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Evolution of changes in carbon monoxide transfer factor in men with chronic obstructive pulmonary disease

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Progression of COPD;
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Summary Progression of chronic obstructive pulmonary disease (COPD) has been studied predominantly by following change in forced expiratory volume in 1 s (FEV_1) which reflects both primary airway disease and associated alveolar disease. Carbon monoxide transfer (T_{LCO}) (the product of the transfer coefficient K_{CO} and alveolar volume V_A) is the only simple, widely available test of alveolar function, but few studies have followed long-term changes in an individual.

Seventeen middle-aged men with moderate chronic airflow obstruction (mean FEV_1 56% of predicted values) were observed with yearly measurements of FEV_1, T_{LCO} and K_{CO} over a mean of 18.9 yr. At the end of follow-up FEV_1 had fallen to 29% of predicted values. V_A, measured by single breath dilution, fell in each man. K_{CO} at recruitment ranged from 41% to 110% predicted and remained $>75\%$ predicted in eight men at the end of follow-up supporting a phenotype of COPD with predominant airway disease and little emphysema. Fall in FEV_1 was faster (2.03% predicted FEV_1/yr) in seven men with low initial $K_{CO}<75\%$ pred. than in men with initial $K_{CO}>75\%$ pred. (1.14% predicted FEV_1/yr, $P = 0.006$).

Repeated measurements of CO transfer in an individual should increase the present poor knowledge of the contribution of alveolar disease to the progression of chronic airflow obstruction.

Introduction

Progression of chronic obstructive pulmonary disease (COPD) has been studied predominantly by following change in forced expiratory volume in 1 s (FEV_1),[1–4] which is influenced both by primary airway disease and associated alveolar disease (emphysema). The respective roles of these two components in determining progression probably vary between individuals. Carbon monoxide transfer (diffusing capacity) is the longest established and simplest routine test of alveolar function, but relatively little is known about the evolution of changes in CO transfer in an individual over time or

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its value in monitoring the rate of progression of COPD. In this paper, we describe the long-term evolution of values of CO transfer in 17 male smokers or ex-smokers who were identified in middle-age when they had moderate airflow obstruction and were subsequently observed for a mean of 18.9 yr.

Methods

Recruitment and follow-up of subjects

Men < 65 yr old with moderate airways obstruction (FEV_1 40–80% of predicted value[5] with reduced FEV_1/VC ratio) which was apparently related to smoking were recruited into a long-term follow-up clinic. The men were detected during various surveys of lung function conducted from this hospital[1,6] and were mainly office workers in West London. Men with other significant conditions affecting the natural history of lung function such as post-tuberculous scarring, bronchiectasis, homozygous α_1-antitrypsin deficiency or men with an overt history of past or present asthma were not included in this analysis. All the remaining identified men who completed a minimum of 10 yr follow-up are included in this report.

Men were followed at 4 monthly intervals; at each of these visits a modified MRC questionnaire[7] was applied, physical examination made, spirometry before and after bronchodilation with inhaled β_2-agonist and mixed venous P_{CO_2} were measured and any treatment checked. If necessary, visits were postponed to avoid periods of acute exacerbation of disease or of potentially complicating illness or procedures. Each year posterior–anterior and lateral chest radiographs, electrocardiograms, haemoglobin estimations and single breath carbon monoxide transfer measurements were made.

Lung function

Forced expiratory volume in 1 s (FEV_1) and slow vital capacity (VC) were measured with a dry spirometer. On each occasion the largest values from three satisfactory measurements were taken. Total lung capacity (TLC) was measured by whole body plethysmography[8] at recruitment only. Values of spirometry and TLC were compared to EC reference values.[5]

Carbon monoxide transfer factor (T_{LCO}) was measured by the single breath method.[9] All details of the method and analysis were unchanged throughout the follow-up and correspond closely to the current recommendations of the American Thoracic Society[10] and European Respiratory Society.[5] Alveolar volume (V_A) was calculated from the single breath dilution of helium. The apparatus and estimated anatomical dead space (V_D anat) were subtracted from the inspired volume, on the assumption that V_D anat (ml) = age (yr) + weight (lb) of each man. A correction was applied to the expired gas concentrations to allow for absorption of carbon dioxide (assumed to be 5%) from the expired sample before its analysis. On each occasion haemoglobin was measured and the T_{LCO} results were corrected to a standard haemoglobin concentration of 14.3 g/l. No allowance was made for the effect of carbon monoxide back pressure. The mean value of 2 or 3 measurements with appropriate inspired volume, breath-holding time and an adequate alveolar sample[5,10] at each visit was used.

T_{LCO} is the product of the subject's V_A expressed at STPD and the rate constant (minutes^{-1}) for CO uptake (k_{CO}, the Krogh coefficient) divided by the total gas pressure in the lungs (barometric pressure Pb, minus water vapour pressure P_{H_2O}).

$$T_{LCO} = (k_{CO} \times V_A)/(P\text{b} - P_{H_2O}).$$

V_A is measured at full inflation. In SI units T_{LCO} is expressed as mmol CO.min^{-1} per pressure unit which involves dividing V_A ml STPD by 22.4.

The Krogh coefficient is now rarely employed; instead the carbon monoxide transfer coefficient is substituted whose SI units of mmol.min^{-1} kPa^{-1} l (BTPS)$^{-1}$, give the appearance of being a ratio, an impression sometimes enhanced by terminology (T_L/V_A or D_L/V_A). In fact the CO transfer coefficient in SI units equals k_{CO}/2.56. To emphasize that the primary measurement of CO transfer in the single breath technique is the rate constant, we use the unambiguous K_{CO} as the abbreviation for the CO transfer coefficient. V_A was expressed in litres BTPS. Values of T_{LCO} and K_{CO} were compared to reference values obtained from West London subjects[11] and also to normal values reported from this laboratory.[12] Mixed venous P_{CO_2} was measured by the rebreathing method.[13]

Atopic status

Serum total IgE was measured by the PRIST technique (Phadebas) and the results expressed as the geometric mean. Prick skin tests to nine common aeroallergens (*Aspergillus fumigatus*, *Alternaria*, *Cladosporium*, grass pollen, cat and dog dander, mixed feathers, wool and *Dermatophagoides pteronyssinus*) were performed on all men.

Statistical analysis

For most analyses comparisons were of mean values and changes between entry and final values; difference between means was assessed by the two-tail *t*-test (paired and unpaired) and statistical significance was accepted at 0.05 level. The slope of decline in FEV_1 and in K_{CO} in each individual was expressed as a linear regression on age throughout follow-up.

Results

Clinical features of subjects at enrolment and during follow-up (Table 1)

At recruitment 11 men were current smokers and six were ex-smokers with a mean (SEM) of 35.1 (5.2) pack-years. During follow-up, six of the remaining smokers quit. Ten men had persistent chronic cough and sputum production throughout follow-up. In three men chronic cough and sputum resolved after quitting smoking, and four denied perennial cough or sputum production throughout.

Extensive efforts were made to detect asthmatic features both at recruitment and during follow-up. Prick skin tests to common aero-allergens were negative in 16 men; the remaining man had a past history of hay-fever and a positive prick skin test to grass pollen (prick skin tests to other common aero-allergens were all negative). Annual differential white blood cell counts in venous blood showed no eosinophilia. Total IgE results (available in 13 men) were in the normal range: geometric mean 32.2 ku l^{-1}.[14] Most men ($\frac{13}{17}$) had negative elective trials of oral prednisolone assessing changes in peak expiratory flow and spirometry, sometimes on more than one occasion. Two of the men at recruitment, both with normal K_{CO} values and normal chest radiographs, had a bronchodilator response $>10\%$ of predicted FEV_1 (11.5% and 17.5%, respectively). Both these men had two negative trials of oral prednisolone and had no significant sputum eosinophilia, but were treated throughout follow-up with inhaled glucocorticosteroids (beclomethasone dipropionate) despite these negative results. Four other men had extended trials of this treatment without benefit in spirometry or symptoms. None were treated with long-term oral glucocorticosteroids, but bronchodilators were increasingly used during follow-up as obstruction increased. Antibiotics were given as required for respiratory infections. Chest radiographs were assessed annually (and initially blind to previous films) by an experienced radiologist with particular experience in the assessment of emphysema; at recruitment he detected emphysema in four of the men which was confirmed during annual follow-up. Possible emphysema in a fifth man was noted less consistently. Computed tomograms were not available in any of these men. During follow-up five men developed fatal carcinoma (two bronchial carcinoma, but with considerable COPD also, two large bowel, one prostate). In these patients the final follow-up data presented were obtained before any complicating lung disease developed. At the end of the follow-up period 10 men were known to have died (five due to carcinoma and five directly due to COPD), three

Table 1 Anthropometry and lung function at beginning and end of follow-up in 17 men with COPD.

		Entry		Final	
		Mean (SEM)	Range	Mean (SEM)	Range
Age	yr	54.1 (1.4)	42–65		
Height	m	1.74 (0.02)	1.63–1.88		
Weight	kg	68.7 (3.0)	50–90	67.1 (3.3)	49–88
Follow-up	yr	18.9 (1.1)	10–29		
FEV_1	Litres	1.90 (0.1)	1.43–2.65	0.82 (0.09)	0.3–1.6
	% pred.	55.7 (2.5)	42–79	28.8 (2.9)	9–55
VC	Litres	3.78 (0.2)	2.55–6.30	2.46 (0.19)	1.1–4.7
FEV_1/VC	%	51.3 (2.3)	35.6–70.6	34.3 (3.2)	11–60
T_{LCO}	SI units	7.92 (0.6)	3.55–12.7	4.15 (0.5)	1.0–9.8
	% pred.	84.5 (7.2)	44–145	52.3 (6.9)	13–120
V_A	L BTPS	6.93 (0.3)	5.45–11.0	4.45 (0.3)	3.1–7.7
	% pred.	102.7 (3.6)	75–139	65.8 (3.0)	47–97
K_{CO}	SI units	1.18 (0.1)	0.61–1.72	0.96 (0.1)	0.2–1.9
	% pred.	73.9 (5.9)	41–110	68.0 (8.7)	21–139

SI units: T_{LCO}, mmol min^{-1} kPa^{-1} and K_{CO}, mmol min^{-1} kPa^{-1} l^{-1}.

were known to be alive and four were lost to follow-up. Only one man developed a raised mixed venous P_{CO_2} and this occurred in the last few months before his death from COPD. None developed significant oedema, right-sided ECG changes or marked enlargement of the heart on chest radiographs.

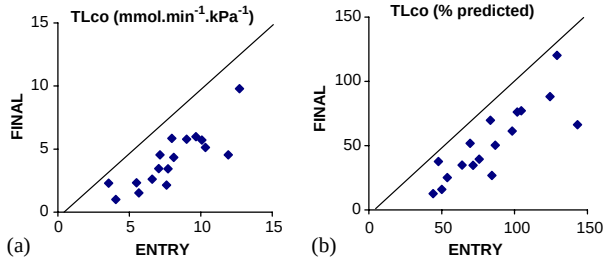

Figure 1 Relation between (a) T_{LCO} and (b) T_{LCO}% predicted at beginning and end of follow-up in the 17 men.

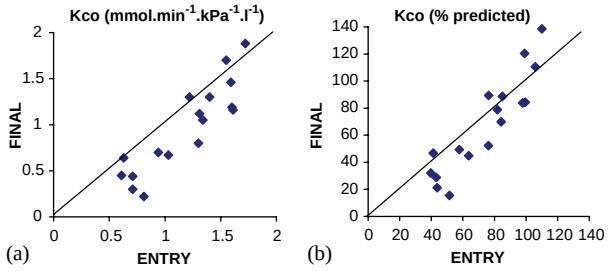

Figure 2 (a) Relation between (a) K_{CO} and (b) K_{CO}% predicted at beginning and end of follow-up in the 17 men.

Lung function

Mean values of baseline spirometry and carbon monoxide transfer are shown in Table 1. TLC was on average 113% of the predicted value, with four men having values greater than 130% predicted, VC was 88% of the predicted value. At entry there was a wide range of individual values of T_{LCO} (Fig. 1) and K_{CO} (Fig. 2), seven of the 17 men having initial values of K_{CO} less than 75% of predicted values. These seven men included the five men with a consistent or possible diagnosis of emphysema on the chest radiograph.

Annual values of K_{CO} in four representative men are shown in Fig. 3. A significant decline in K_{CO} on age was found in only six of these men (see examples Fig. 3c and d) which included five of the seven men in whom K_{CO} was $<75\%$ predicted at entry. The final K_{CO} was lower than entry K_{CO} in 13 men (Fig. 2a), one man with a normal K_{CO} at entry showed a significant rise with time (Fig. 3a). To summarize these results we have used entry and final measurements of CO transfer in each man.

V_A fell in every man as FEV_1 deteriorated (Fig. 4), the average fall being 35% from the initial value. As a result absolute values of T_{LCO} (Fig. 1a) and T_{LCO} % predicted (Fig. 1b) also fell during follow-up in every man.

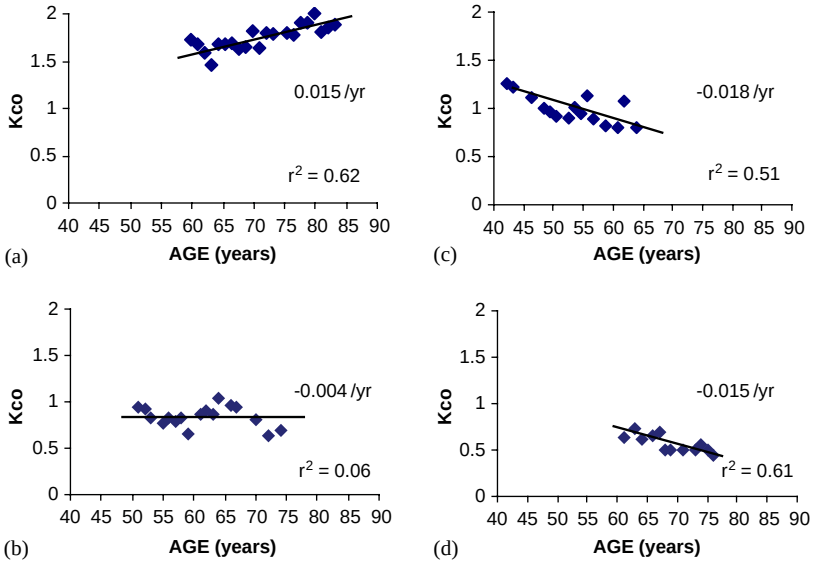

Figure 3 Annual values of K_{CO} (mmol min^{-1} kPa^{-1} l^{-1}) for four men plotted against each man's age. Slopes are indicated in SI units per year. (a) High normal value (110% predicted) at entry with subsequent significant rise, (b) reduced value (58% predicted) at entry but no consistent trend over subsequent years, (c) slightly reduced values (76% predicted) at entry with significant subsequent decline and (d) reduced value (40% predicted) at entry with significant subsequent decline.

At entry K_{CO} was not significantly related to FEV_1 (% predicted) or to FEV_1/VC. We examined subsequent annual decline in FEV_1 in men with initial K_{CO} greater ($n = 10$) and less than 75% predicted (absolute value of $K_{CO} < 1.03$ SI units). Men with initial $K_{CO} < 75\%$ predicted had lower weight and body mass index (BMI: weight/height^2) and a slightly larger TLC (122% vs. 107% predicted, $P = 0.154$) but similar mean FEV_1% predicted to the group with higher initial K_{CO} (Table 2 and Fig. 5). FEV_1 fell faster (2.03% predicted FEV_1 year^{-1}) in the men with initial values of K_{CO} <75% pred. than in men with initial $K_{CO} > 75\%$ pred. (1.14% predicted FEV_1 year^{-1}) ($P = 0.006$). Absolute rates of FEV_1 (ml yr) decline were also significantly different between the two groups ($P = 0.011$). Decline of FEV_1 during follow-up in each individual was inversely related to the initial values of K_{CO} expressed either as % predicted ($r = 0.592$, $P = 0.023$) or as absolute values ($r = 0.539$, $P = 0.025$).

During follow-up the annual decline in K_{CO} averaged 0.16 SI units in the men whose initial K_{CO} was <75% predicted and 0.08 SI units in the 10 men whose initial K_{CO} was >75% predicted (Table 2); the latter rate corresponded closely to the predicted rate of decline in normal subjects.

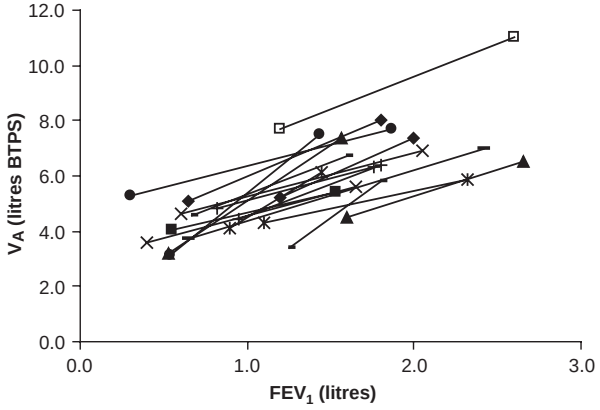

Figure 4 Relation between absolute values of FEV_1 and V_A at beginning (right hand points) and end of follow-up (left-hand points) in the 17 men.

Discussion

We have examined the long-term evolution of CO transfer in 17 middle-aged men, who were identified with moderate chronic airflow obstruction and then followed for nearly two decades. We found an initial wide spread of values of CO transfer coefficient, which was sustained during follow-up. Men with initially reduced values of CO transfer coefficient had significantly faster subsequent decline in FEV_1.

Technical factors

The year-by-year variability in K_{CO} was usually 0.2 SI units or less against an initial spread of values in individual men which was more than 1.0 SI units (Fig. 2a). A recent study of repeat K_{CO} measurements at a 7-day interval in patients with

Table 2 Relation of initial K_{CO} to patient characteristics and changes in CO transfer and FEV_1 during follow-up.

		K_{CO}% predicted at entry			
		Group A <75% pred.		Group B >75% pred.	
Number		7		10	
Age at entry		54.7 (5.3)		53.7 (6.2)	
Years of follow-up		17.7 (1.5)		19.7 (1.6)	
		Entry	Final	Entry	Final
Weight	kg	61.4 (3.3)	60.6 (4.5)	73.8 (3.8)	71.7 (4.1)
BMI	kg m^{-2}	20.1 (0.9)	19.7 (1.0)	24.6 (1.0)	23.9 (1.1)
TLC	litres	8.3 (0.77)		7.2 (0.33)	
T_{LCO}	SI units	5.72 (0.57)	2.20 (0.30)	9.46 (0.58)	5.51 (0.54)
	% pred.	59.4 (5.5)	26.8 (3.7)	101.7 (7.7)	70.1 (7.2)
V_A	litres	7.63 (0.64)	4.74 (0.57)	6.43 (0.21)	4.25 (0.20)
K_{CO}	SI units	0.78 (0.06)	0.49 (0.07)	1.46 (0.05)	1.30 (0.10)
	% pred.	48.7 (3.5)	34.1 (5.0)	91.6 (3.9)	91.7 (8.0)
FEV_1	% pred.	55.7 (3.8)	21.2 (3.0)	55.8 (3.4)	34.2 (3.7)
Decline in FEV_1	ml yr^{-1}	77 (9.3)		49 (4.7)	
	% pred. yr^{-1}	2.03 (0.27)		1.14 (0.14)	

Mean (SEM) SI units: T_{LCO}, mmol min^{-1} kPa^{-1} and K_{CO}, mmol min^{-1} kPa^{-1} l^{-1}.

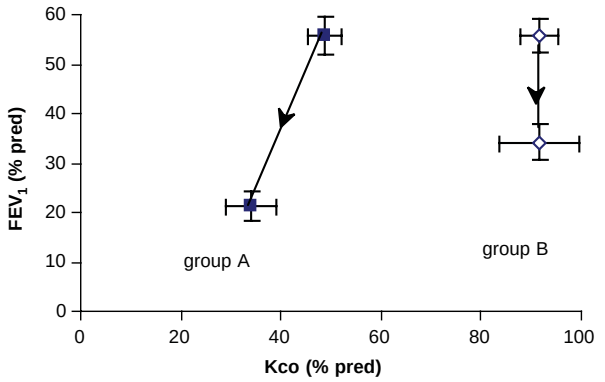

Figure 5 Relation of initial K_{CO} (% predicted) to subsequent decline in FEV_1 Bars indicate SEM. The 17 men were divided into those with initial K_{CO} <75% predicted (group A, $n = 7$) and >75% predicted (group B, $n = 10$). Initial mean FEV_1 (% predicted) was identical in the two groups, but subsequent decline was greater in group A (see text).

emphysema found the coefficient of variability was 0.20 SI units.[15]

Originally V_A during breathholding was calculated as the sum of the inspired volume during the manoeuvre and residual volume (RV) measured by the helium multibreath dilution method[16] (V_A,mb). Subsequently, V_A has usually been estimated from the dilution of helium or other insoluble marker gas used in the procedure itself (V_A,sb) so avoiding the need for a separate measurement of RV. While V_A,mb and V_A,sb are similar in normal subjects, V_A,sb underestimates V_A,mb when there is airflow obstruction.[17] In the present study, V_A,sb fell in all subjects as airflow obstruction worsened (Fig. 4). We did not obtain further values of TLC during follow-up, but annual posterior–anterior and lateral chest X-rays in each man showed no changes in volume. Furthermore, as COPD progresses plethysmographic TLC either remains unchanged or slightly increases.[18]

All measurements of T_{LCO},sb are obtained by multiplying K_{CO} times V_A. Because changes in V_A,sb are so large in COPD we believe that changes in T_{LCO} cannot be interpreted without examining change in K_{CO} which is a better indication of alveolar function. Our emphasis on K_{CO} has been disputed, as published fully elsewhere.[19–21]

Generalizability of results

While observation of the present highly selected group of men with airflow obstruction can illustrate the varying patterns of change in CO transfer over time, the present data cannot be used to estimate the frequency of such patterns in the wider at-risk population.

Assessment of change in K_{CO} and V_A

Normal subjects

In normal subjects TLC does not change with age[5] so that any true decline in T_{LCO} is due to decline in K_{CO}. In cross-sectional studies the age coefficient for K_{CO} is consistently ~0.01 SI units yr^{-1} or less.[22] Only a small study from our own laboratory has reported longitudinal values over a similar period to the present study;[12] this study showed no change in T_{LCO}, V_A,sb or K_{CO} over 22 yr in middle-aged never smoking men. These results sharply contrast with two 8 yr follow-up studies which concluded that T_{LCO} declined at an accelerating rate with increasing age with a much greater annual decline of ~0.016[23] or even 0.035[24] SI units yr^{-1} at 60 yr.

COPD

Few previous studies have followed individuals with regular measurements for sufficiently long periods to describe the evolution from moderate-to-severe airflow obstruction.[25,26] During follow-up all 17 men had significant falls in FEV_1, T_{LCO} and V_A,sb. A fall in V_A,sb can be a direct consequence of emphysema replacing ventilated lung and reducing VC, but also occurs with worsening gas mixing consequent on uneven airway narrowing. Thus a fall in T_{LCO} is a much less specific indicator of alveolar disease than K_{CO}; indeed several of the present men maintained a normal K_{CO} throughout follow-up. Among the men who had an initial K_{CO} of <75% predicted, the fastest individual rate of decline was 0.051 SI units yr^{-1} in a man with radiological evidence of emphysema. In contrast a 2 yr follow-up of 43 men (mean age 52 yr) with severe α_1-antitrypsin deficiency has reported an average annual decline of 0.04 SI units yr,[27] four times the normal change predicted by cross-sectional studies.

The mechanisms potentially reducing K_{CO} in emphysema are a reduction in alveolar wall surface area-to-volume ratio (reflecting the increase in size of the alveoli and breakdown of their walls)[28] and/or an irreversible reduction in pulmonary capillary volume. Early clinico-pathological studies found an inverse correlation of varying strength between values of T_{LCO} and K_{CO} and the extent of macroscopic emphysema.[29] Several mechanisms may weaken this relationship. First, as already discussed, if V_A,sb is used to calculate T_{LCO}, T_{LCO} may be reduced by the development of airway disease alone. It is not always clear whether V_A,sb or V_A,mb has been used to calculate T_{LCO} in the literature.

Second, grossly emphysematous areas contribute little to the VC and the expired gas used for measuring K_{CO}, so any relation between CO transfer and gross macroscopic emphysema presumably depends on macroscopic emphysema being accompanied by microscopic emphysema in the remaining functioning lung. Two studies have found preoperative K_{CO} was strongly related to average airspace size (i.e. microscopic emphysema) rather than to macroscopic emphysema in surgical specimens.[30,31] Third, there is a fundamental difference between the information provided by quantitative pathology (or lung density, measured by computed tomography, CT) which emphasizes the extent of gross alveolar destruction, and by K_{CO}, which indicates the function in the remaining lung. Due to the heterogeneity of disease the value of K_{CO} will inevitably be weighted by the 'best' remaining lung which contributes most to the ventilated volume. Indeed when the total pulmonary vascular bed is greatly reduced, local blood flow in surviving normal and near-normal areas of lung is increased giving a 'compensatory' increase in local pulmonary capillary volume and K_{CO}. While K_{CO} indicates the 'quality' of the remaining lung, the total ability of the lungs to take up oxygen depends on the ventilated volume, a minimal estimate of which is given by V_A,sb. Even in those men whose K_{CO} did not change in follow-up, overall ability to take up oxygen in the lung will have deteriorated due to decline in V_A,sb and this is correctly reflected in the fall in T_{LCO}.

In asthma, redistribution of cardiac output to better ventilated areas of lung due to pulmonary vasoconstriction in poorly ventilated areas, may increase local pulmonary capillary volume and K_{CO}, and account for finding an above normal K_{CO} value as FEV_1 falls in asthma.[32] The slow increase in K_{CO} over many years we observed in a man with progressive airflow obstruction but apparently normal alveolar function (Fig. 1a) might be caused by similar changes in regional pulmonary capillary volume.

Single measurements of T_{LCO} in patients with COPD have shown that a reduced value in early disease is associated with accelerated decline in FEV_1,[33] and in advanced disease predicts exercise capacity[34] and influences mortality.[35,36] In population studies a reduced T_{LCO} predicts all cause mortality more strongly than a reduced FEV_1.[37] At present very little is known about the evolution of changes in CO transfer and how it relates to change in spirometry, although repeated measurements are being made in recent studies of α_1-antitrypsin deficiency[27] and its treatment.[38] In cross-sectional studies considerable reductions in CO transfer and lung recoil pressure have been described in emphysema without much reduction in maximum expiratory flow[18,39,40] but the frequency of this pattern is uncertain. The importance of emphysema in the genesis of airflow obstruction remains surprisingly uncertain[41,42] largely because of the absence of longitudinal studies delineating the alveolar and airway components.

In summary, we found considerable differences in K_{CO} among men with airways obstruction which were sustained over many years, with some men maintaining a near normal K_{CO}, supporting earlier concepts of a phenotype of COPD with predominant chronic airway disease. Low K_{CO} values predicted COPD with particularly accelerated decline in FEV_1. Repeated measurements of CO transfer in an individual are needed to increase the present poor knowledge of the natural history of the contribution of alveolar disease to the progression of COPD.

Acknowledgements

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References

1. Fletcher CM, Peto R, Tinker CM, Speizer FE. *The natural history of chronic bronchitis and emphysema*. Oxford: Oxford University Press; 1976.
2. Camilli AE, Burrows B, Knudson RJ, et al. Longitudinal change in forced expiratory volume in one second in adults: effects of smoking and smoking cessation. *Am Rev Respir Dis* 1987;**135**:794–9.
3. Tager IB, Segal MR, Speizer FE, Weiss ST. The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. *Am Rev Respir Dis* 1988;**138**: 837–49.
4. Anthonison NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1: the Lung Health Study. *JAMA* 1994;**272**:1497–505.
5. European Respiratory Society. Standardized lung function testing. *Eur Respir J* 1993;**5**(Suppl):16.
6. Tattersall SF, Benson MK, Hunter D, et al. The use of tests of peripheral lung function for predicting future disability from airflow obstruction in middle-aged smokers. *Am Rev Respir Dis* 1978;**118**:1035–50.
7. Medical Research Council. Standardised questionnaire on respiratory symptoms. *BMJ* 1960;**2**:1665–8.
8. DuBois AB, Botelho SY, Bedell GN, et al. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. *J Clin Invest* 1956;**35**:322–6.

9. Jones RS, Meade FA. Theoretical and experimental analysis of anomalies in the estimation of pulmonary diffusing capacity by the single-breath method. *Q J Exp Physiol* 1961;**46**:131–43.
10. American Thoracic Society. Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique—1995 update. *Am J Respir Crit Care Med* 1995;**152**:2185–98.
11. Roberts CM, MacRae KD, Winning AJ, et al. Reference values and prediction equations for normal lung function in a non-smoking white urban population. *Thorax* 1991;**46**:643–50.
12. Watson A, Joyce H, Pride NB. Changes in carbon monoxide transfer over 22 years in middle-aged men. *Respir Med* 2000;**94**:1103–8.
13. Campbell EJM, Howell JBL. Rebreathing method for measurement of mixed venous P_{CO_2}. *BMJ* 1962;**2**:630–2.
14. Kerkhof M, Droste JHJ, deMonchy JGR, et al. Distribution of total serum IgE and specific IgE to common aeroallergens by sex and age, and their relationship to each other in a random sample of the Dutch general population aged 20–70 years. *Allergy* 1996;**51**:770–6.
15. Robson AG, Innes JA. Short term variability of single breath carbon monoxide transfer factor. *Thorax* 2001;**56**:358–61.
16. Ogilvie CM, Forster E, Blakemore WS, Morton WJ. A standardized breath-holding technique for clinical measurement of the diffusing capacity for carbon monoxide. *J Clin Invest* 1957;**36**:1–17.
17. Roberts CM, MacRae KD, Seed WA. Multi-breath and single breath helium dilution lung volumes as a test of airways obstruction. *Eur Respir J* 1990;**3**:515–20.
18. Demedts M, Aumann J. Early emphysema: ten years evolution. *Chest* 1988;**94**:337–42.
19. Chinn DJ, Cotes JE, Flowers R, Marks AM, Reed JW. 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). *Eur Respir J* 1997;**10**:764–5.
20. Cotes JE, Hughes JMB, Pride NB. Carbon monoxide transfer coefficient K_{CO} (T_L/V_A): a flawed index. *Eur Respir J* 2001;**18**:893–4.
21. Hughes JMB, Pride NB. In defence of the carbon monoxide transfer coefficient K_{CO} (T_L/V_A). *Eur Respir J* 2001; **17**:168–74.
22. Hughes JMB, Pride NB. Carbon monoxide transfer coefficient (transfer factor/alveolar volume) in females versus males. *Eur Respir J* 2003;**22**:186–7 (Correction **22**:570).
23. Viegi G, Sherrill DL, Carrozzi L, et al. An 8-year follow-up of carbon monoxide diffusing capacity in a general population sample of northern Italy. *Chest* 2001;**120**:74–80.
24. Sherrill DL, Enright Pl, Kaltenborn WT, Lebowitz MD. Predictors of longitudinal change in diffusing capacity over 8 years. *Am J Respir Crit Care Med* 1999;**160**:1883–7.
25. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease. A prospective study of 200 patients. *N Engl J Med* 1969;**280**:397–404.
26. Burrows B, Bloom JW, Traver GA, Cline MG. The course and prognosis of different forms of chronic airways obstruction in a sample from the general population. *N Engl J Med* 1987;**317**:1309–14.
27. Dowson LJ, Guest PJ, Stockley RA. Longitudinal changes in physiological, radiological and health status measurements in alpha(1)-antitrypsin deficiency and factors associated with decline. *Am J Respir Crit Care Med* 2001;**164**: 1805–9.
28. Coxson HO, Rogers RM, Whittall K, et al. A quantification of the lung surface area in emphysema using computed tomography. *Am J Respir Crit Care Med* 1999;**159**:851–6.
29. Thurlbeck WM, Wright JL. *Thurlbeck's chronic airflow obstruction*, 2nd ed. Hamilton, London: BC Dekker; 1999.
30. McLean A, Warren PM, Gillooly M, et al. Microscopic and macroscopic measurement of emphysema: relation to carbon monoxide gas transfer. *Thorax* 1992;**47**:144–9.
31. Gevenois PA, de Vuyst P, de Maertelaer V, et al. Comparison of computed density and microscopic morphometry in pulmonary emphysema. *Am J Respir Crit Care Med* 1996;**154**:187–92.
32. Collard P, Njinou B, Nejadnik B, et al. Single breath diffusing capacity for carbon monoxide in stable asthma. *Chest* 1994;**105**:1426–9.
33. Cauberghs M, Clement J, Van de Woestijne KP. Functional alterations accompanying rapid decline in ventilatory function. *Am Rev Respir Dis* 1993;**147**:379–84.
34. Mohsenifar Z, Lee SM, Diaz P, et al. Single-breath diffusing capacity of the lung for carbon monoxide: a predictor of *P*aO2, maximum work rate and walking distance in patients with emphysema. *Chest* 2003;**123**:1394–400.
35. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1979;**119**:895–902.
36. Dubois P, Machiels J, Smeets F, et al. CO transfer capacity as a determining factor of survival for severe hypoxaemic COPD patients under long-term oxygen therapy. *Eur Respir J* 1990;**3**:1042–7.
37. Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998;**147**:1011–8.
38. Dirksen A, Djikman JH, Madsen F, et al. A randomised clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* 1999;**160**:1468–72.
39. Hogg JC, Wright JL, Wiggs BR, Coxson HO, Opazo Saez A, Pare PD. Lung structure and function in cigarette smokers. *Thorax* 1994;**49**:473–8.
40. Thurlbeck WM, Hogg JC. Lung structure and function in cigarette smokers (correspondence). *Thorax* 1994;**49**:1276–7.
41. Black LF, Hyatt RE, Stubbs SE. Mechanism of expiratory airflow limitation in chronic obstructive pulmonary disease associated with alpha(1) antitrypsin deficiency. *Am Rev Respir Dis* 1972;**105**:891–9.
42. Petrik Pereira R, Hunter D, Pride NB. Use of lung pressure–volume curves and helium sulphur hexafluoride washout to detect emphysema in subjects with mild airflow obstruction. *Thorax* 1981;**36**:29–37.