduction of slope occurs, however, it also affects the position indices TL_{100} and KCO_{100} . These indices, unlike the slope indices, were significantly reduced in the patients with definite or borderline emphysema and with disease of the lung parenchyma; in the latter group the reduction exceeded that obtained for TL_{rest} . The position indices also identified reductions during exercise (<-2 SD) in four patients with normal transfer factor at rest who might reasonably have been expected to have had defective gas transfer on clinical grounds. Theoretically this result could have been influenced by the use of reference values for control subjects who were on average younger than the patients. Age

was, however, included as a significant term in the regression equations. The result could also have been due to deviations from normal in the cardiac frequency response to exercise; this was not the case, however, since in the assessments which preceded the study the exercise cardiac frequencies were found to be within normal limits¹⁰; they were also similar to this for the present control subjects (see tables). Our findings fail to support the suggestion that the relationship between change in gas transfer and change in cardiac frequency may provide a useful indication of early abnormality but suggest that two other indices of exercise gas exchange, TL_{100} and KCO_{100} , contribute information on the function of the lung parenchyma which is not contained in measurements made at rest. These latter indices merit further scrutiny.

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