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A standardised method of estimating KCO on exercise

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ABSTRACT This study was designed to standardise a progressive exercise test for the assessment of change in carbon monoxide transfer coefficient (KCO) with exercise and to examine the variation between subjects and the reproducibility within subjects. Normal subjects exercised on a bicycle ergometer while ventilation, heart rate, and expired gas concentrations were recorded continuously. Preliminary studies showed that reduction of the breath hold time to six seconds made measurements of KCO during heavy exercise more comfortable without affecting the result. When KCO was measured immediately after exercise it was lower than when measured during exercise. KCO was measured in 50 normal subjects at rest and at three different work loads maintained for three minutes with a pause of five minutes between each. The relationships between KCO and both oxygen consumption and work load were linear in all subjects but the relationship between KCO and heart rate was distorted by high resting heart rates in some subjects. The mean slope of the relationship between KCO and oxygen consumption ($\dot{V}O_2$) was steeper in women than in men (mean slopes 0·627 and 0·348 mmol min^{-1} kPa^{-1} l^{-1} per l min^{-1} respectively), and the same was true for the relationship between KCO and work rate. The heart rate rose more steeply in relation to $\dot{V}O_2$ in women, so that the relationship of KCO to heart rate was similar in men and women (mean slope 0·01 mmol min^{-1} kPa^{-1} l^{-1} per beat min^{-1}). Repeat studies on five occasions in five individuals gave coefficients of variation for the slopes of the relationships between KCO and $\dot{V}O_2$, work rate, and heart rate of 5–10%.

In her original studies of carbon monoxide diffusing capacity (DLCO), Krogh showed that the measurement increased during muscular work.[1] Ogilvie and colleagues,[2] when developing the single breath technique now in common use, observed a linear relationship between DLCO and energy expended on exercise. Ingram and colleagues[3] recently studied the change of transfer coefficient (KCO) with heart rate during progressive exercise and found it to be a more sensitive index of abnormal pulmonary function than resting measurements in patients with pulmonary sarcoidosis.

We have attempted to standardise a progressive exercise test to measure change in KCO on exercise, examining the variation between subjects and the reproducibility within subjects.

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Methods

Normal subjects were recruited from hospital staff and all gave informed verbal consent. They had no known cardiac or respiratory disease and had values of one second forced expiratory volume (FEV_1), vital capacity (VC), DLCO, and KCO at rest greater than 80% of predicted values.[4,5] The studies were performed with the subject sitting on a bicycle ergometer (Lode) and breathing via a mouthpiece attached to a valve that could be switched to atmosphere or to the inspiratory port of the single breath transfer test system (PK Morgan, Model C). Between estimations of DLCO and KCO expired ventilation was measured by integration of the airflow through a Fleisch pneumotachograph. The expired air, after passing through a mixing chamber, was analysed continuously for carbon dioxide and oxygen with a mass spectrometer (Centronic MGA 200). The electrocardiogram was continuously monitored. Single breath DLCO was measured by the method of Ogilvie *et al*[2] on the basis of the simultaneously estimated alveolar volume (VA).[6] KCO was calculated as DLCO/VA. All measurements were standardised to a haemoglobin concentration of 14·6 g/dl.[7]

Measurements of DLCO and KCO were made at rest and at three levels of exercise. For most of the men the work loads chosen were 50, 100, and 150 w and for most of the women 25, 50, and 75 watts. For each subject the values obtained were plotted against oxygen consumption ($\dot{V}O_2$), work load, heart rate, and minute ventilation. Statistical analysis was performed by linear regression of data from each subject and the correlation was considered acceptable if r exceeded 0·98 ($p < 0.02$). Linearity was also tested formally by applying the F test[8] to the pooled data for men and for women.

PRELIMINARY STUDIES

Variation of breath hold time

Since some subjects experienced difficulty in breath holding for 10 seconds during heavy exercise we explored the possibility of using a shorter breath hold time. Nine normal subjects (four men and five women) cycled continuously at a steady work load that was preselected to be comfortable for the individual. Measurements of DLCO and KCO were made every three minutes while they were cycling. The breath hold time was varied in the sequence 10, six, and 10 seconds. On a subsequent occasion the same subjects repeated the study during continuous exercise with a breath hold time of six seconds on three successive occasions three minutes apart.

There were no significant differences between the 10 and six second values (fig 1) or between successive six second values. We concluded that it was acceptable in the definitive study (see below) to use a six second breath hold time during exercise and that KCO had reached a stable level after three minutes of exercise.

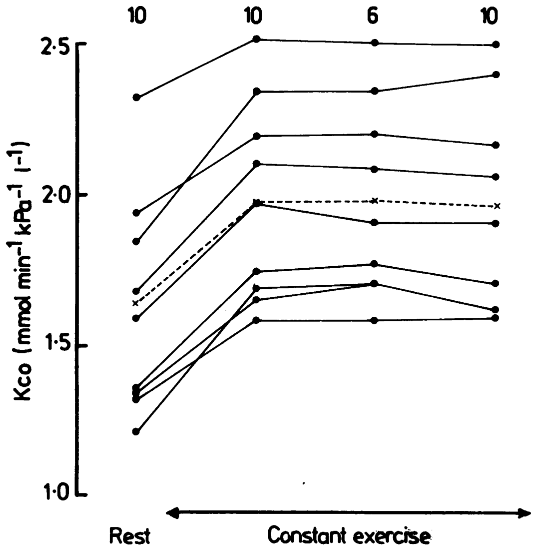

Fig 1 *Effect of varying breath hold time in nine subjects. KCO is shown at rest and at a constant level of exercise with breath hold times of 10, six, and 10 seconds. The broken line shows mean values.*

Timing of measurements

Seven normal subjects were studied with a method similar to that adopted by Ingram *et al*.[3] After measurements of DLCO and KCO at rest they cycled for three minutes and then stopped pedalling, and a further measurement of DLCO and KCO was performed immediately, before cycling was resumed at a higher work load. On a second occasion at an identical work load measurements were made at the end of each exercise period while the subject continued to cycle. Comparison of the two methods showed that measurements obtained immediately after cessation of pedalling were consistently lower than those obtained during exercise (table 1).

Because cessation of exercise introduced an additional potential variable—that is, the length of time between stopping cycling and making the measurement—we abandoned this method as a slight delay in recording would alter the result.

DEFINITIVE STUDY

The fifty subjects (table 2) consisted of 26 men (19 non-smokers, three ex-smokers, and four smokers) and 24 women (19 non-smokers, three ex-smokers, and two smokers). As a result of the preliminary studies we used a breath hold time of six seconds and measured DLCO and KCO while the subject was exercising. A short rest was allowed between each period of exercise to avoid exhausting the subjects and to increase the applicability of the test in clinical practice.

Measurements of DLCO and KCO were made after five minutes' rest on the bicycle with the subject

Table 1 *Comparison of KCO values in seven subjects obtained immediately after cessation of exercise and during continued exercise*

Exercise level	*0*	*1*	*2*	*3*
During continued exercise:				
Mean	1·68	1·98	2·20	2·37
SD	0·20	0·23	0·27	0·32
Immediately after exercise:				
Mean	1·64	1·83	2·00	2·19
SD	0·15	0·17	0·17	0·20

Table 2 *Lung function values in the 50 normal subjects*

	n		*Age (y)*	*Height (m)*	*FEV_1*	*VC*	*DLCO*	*KCO*
					(% predicted)			
Men	26	Mean	33·1	1·76	117·9	114·4	96·2	96·4
		SD	8·9	0·07	14·7	12·0	9·7	11·3
		Range	24–55	1·60–1·93	90–159	100–143	81–116	81–118
Women	24	Mean	28·5	1·62	114·5	110·0	97·3	99·9
		SD	7·9	0·06	14·0	11·6	12·3	12·4
		Range	18–45	1·54–1·72	88–150	87–137	82–127	85–123

VC—vital capacity; DLCO—carbon monoxide diffusing capacity; KCO—transfer coefficient.

breathing quietly from atmosphere via the mouthpiece. The subject then cycled at the lowest work load for three minutes, at the end of which DLCO and KCO were measured while cycling continued. After five minutes' rest the procedure was repeated at a higher work load and after a further five minutes' rest at the third and highest work load.

Reproducibility

Studies were repeated in five subjects (three men and two women) with the method described above on five separate occasions over a period of 60 days at the same time of day for each individual.

Results

KCO increased progressively with increasing work rate in all subjects.

Analysis using the F statistic of the pooled data from the men and the women confirmed that the relationships of KCO to Vo_2, work load, and heart rate were linear. The r value for the relationships between KCO and both Vo_2 and work load exceeded 0·98 in all subjects. In the case of KCO and heart rate, however, the r value was less than 0·98 in seven of the 50 subjects (three men, four women); in each case this was due to distortion by a high resting heart rate. The results for the relationship between KCO and heart rate are therefore based on 43 subjects. No significant differences were found between smokers and non-smokers, so the results have been combined.

Mean values for KCO and Vo_2 and for KCO and heart rate for the three levels of exercise are shown in figures 2 and 3. The individual slopes of the relationship between KCO and Vo_2 were significantly higher in women than in men: mean (SD) 0·627 (0·19) and 0·348 (0·10) mmol min^{-1} kPa^{-1} l^{-1} per l min^{-1} respectively ($p < 0·001$). KCO plotted against work load showed a similar result, with a mean (SD) slope in the women of 0·0088 (0·0024) and in the men of 0·0048 (0·0014) mmol min^{-1} kPa^{-1} l^{-1} per watt ($p < 0·001$). When KCO was related to heart rate, there was no significant difference in mean slope between men and women (0·0098 and 0·0102 mmol min^{-1} kPa^{-1} l^{-1} per beat min^{-1}: $p > 0·3$).

REPRODUCIBILITY

The results in the five subjects studied on five occasions showed no significant differences within subjects as assessed by analysis of variance (fig 4). The mean coefficients of variation for the relationship between KCO and oxygen consumption, work load, and heart rate were 5·9%, 7·5%, and 9·0% respectively. These were all less than the corresponding

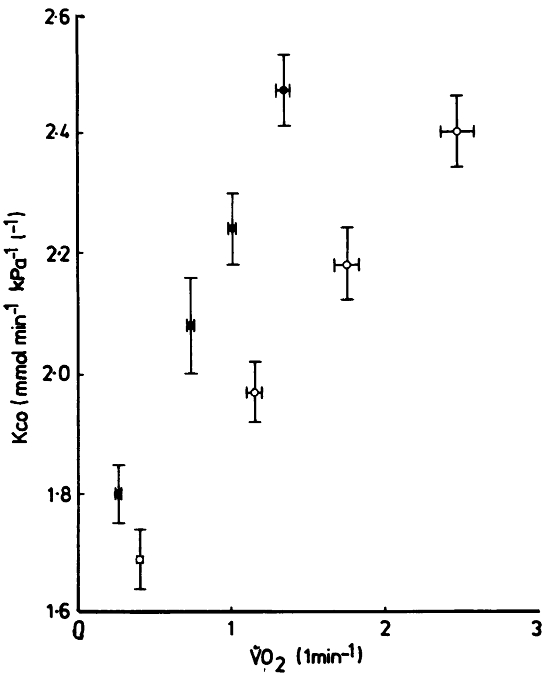

Fig 2 *Mean values (with 1 standard error) of KCO and oxygen consumption ($\dot{V}o_2$) for 26 men (open circles) and 24 women (closed circles) at rest and at three levels of work. Mean values of the individual slopes for men and women were 0·627 and 0·348 mmol min^{-1} kPa^{-1} l^{-1} per l min^{-1} respectively and were significantly different ($p < 0·001$).*

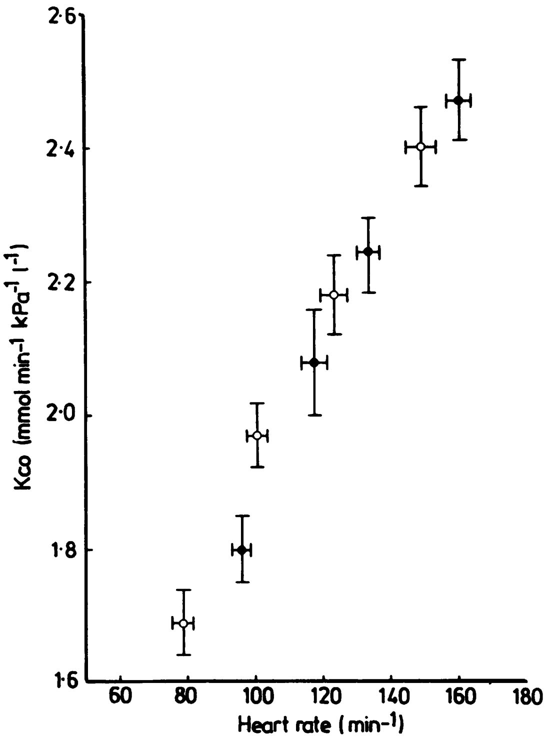

Fig 3 *Mean values (with 1 standard error) of Kco and heart rate (HR) for 23 men (open circles) and 20 women (closed circles), at rest and at three levels of work. Mean slopes for the men and women did not differ significantly, the overall mean slope being 0·01 mmol min^{-1} kPa^{-1} l^{-1} per beat min^{-1}.*

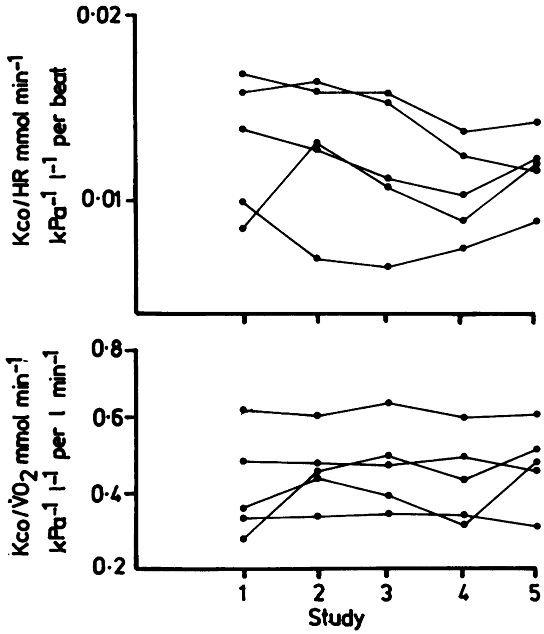

Fig 4 *Individual values of Kco/heart rate (HR) and Kco /oxygen consumption ($\dot{V}O_2$) in five subjects on five separate occasions.*

relationships with DLCO, which were 10·3%, 10·1%, and 11·6% respectively. The alveolar volume calculated from the single breath test was lower on exercise and variability in the volume inspired may account for the greater variability of the DLCO relationships. When the DLCO relationship was used the number of individual slopes rejected was higher. For these reasons only KCO data have been presented here.

Discussion

It is well established that the diffusing capacity for carbon monoxide increases on exercise. This has been shown most frequently with steady state techniques, but the single breath method gives similar results and the rise on exercise probably reflects increases in pulmonary capillary blood flow and volume.[9] Both the single breath[9-11] and steady state[11 12] diffusing capacities increase in linear fashion with increasing oxygen consumption, but the single breath method also allows measurement of KCO. When the reproducibility of the DLCO and the KCO relationships were compared, the coefficients of variation for the DLCO were always higher than for the KCO relationships. KCO has the advantage of being relatively independent of the volume inspired[6] and better reproducibility would therefore be expected.

The preliminary studies showed a reduction in KCO when measurements were made immediately after exercise. The problem of breath holding during exercise was considerably reduced by using a six second instead of a 10 second breath hold time, and this did not alter the results. Use of the relationships between KCO and heart rate has the advantage that men and women could be considered together, so that only one set of normal values is required. The results of seven patients were excluded, however, on account of failure to achieve acceptable linearity. In each case this appeared to be a consequence of a high resting heart rate. The relationship between KCO and both oxygen consumption and work load showed different values for men and women but reproducibility was better and no results had to be excluded. The differences between the relationship of KCO to heart rate on the one hand and to oxygen consumption and work rate on the other reflect the steeper relationship between heart rate and oxygen consumption in women, which results from their lower lean body mass.[13] As a simpler alternative to $\dot{V}O_2$, KCO may be expressed in relation to work load, which does not require continuous gas analysis and had comparable reproducibility. Ingram and colleagues[3] have shown that measurement of KCO during exercise is a sensitive test. The method described here is simple, reproducible, and well tolerated. Its clinical role is likely to be in patients with relatively normal respiratory function at rest.

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