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Technical note

Correction of the single breath carbon monoxide transfer factor in exercise for variations in alveolar oxygen pressure

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Abstract

Background **– Carbon monoxide transfer factor (TLCO) varies inversely with the partial pressure of alveolar oxygen (PAO_2). During exercise the PAO_2 in the alveolar gas sample bag decreases so the TLCO increases more than would be expected from the effects of exercise alone. The effects of PAO_2 on the estimation of TLCO during exercise have been investigated and studies have been performed to determine whether it is appropriate to standardise to a PAO_2 of 16 kPa.**

Methods **– TLCO was estimated at rest and at a single level of exercise in six normal subjects using test gas mixtures of 0·3% carbon monoxide, 14% helium, and oxygen in three different percentages (17%, 21%, and 27%), remainder nitrogen. In three of the subjects an incremental exercise test with estimates of oxygen consumption ($\dot{V}O_2$) and cardiac frequency (fC) was also performed using a mixture containing 18% oxygen.**

Results **– TLCO decreased as levels of inspired oxygen increased. When standardised to a PAO_2 of 16 kPa TLCO became independent of the inspired oxygen concentration. The significance of the curvilinear relations of TLCO and transfer coefficient to $\dot{V}O_2$ and fC improved.**

Conclusion **– The single breath breath holding TLCO should be standardised to a PAO_2 of 16 kPa when estimated during exercise.**

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The single breath breath holding transfer factor for carbon monoxide (TLCO) is inversely related to the alveolar partial pressure of oxygen (PAO_2), the reaction rate of carbon monoxide with oxyhaemoglobin being dependent on the concentration of oxygen.[1–3] During measurements on exercise the PAO_2 decreases, as estimated from the expired gas sample, as the level of exercise increases from rest. The increases in TLCO seen on exercise will therefore not only reflect changes in the volume of blood in the alveolar capillaries and diffusing capacity of the alveolar-capillary membrane,[4] but also decreases in PAO_2.

Kanner and Crapo[5] have recently investigated the effect of varying PAO_2 on TLCO at rest and have derived an equation which standardises TLCO to a PAO_2 of 16 kPa. This equation would permit standardisation of TLCO and overcome variations in the inspired level of oxygen and the effects of altitude.

The purpose of this study was to determine the effect of applying this equation to estimates of TLCO made during exercise.

Methods

SUBJECTS

Six women who were familiar with the exercise protocol participated in the study. Their mean (range) age was 23·5 (20–27) years and body mass was 53·3 (47·1–54·9) kg. All were non-smokers and had no known cardiorespiratory disease. The level of customary occupational and leisure activity[6] was recorded. All had an occupational activity of grade 2B (sitting or standing, some walking; mostly indoors). Three had a leisure activity of grade 3 (regular activity), the others taking part in regular hard physical training (grade 4). All gave informed verbal consent and the study was approved by the local ethical committee.

TRANSFER FACTOR

Single breath TLCO was measured according to the method of Ogilvie *et al*,[2] using the simultaneously estimated alveolar volume (VA).[7] TLCO was accepted if the volume inspired was greater than 80% of the vital capacity and the inspired and expired times were within those recommended.[8] TLCO was calculated according to the American Thoracic Society (ATS) recommendations[8] with the carbon monoxide transfer coefficient (KCO) calculated as TLCO/VA,BTPS. All measurements were standardised to a haemoglobin concentration of 14·6 g/dl.[9] Measurements of carbon monoxide back tension were not made as this has been found to be unnecessary.[10]

EXERCISE PROTOCOL

The gas analysers and mass spectrometer were calibrated before any studies were performed. A four point calibration was performed on the mass spectrometer for nitrogen, oxygen, carbon dioxide, and argon, and a two point calibration on the carbon monoxide analyser. The volume of the spirometer was checked weekly with a seven litre calibration syringe (Hans Rudolf).

The exercise protocol used was that of Neville *et al*[11] using six seconds of breath holding. Subjects were seated on the cycle ergometer (Lode, Holland) and resting measurements of oxygen uptake ($\dot{V}O_2$) and cardiac frequency (fc) were made following a period of five minutes of quiet breathing. Estimates of resting TLCO and KCO were then obtained. The subjects then cycled for three minutes at a preset workload and a constant pedal rate of 60 rpm. At the end of the three minutes they continued to cycle and a single estimate of TLCO and KCO was obtained. For the incremental studies (study 2) the subject then rested for five minutes before the next level of exercise. An electrocardiogram was monitored continuously and a single lead ECG was recorded immediately before the breath hold test.

Mixed expired air was collected in a Tissot spirometer and analysed for oxygen and carbon dioxide using a mass spectrometer (VG Gas Analysis, UK). Inspired and expired oxygen concentrations and expired carbon dioxide concentrations from the TLCO estimates were also analysed using the mass spectrometer. Inspired and expired helium and carbon monoxide levels from the TLCO manoeuvre were analysed using a thermal conductivity and dispersive infrared gas analyser respectively. When analysing helium, carbon dioxide was absorbed, and the analyser compensated electrically for the different levels of inspired and expired oxygen.[12]

Study 1

To determine whether the equation of Kanner and Crapo was applicable to exercise, three exercise tests were performed with the above protocol. Measurements of TLCO, KCO, $\dot{V}O_2$, and fc were made at rest and at a single level of exercise (100 watts). The test gas mixture was 0·3% carbon monoxide, 14% helium, and oxygen in three different percentages (17%, 21%, and 27%), with nitrogen making up the remainder. Each exercise test was performed at the same time of day to avoid any possible diurnal variation, and subjects were asked not to eat and drink for one hour before exercise. Gas mixtures were allocated to each exercise test for a given subject in a single blind randomised manner.

Transfer factor and KCO were calculated as above with the expired helium concentration being corrected for the actual expired carbon dioxide. The equation of Kanner and Crapo:[5]

$$T_{LCO,STAN} = T_{LCO,OB} \times [1 + 0{\cdot}0035(P_{AO_2} - 120)] \text{ mmol/min/kPa}$$

was applied to the data, where TLCO,STAN and TLCO,OB are the standardised and observed values of TLCO respectively, and P_{AO_2} is in mm Hg.

Study 2

To determine the effect of standardising for alveolar oxygen on the relations of TLCO and KCO to $\dot{V}O_2$ and fc, the above exercise protocol was performed with increasing workloads of 25, 50, 75, and 100 watts. The gas mixture used was 0·3% carbon monoxide, 14% helium, 18% oxygen, remainder nitrogen.

DATA ANALYSIS

The data were analysed with the Minitab package.[13] To obtain the relation between the change in TLCO with increasing P_{AO_2} the percentage difference in TLCO was determined. The relation was assessed by linear regression analysis, with its significance being established by analysis of variance as applied to regression. The relations of TLCO and KCO to $\dot{V}O_2$ and fc were determined by quadratic polynomial regression analysis[10] before and after standardisation for P_{AO_2}, and the indices of TLCO and KCO at an fc of 150 beats/min and a $\dot{V}O_2$ of 1·0 l/min were calculated.

Results

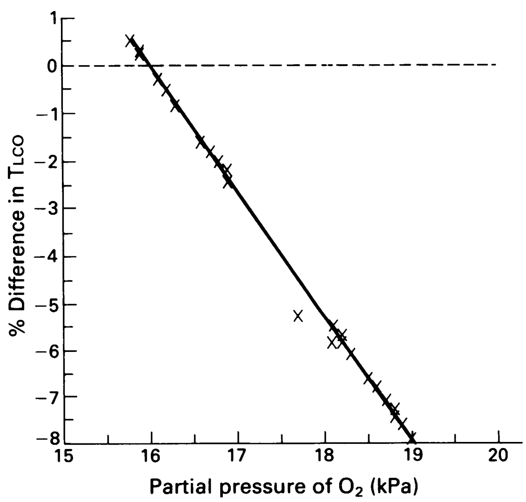
All six subjects completed the exercise tests for study 1 without difficulty. Three of the six subjects were exercised in study 2. All estimates of TLCO were technically acceptable according to the ATS criteria,[8] and each subject achieved an fc of greater than 80% predicted, indicating a maximum exercise test.

Study 1

The relation of the percentage difference between unstandardised and standardised TLCO ($T_{LCO_{diff}}$) to alveolar partial pressure of oxygen at rest and on exercise is shown in the figure and given by the equation:

$$T_{LCO_{diff}} = 42{\cdot}4 - 2{\cdot}65 P_{AO_2} \ (SE = 0{\cdot}21, \ r = 0{\cdot}99, \ p < 0{\cdot}001)$$

from which the calculated P_{AO_2} was 16·0 kPa when $T_{LCO_{diff}}$ is zero.



Relation of the percentage difference between unstandardised and standardised TLCO to the partial pressure of alveolar oxygen (kPa).

Study 2

The resting TLCO and KCO increased after standardisation (table 1). As exercise increased the PAO_2 fell, and the TLCO and KCO at an fc of 150 beats/min and at a $\dot{V}O_2$ of 1·0 l/min were lower after standardisation to 16 kPa (table 1). The coefficient of variation for each subject for the VA was 3·65%, 2·0% and 2·2%, and there was no significant reduction ($p < 0·05$) in VA as the exercise level increased. After standardisation the coefficients of determination for the relations of TLCO and KCO to $\dot{V}O_2$ and fc improved in all subjects and all had a significantly improved correlation (table 2). The TLCO at 100 watts from study 1 using an inspired oxygen concentration of 17% in the three subjects was 11·1, 8·81, and 10·12 mmol/min/kPa compared with 11·86, 9·25, and 10·37 mmol/min/kPa in study 2 using an inspired oxygen concentration of 18%.

Discussion

There has recently been interest in attempting to standardise the calculations of TLCO and recommendations have been made.[14–16] One point of disagreement between the American and European recommendations is the level of inspired oxygen to be used during the test, and whether any standardisation for PAO_2 should be arithmetic or simply by choosing the most appropriate inspired oxygen concentration. Furthermore, the European recommendations suggest standardisation to 14·5 kPa rather than to 16 kPa as proposed by the American Thoracic Society.[8] To allow for differences in the inspired oxygen concentrations on TLCO at rest, Kanner and Crapo derived an empirical equation to standardise TLCO and KCO to a PAO_2 of 16 kPa. The equation of Kanner and Crapo has not been applied to estimates of TLCO during exercise.

It was the purpose of this study to investigate the effect of a decreasing PAO_2 during breath holding as the level of exercise increased. There are two reasons why applying this correction might increase the accuracy of the test as an indicator of normality. Firstly, the inspired oxygen concentration will determine the PAO_2 which is related, though not tied to, the partial pressure of capillary oxygen (Pco_2).[3] As the level of exercise increases so the PAO_2 obtained during breath holding will decrease, resulting in a decrease in Pco_2 and hence an increase in TLCO. Secondly, $\dot{V}O_2$, and therefore PO_2, during breath holding depends on the flow of reduced haemoglobin into the lungs. For any given blood flow the rate of decline in PO_2 will vary inversely with the alveolar volume. Our results confirm these theoretical predictions. We suggest that TLCO should be standardised for PAO_2 if changes in TLCO and KCO are to reflect increases in the vascularity of the lungs and in the area of the diffusion pathway.

In conclusion, an empirical correction of TLCO to allow for PAO_2 can be used during exercise. Use of this correction reduces the error in the prediction of change of TLCO with exercise and appears to yield valid results regardless of the level of exercise or of oxygen uptake. It is recommended for use in the calculation of TLCO in exercise.

Table 1 Indices of TLCO (mmol/min/kPa) and KCO (mmol/min/kPa/l) at rest and during exercise in study 2

Index	Subject 1		Subject 2		Subject 3	
	A	B	A	B	A	B
$TLCO_{Rest}$	10·5	10·7	8·6	8·9	7·1	7·3
KCO_{Rest}	2·18	2·23	2·00	2·11	1·94	2·02
$TLCO_{1·0}$	12·5	11·7	10·2	10·1	9·1	8·8
$KCO_{1·0}$	2·58	2·43	2·44	2·41	2·55	2·47
$TLCO_{150}$	12·6	11·8	10·8	10·4	9·4	9·1
KCO_{150}	2·61	2·48	2·60	2·53	2·59	2·48

TLCO = carbon monoxide transfer factor; KCO = carbon monoxide transfer coefficient. $TLCO_{1·0}$ and $KCO_{1·0}$ are estimates at 1·0 l/min oxygen uptake, while $TLCO_{150}$ and KCO_{150} are estimates at a cardiac frequency of 150 beats/min. For each subject column A is unstandardised and column B is standardised for PAO_2.

Table 2 Coefficients of determination for the relationships of TLCO and KCO to $\dot{V}O_2$ and fc

Subject	TLCO to $\dot{V}O_2$		KCO to $\dot{V}O_2$		TLCO to fc		KCO to fc	
	A	B	A	B	A	B	A	B
1	0·886	0·912*	0·829	0·927*	0·953*	0·954*	0·840	0·930*
2	0·966*	0·990**	0·967*	0·979*	0·987**	0·997**	0·916*	0·932*
3	0·991**	0·991**	0·994**	0·996**	0·979*	0·982**	0·986**	0·990**

TLCO = carbon monoxide transfer factor; $\dot{V}O_2$ = oxygen consumption; KCO = carbon monoxide transfer coefficient; fc = cardiac frequency. For each subject column A is unstandardised and column B is standardised for PAO_2.
* $p < 0·05$; ** $p < 0·01$.

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