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

SS CHU, JE COTES

From the Respiration and Exercise Laboratory, University Departments of Occupational Health and Hygiene and of Physiological Sciences, Newcastle upon Tyne

ABSTRACT Transfer factor (Tl) and KCO 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 KCO at an exercise cardiac frequency of 100 beats/min (Tl100 and KCO100) and the slopes of the regression of exercise transfer factor and KCO on exercise cardiac frequency (ΔTl/ΔFC and ΔKCO/ΔFC) were obtained. The discriminatory performance of these indices in detecting defective gas transfer was compared with that of Tl and KCO at rest (Tlrest and KCORest). 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 Tl100 and KCO100 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 radiograph or is inconsistent with the observed ability to increase oxygen uptake during activity. Transfer factor increases during exercise and recently Ingram and colleagues suggested using as an index the slope of the regression of exercise KCO (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 FEV1 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,
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 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. 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 (VA) 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 VA was minimised by standardising the results for each subject to their largest recorded alveolar volume. 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 configuration 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 (TLrest) were taken from a standard source 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. 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/ΔfC) and position, the latter being taken as the value for TL and KCO when the cardiac frequency was 100 beats/min (TL100). Mathematical analysis, including multiple regression analysis, $t$ tests, and paired $t$ tests, were undertaken with the help of an IBM 370 computer and the

![Diagram](http://thorax.bmj.com/)

**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. 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
representatives from each of the groups of subjects
with normal, borderline, and reduced transfer factor
are given in figure 2. This shows that the relation-
ship 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 fac-
tor based on three way analysis of variance of dupli-
cate results on four subjects, at rest and during exer-
cise, was 4.55%. The between subject variability
was significantly larger (p < 0.01).

For the present healthy subjects TLrest and the
indices of position, TL100 and KCO100, were related to
age and other variables by the following relations-
ships:

\[
TL_{rest} \text{ (mmol min}^{-1} \text{ kPa}^{-1} \text{)} = 
27.4 \text{ st} - 0.058 A - 33.9 (1.63)
\]

\[
TL_{100} \text{ (mmol min}^{-1} \text{ kPa}^{-1} \text{)} = 
32.3 \text{ st} - 0.06 A - 41.1 (1.849)
\]

\[
KCO_{100} \text{ (mmol min}^{-1} \text{ kPa}^{-1} \text{)} = 
0.61 \text{ st} - 0.01 A - 0.15 G + 1.34 (0.343)
\]

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 (\(\Delta TL/\Delta F\) and
\(\Delta KCO/\Delta F\)) did not differentiate between the
healthy subjects and the three groups of patients.
By contrast, the position indices \(TL_{100}\) and \(KCO_{100}\)
were significantly lower in the patients with emphysem
a and with disease of the lung parenchyma than in the
healthy subjects; for the group with disease of the
lung parenchyma the reduction in \(TL_{100}\) was greater
than that in \(TL_{rest}\) (table 1). The slope indices were
unhelpful in differentiating those with normal trans-

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

<table>
<thead>
<tr>
<th>Index (see under “Methods”)</th>
<th>Healthy</th>
<th>Emphysema (a)</th>
<th>Disease of lung parenchyma (b)</th>
<th>Other lung conditions (c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>37 (3-0)</td>
<td>8 (2-2)**</td>
<td>18 (2-1)**</td>
<td>13 (2-6) NS</td>
</tr>
<tr>
<td>TLrest (mmol min(^{-1}) kPa(^{-1}))</td>
<td>1.70 (0.23)</td>
<td>0.01 (0.10)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01) NS</td>
</tr>
<tr>
<td>KCOrest (mmol min(^{-1}) kPa(^{-1}) l(^{-1}))</td>
<td>1.03 (0.34)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01) NS</td>
</tr>
<tr>
<td>TLrest (SD)</td>
<td>0.03 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01)</td>
<td>0.01 (0.01) NS</td>
</tr>
<tr>
<td>ΔTL/ΔF (mmol min(^{-1}) kPa(^{-1}) beat(^{-1}))</td>
<td>0.056 (0.033)</td>
<td>0.005 (0.005)</td>
<td>0.005 (0.005)</td>
<td>0.005 (0.005) NS</td>
</tr>
<tr>
<td>ΔKCO/ΔF (mmol min(^{-1}) kPa(^{-1}) l(^{-1}))</td>
<td>0.005 (0.005)</td>
<td>0.005 (0.005)</td>
<td>0.005 (0.005)</td>
<td>0.005 (0.005) NS</td>
</tr>
<tr>
<td>TL100 (mmol min(^{-1}) kPa(^{-1}))</td>
<td>11.65 (3.7)</td>
<td>7.26 (2.00)**</td>
<td>7.31 (2.26)**</td>
<td>9.37 (2.75)*</td>
</tr>
<tr>
<td>TL100 (SD)</td>
<td>0.20 (0.10)</td>
<td>0.15 (0.10)**</td>
<td>0.14 (0.10)**</td>
<td>0.16 (0.10)**</td>
</tr>
<tr>
<td>KCO100 (mmol min(^{-1}) kPa(^{-1}))</td>
<td>1.94 (0.37)</td>
<td>1.15 (0.17)**</td>
<td>1.40 (0.35)**</td>
<td>1.66 (0.45)*</td>
</tr>
<tr>
<td>KCO100 (SD)</td>
<td>0.07 (0.03)</td>
<td>0.06 (0.03)</td>
<td>0.06 (0.03)</td>
<td>0.05 (0.03)</td>
</tr>
<tr>
<td>TC30 (mm(^{-1}) l(^{-1}))</td>
<td>99-9 (12-5)</td>
<td>101-6 (18-1) NS</td>
<td>107-2 (15-2) NS</td>
<td>90-1 (13-9)*</td>
</tr>
</tbody>
</table>

(a) Definite or probable; (b) asbestosis, coalworkers’ pneumoconiosis, extrinsic allergic alveolitis, sarcoidosis; (c) bronchitis, asthma, siderosis. TC30—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 TLrest (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.

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

<table>
<thead>
<tr>
<th>Index (see under “Methods”)</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>TLrest (mmol min(^{-1}) kPa(^{-1}))</td>
<td>9.61 (2.76)</td>
<td>5.11 (0.97)**</td>
</tr>
<tr>
<td>KCOrest (mmol min(^{-1}) kPa(^{-1}) l(^{-1}))</td>
<td>1.61 (0.34)</td>
<td>1.04 (0.25)**</td>
</tr>
<tr>
<td>TLrest (SD)</td>
<td>0.32 (0.97)</td>
<td>2.46 (1.08)**</td>
</tr>
<tr>
<td>ΔTL/ΔF (mmol min(^{-1}) kPa(^{-1}) beat(^{-1}))</td>
<td>0.056 (0.033)</td>
<td>0.057 (0.059) NS</td>
</tr>
<tr>
<td>ΔKCO/ΔF (mmol min(^{-1}) kPa(^{-1}) l(^{-1}))</td>
<td>0.010 (0.005)</td>
<td>0.013 (0.010) NS</td>
</tr>
<tr>
<td>TL100 (mmol min(^{-1}) kPa(^{-1}))</td>
<td>10.7 (3-20)</td>
<td>6.02 (1.26)**</td>
</tr>
<tr>
<td>KCO100 (mmol min(^{-1}) kPa(^{-1}))</td>
<td>1.79 (0.39)</td>
<td>1.21 (0.33)**</td>
</tr>
<tr>
<td>TL100 (SD)</td>
<td>0.428 (1.12)</td>
<td>2.42 (1.33)**</td>
</tr>
<tr>
<td>KCO100 (SD)</td>
<td>0.32 (0.97)</td>
<td>1.84 (1.05)**</td>
</tr>
<tr>
<td>TC30 (minute(^{-1}))</td>
<td>98.7 (15.2)</td>
<td>104.8 (12.8) NS</td>
</tr>
</tbody>
</table>

*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.
Lung transfer factor during exercise in lung disease

...factor at rest from those with abnormal transfer factor at rest (table 2). With 2 SD as a criterion of reduction, TLrest and TL100 jointly identified 13 patients with reduced gas transfer. TL100 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, 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 volume 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 (TI/ΔfC and ΔKCO/ΔfC) provide an early indication of abnormality. When a reduction of slope occurs, however, it also affects the position indices TL100 and KCO100. 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 TLrest. 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 limits; 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, TL100 and KCO100 contribute information on the function of the lung parenchyma which is not contained in measurements made at rest. These latter indices merit further scrutiny.

We are indebted to Drs JEM Hutchinson and HS Fulton of the Pneumoconiosis Medical Panel, Newcastle upon Tyne, and Dr SJ Pearce of Dryburn Hospital, Durham, for introductions to the subjects and to the Medical Research Council and the University of Newcastle upon Tyne for financial support. The principal of Shanghai Second Medical College kindly gave leave of absence for SSC to undertake the work, which was financed in part by a research grant from Messrs PK Morgan Ltd. We are also indebted to Dr DJ Chinn for help in setting up the study and Miss SA Robertshaw for statistical advice.

References


Lung transfer factor and KCO at cardiac frequency 100 beats/min as a guide to impaired function of lung parenchyma.

S S Chu and J E Cotes

Thorax 1984 39: 524-528
doi: 10.1136/thx.39.7.524

Updated information and services can be found at:
http://thorax.bmj.com/content/39/7/524

These include:

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/