Influence of smoking habits on change in carbon monoxide transfer factor over 10 years in middle aged men

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Abstract

Background Emphysema is associated with a reduction in carbon monoxide transfer coefficient (TLCO/VA), but little is known about the evolution of changes in TLCO/VA in middle aged smokers at risk of developing chronic airflow obstruction.

Methods TLCO/VA (single breath method) was measured on two occasions 10 years apart in 122 middle aged men.

Results Initially TLCO/VA averaged 97% predicted in never smokers (n = 42, mean age 37.2 years), 99% predicted in ex-smokers (n = 21, mean age 41.9 years), and 85% predicted in those who smoked over 15 cigarettes a day (n = 42, mean age 42.0 years). Mean rates of decrease in TLCO/VA over 10 years, however, were similar in the three groups, so that differences between smokers and non-smokers did not increase during the 10 years. Seventeen men (mean age 40.9 years) who initially were smokers became sustained ex-smokers within two years of the first measurement; in these men mean absolute values of TLCO/VA rose, averaging 89% predicted at the first assessment but 102% predicted 10 years later.

Conclusions By the age of about 40 years TLCO/VA was lower in smokers than in never smokers but this difference did not increase over the following 10 years. Sustained ex-smokers had values similar to those of never smokers even when TLCO/VA was known to have been reduced while they were smoking. Changes in TLCO/VA associated with stopping smoking were considerably larger than could be explained by carbon monoxide back pressure, indicating that mechanisms other than irreversible increase in the size of terminal air spaces underlie the lower values in smokers. To detect emphysema in smokers it is necessary to use reference equations that take account of current smoking.

(Thorax 1993;48:119-124)

are the static pressure-volume curve of the lungs, which requires oesophageal intubation and is impractical on a large scale, and carbon monoxide transfer (TLCO), especially when this is expressed per litre of alveolar volume, VA (carbon monoxide transfer coefficient, TLCO/VA).¹ Cross sectional studies have shown that TLCO/VA is lower in smokers than in never smokers²⁻¹⁰ and that values in both smokers and never smokers decline with age.⁹⁻¹⁵ In recent years several studies have sought to relate the decline in TLCO/VA with age to an increase in alveolar and alveolar duct dimensions, which reduces the alveolar surface area:volume ratio.¹⁰⁻¹³ But although never smokers consistently have higher TLCO/VA values than current cigarette smokers⁹⁻¹⁰ several studies indicate that ex-smokers have values similar to those of never smokers.^{2,6,8,9,15} This could indicate that ex-smokers quit smoking before anatomical damage is produced in the lung, or alternatively that the reduction in TLCO/VA found in many smokers is reversible. So far as we are aware only one small study has studied individuals sequentially while smoking and after quitting.^{16*} We have measured TLCO/VA on two occasions 10 years apart in 122 middle aged men of known and consistent smoking habit.

Methods

SUBJECTS

Subjects were white middle aged men, who were mainly office workers in West London and were originally recruited into a longitudinal study of lung function in 1974.¹⁷ In 1985 122 men were studied again. These men were selected for their consistency of smoking (or non-smoking) habit as assessed by questionnaire at the beginning, middle, and end of the follow up period; reports of habit were supported by inspection of cigarette packs and corroborated by measurements of carboxyhaemoglobin (capillary blood), mixed expired fractional concentration of carbon monoxide (F_{ECO}), and plasma cotinine concentration several times during follow up. For the smokers daily consumption was taken as the average number of cigarettes smoked per day at the beginning, middle, and end of the 10 years; only consistent smokers of more than 15 cigarettes a day were included. We

*A further study showing a rise in TLCO/VA, which could not be explained by reduction in carbon monoxide back pressure, in 14 subjects one week after they had quit smoking has recently been published.³²

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Received 18 February 1992
Returned to authors

29 July 1992
Revised version received
13 August 1992

Accepted 19 August 1992

Most tests of lung function used in epidemiological surveys reflect either airway function alone or a combination of airway and alveolar function, and so do not provide any indication of developing emphysema. The best established tests for indicating emphysema

Table 1 Anthropometric data, spirometric values, and results of the single breath nitrogen test in year 0 and year 10 (mean (SE) values)

	<i>n</i>	Year 0			Year 0		Year 10		Years 0-10	Year 0	Year 10
		Age	Height	TLC	FEV ₁				Decline in FEV ₁	SBN ₂	
		(y)	(m)	(l)	(l)	(%pred)	(l)	(%pred)	(ml/y)	(%/l)	
Never smokers	42	37.2 (1.6)	1.76 (0.01)	6.82 (0.16)	4.31 (0.13)	111 (1.8)	4.12 (0.14)	115 (2.2)	24.3 (3.3)	0.67 (0.05)	0.92 (0.07)
Ex-smokers	21	41.9 (2.1)	1.76 (0.01)	6.75 (0.16)	4.21 (0.16)	113 (3.3)	3.90 (0.18)	113 (3.4)	32.6 (5.0)	0.76 (0.11)	1.17 (0.16)
Quitting smokers*	17	40.9 (2.5)	1.79 (0.06)	6.74 (0.14)	3.96 (0.14)	102 (3.4)	3.69 (0.15)	103 (3.8)	31.6 (6.7)	0.97 (0.14)	1.15 (0.15)
Smokers	42	42.0 (1.5)	1.76 (0.06)	6.62 (0.13)	3.72 (0.11)	99 (2.0)	3.31 (0.14)	96 (2.9)	47.6 (5.4)	1.21 (0.11)	1.82 (0.17)

*Men who were smokers in year 0 but had quit smoking by the end of year 2.

TLC—total lung capacity; FEV₁—forced expiratory volume in one second; SBN₂—plateau value from the single breath nitrogen test.

excluded men with erratic smoking habits (including any who gave up smoking for more than six months and then relapsed or who stopped more than two years after the initial assessment), those with disease likely to interfere with lung function (assessed by questionnaire, reports from the subjects' own practitioners, and chest radiographs), and those taking β adrenoceptor blocking drugs. The men studied were all those available from the original sample who fulfilled all these criteria.

The 122 men were divided into four categories based on the average smoking habit over the 10 years: 42 men who had never smoked (NS), 42 men smoking more than 15 cigarettes/day (S; mean cigarette consumption 29 cigarettes/day at recruitment, 27 cigarettes/day 10 years later); 21 men who had stopped smoking two years or more before the start of the survey and remained non-smokers (ex-smokers, XS); and 17 men who were smokers at the start of the survey (when they smoked a mean of 18 cigarettes/day) but gave up smoking within the following two years and continued not smoking until the end of the survey (quitters, QS). The mean age of all the groups at the start of the survey ranged from 37 to 42 years (table 1).

MEASUREMENTS

Spirometry, the single breath nitrogen test, and a carbon monoxide transfer factor test were performed at the beginning and end of the 10 years. Total lung capacity (TLC) was measured, with a variable volume body plethysmograph,¹⁸ only at the beginning of the period. Carbon monoxide transfer factor was measured by the single breath method.¹⁹ All details of apparatus, method, and calculations were identical in years 0 and 10. Calculations were made on two acceptable breaths. Alveolar volume was calculated from the dilution of helium; the apparatus and estimated anatomical dead space (VD anat) were subtracted from the inspired volume, on the assumption that VD anat (ml) = age (y) + 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 both occasions

haemoglobin was measured and the TLCO results were corrected to a standard haemoglobin concentration of 14.3 g/dl.²⁰ VA is reported in litres BTPS and converted to ml STPD for use in calculation of TLCO. Results were also expressed as TLCO/1 BTPS (transfer coefficient, TLCO/VA). The transfer coefficient is analogous to KCO, the rate of fall in alveolar carbon monoxide. Because TLCO is itself calculated by multiplying KCO by VA, the ratio TLCO/VA is (perhaps paradoxically) not affected by the value of VA. The details of the technique corresponded closely to the recommendations of the American Thoracic Society.²¹ Values were also expressed as percentages of reference values.¹¹

We estimated the effect of carbon monoxide back pressure in the blood on our reported values for TLCO. At the time of the first measurement each subject had a direct measurement of carboxyhaemoglobin made by the spectrophotometric method. To estimate the effect of carbon monoxide back pressure on TLCO, we assumed that true TLCO would increase 0.6% for each 1% of carboxyhaemoglobin present in the blood.⁸ At the end of the 10 years the mixed expired fractional concentration of carbon monoxide (FECO) was measured with an electrochemical sensor (Ecolyzer Series 2000, Analysis Automation Ltd).²²

Forced expiratory volume in one second (FEV₁) and slow vital capacity (VC) were measured with a dry spirometer,²³ and on each occasion the largest of three satisfactory measurements was taken. Values were compared with reference values.²⁴ The single breath nitrogen test was performed at the beginning and end of the survey. On each occasion the fractional concentration of nitrogen (FEN₂) was measured at the mouth during a slow expiration from TLC after a single breath of 100% oxygen initiated from residual volume.¹⁸ On the first occasion the subject performed the test seated in the variable volume plethysmograph and expired volume was measured as change in thoracic gas volume; on the second occasion expired volume was measured with a Collins wet spirometer. Two expirations with VC within 5% of each other (and of VC obtained by spirometry) were obtained in each subject and mean values of

Table 2 Changes in carbon monoxide transfer between year 0 and year 10 (mean (SE) values)

				Year 0		Year 10		Year 0	Year 10	Year 0		Year 10	
	Year 0	Year 10	Year 0	TLCO						TLCO/VA			
Hb (g/dl)			COHb (%)		(mmol min ⁻¹ kPa ⁻¹)	(%pred)	(mmol min ⁻¹ kPa ⁻¹)	(%pred)	VA (l)	(mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	(%pred)	(mmol min ⁻¹ kPa ⁻¹ l ⁻¹)	(%pred)
Never smokers	15.0 (0.14)	15.3 (0.18)	0.39	10.4 (0.25)	96 (1.9)	9.4 (0.24)	95 (1.9)	6.43 (0.17)	6.37 (0.19)	1.62 (0.03)	98 (2.3)	1.51 (0.04)	99 (1.9)
Ex-smokers	15.0 (0.17)	15.2 (0.20)	0.41	10.2 (0.41)	97 (2.6)	9.4 (0.40)	97 (2.5)	6.39 (0.18)	6.13 (0.17)	1.61 (0.05)	100 (3.1)	1.53 (0.05)	104 (2.6)
Quitting smokers	14.8 (0.20)	15.5 (0.21)	1.98	9.2 (0.31)	84 (3.1)	9.1 (0.23)	91 (2.7)	6.46 (0.17)	6.13 (0.16)	1.43 (0.04)	89 (3.0)	1.50 (0.04)	102 (2.6)
Smokers	15.5 (0.14)	15.9 (0.18)	4.03	8.4 (0.31)	80 (2.6)	7.3 (0.33)	76 (2.4)	6.16 (0.15)	5.87 (0.15)	1.36 (0.03)	85 (2.2)	1.25 (0.04)	86 (2.7)

Hb—haemoglobin; COHb—carboxyhaemoglobin; TLCO—single breath transfer factor for carbon monoxide, corrected to a haemoglobin value of 14.3 g/dl but not corrected for carbon monoxide back pressure; VA—alveolar volume.

phase III of the nitrogen slope (expressed as change in % FEN₂/litre expired volume, SBN₂) are reported. Closing volume (CV) was also measured on these traces and expressed as a percentage of expired VC (CV/VC%).

Results

The four subgroups of the 122 men were similar in mean age, height, and total lung capacity (table 1). The two subgroups of men who were cigarette smokers initially had a lower mean FEV₁ than never smokers and ex-smokers. Over the subsequent 10 years decline in FEV₁ was greatest in those who smoked more than 15 cigarettes a day and slowest in never smokers. Initially the two subgroups of smokers had more abnormal SBN₂ than never smokers and ex-smokers. Over the subsequent 10 years the changes were small except in those who continued to smoke more than 15 cigarettes a day. The continuing heavy smokers therefore showed the expected lower values of FEV₁, accelerated decline of FEV₁ over the 10 years, and abnormal results in the single breath nitrogen test; although they also showed the highest initial CV/VC ratios (mean 21.0%) this ratio did not increase over the 10 year follow up period.

Values for TLCO and TLCO/VA shown in table 2 are corrected to a haemoglobin value of 14.3 g/dl but not corrected for carbon monoxide back pressure. Initially TLCO values were 10% or more lower in terms of % predicted in the two smoking subgroups than in never smokers and ex-smokers, in whom mean values were similar. After 10 years the mean absolute decline in TLCO was similar in the three groups with consistent smoking or non-smoking habits, but the decline was negligible in smokers who quit in the first two years of follow up. When the results were expressed as % predicted values to allow for expected changes with age, never smokers and ex-smokers showed no mean change while continuing smokers showed a reduction over the 10 year follow up. In contrast, over the 10 years in smokers who quit TLCO expressed as % predicted values actually

improved to values similar to those in never smokers and ex-smokers.

Values of TLCO/VA showed some of the same features (table 2), with lower initial values in the two subgroups of smokers than in never smokers and ex-smokers (unpaired *t* tests: QS *v* NS *p* = 0.04; S *v* NS *p* < 0.00001; NS *v* XS *p* = 0.74; QS *v* S *p* = 0.19). In continuing smokers there was a decline in TLCO/VA in terms of absolute values but not in terms of % predicted values (paired *t* test, *p* = 0.56), indicating that some of the decline in TLCO was related to decline in VA, which was in turn associated with decline in FEV₁. (Continuing smokers showed the largest differences between initial TLC and VA both at the beginning and at the end of the survey.) In quitters the mean value of TLCO/VA actually improved over 10 years, in contrast to the highly significant declines that occurred in the other three groups (paired *t* test: NS and S *p* < 0.0001; XS *p* = 0.04). When the results were expressed as % predicted values there was a highly significant rise in quitters over the 10

Figure 1 Mean (SE) values of carbon monoxide transfer coefficient (TLCO/VA), expressed as percentages of predicted values, at recruitment (hatched columns) and 10 years later (white columns). NS—never smokers; XS—ex-smokers at recruitment; QS—smokers who quit within first two years after recruitment; S—continuing smokers. The difference between initial and 10 year values in QS was significant (paired *t* test, *p* = 0.0014).

Figure 2 Individual changes in carbon monoxide transfer coefficient (TLCO/VA), expressed as percentages of predicted values, over 10 years in 17 smokers who were still smoking at recruitment but gave up within the following 24 months. ○ Value at recruitment; ● value 10 years later.

years (paired *t* test, *p* = 0.0014); mean values were then very similar to those of the other two non-smoking groups (fig 1). Fourteen of the 17 quitters showed a rise in TLCO/VA (% predicted); the three quitters who showed a small fall comprised three of the four men with the highest initial values (fig 2).

We estimated how much of the differences in carbon monoxide transfer were due to back pressure of carbon monoxide associated with smoking. At the first survey mean values of carboxyhaemoglobin (table 1) were similar in never smokers and ex-smokers; the values in quitters (1.98%) and current smokers (4.03%) were relatively low; most men were studied in the mornings (and all by 14 00 hours). At the survey 10 years later we did not measure carboxyhaemoglobin directly, but mean values of F_ECO were similar in the three non-smoking groups (NS 3.4 ppm, XS 3.6 ppm, QS 3.8 ppm). Confirmation of reported smoking habits was also obtained from appropriate plasma cotinine concentrations. In the group of continuing smokers, who reported a fall in mean daily consumption from 29 to 27 cigarettes a day, F_ECO was 14.9 ppm, a value consistent with a carboxyhaemoglobin value in year 10 similar to that measured directly in year 0. On the assumption that TLCO should be increased 0.6% for each 1% of carboxyhaemoglobin in the blood, the mean values of TLCO/VA in continuing smokers in year 0 and year 10 would be 1.39 and 1.29 ml min⁻¹ kPa⁻¹ l⁻¹ respectively (compared with the values of 1.36 and 1.25 shown in table 2). The correction is negligible in never smokers and ex-smokers. The estimated effect in quitters is to increase the mean value of TLCO/VA in year 0 from 1.44 to 1.46 ml min⁻¹ kPa⁻¹ l⁻¹ and so to reduce the rise in TLCO/VA by 0.02 ml min⁻¹ kPa⁻¹ l⁻¹. Hence the reduction in carbon monoxide back pressure in quitters accounted for only a small part—probably less than 20%—of the observed differences in trends with time in quitters.

Discussion

The present results show that TLCO and TLCO/VA are reduced in current smokers

while values in established ex-smokers are very similar to those in never-smokers. The longitudinal results show that decline in TLCO was faster in continuing smokers than in never smokers; this acceleration was due to a reduction in accessible VA rather than in TLCO/VA. Smokers who stopped in the first two years of the study showed no significant decline in TLCO/VA over the 10 years and in most individuals TLCO/VA rose; only a small part of these changes could be attributed to reduction in carbon monoxide back pressure in venous blood. These results therefore provide direct evidence of a reversible component in the reduction of TLCO/VA in current smokers—which was suspected from previous cross sectional studies.

We took considerable care to use a standard technique to measure TLCO on the two occasions; although it would have been ideal to measure carboxyhaemoglobin in year 10 as well as in year 0, calculations that assumed that carboxyhaemoglobin was zero in the QS group in year 10 indicate that changes in carbon monoxide back pressure could account for at most 20% of the observed differences in behaviour between the S and QS groups. In most previous large scale studies no correction has been made for the effects of blood carbon monoxide, reliance being placed on asking smokers to abstain for the preceding hours. We asked our subjects not to smoke on the morning of the test and TLCO was measured at the end of a series of tests; but the measured carboxyhaemoglobin values indicate that the smokers were unable to abstain completely. Blood carbon monoxide depresses TLCO/VA by two mechanisms, pre-existing carboxyhaemoglobin reducing the haemoglobin available for further carbon monoxide uptake, while the carbon monoxide pressure in the pulmonary venous blood acts as a back pressure to the calculated alveolar pressure of carbon monoxide, which is usually assumed to be the actual driving pressure for carbon monoxide transfer. Earlier workers have also suggested that these effects of blood carbon monoxide cannot alone account for the lower TLCO and TLCO/VA in smokers;^{4,9} on average, TLCO is about 1.7 mmol min⁻¹ kPa⁻¹ l⁻¹ lower in smokers than non-smokers.⁹ Our direct measurements of carboxyhaemoglobin in heavy cigarette smokers confirm that at most 15% of the mean differences in TLCO/VA between smokers and non-smokers could be attributed to carbon monoxide back pressure. We also corrected our results for differences in total haemoglobin. Haemoglobin values were only slightly higher in the current smokers than non-smokers, so that this correction had little effect. In more advanced airways obstruction, with hypoxaemia and secondary polycythaemia, the effect could be considerable.

In our survey we had hoped to use carbon monoxide transfer to detect the development of emphysema. Certainly the severer degrees of emphysema are associated with a reduction in TLCO/VA as measured by the single breath method. This has been established both when

emphysema has been inferred in life from computed tomograms^{1 25} and when it has been assessed directly by morphometry in lungs obtained at lobectomy¹ or necropsy.²⁶ Little, however, is known about the evolution of changes in TLCO/VA in individuals. The most striking of the present results was the rise in absolute TLCO/VA in the men who quit smoking between the two surveys, which contrasts with the decline in mean TLCO/VA found in the three groups with consistent smoking or non-smoking habits over the 10 years (table 2). One previous longitudinal study found possible increases in TLCO three and six weeks after quitting in five or six subjects.¹⁶ Indirect evidence from cross sectional studies is also compatible with a reversible component in the reduction in TLCO/VA in smokers. Established ex-smokers had values similar to those of never smokers in several previous studies^{2 6 8 9 15} as well as in the present study. Reductions in TLCO²⁷ and TLCO/VA²⁸ have been found in smokers less than 30 years of age, when emphysema is rare, leading Tockman *et al*²⁹ to suggest that a reduction in TLCO occurs rapidly with the onset of smoking.

Our results provide no direct evidence on the mechanism or the time course of the reversible component of reduction in TLCO/VA. Values of TLCO/VA are sensitive to uneven distribution of inspired gas, of the diffusion-alveolar volume ratio, and of the perfusion-diffusion ratio, and subtle changes in any of these distributions could affect measured TLCO/VA in the expired gas. Pulmonary vasoconstriction has also been suggested as a possible mechanism.^{9 27} Acute decreases in TLCO have been observed in some patients with Raynaud's disease after the induction of digital vasospasm by immersion in cold water;³⁰ conceivably pulmonary vasoconstriction could be induced by the direct effect of nicotine or by the effects of cigarette smoke in causing the release of vasoconstrictor mediators, such as histamine or the leukotrienes.

The presence of a reversible component in the reduction of TLCO/VA in smokers compromises its usefulness as a test for detecting emphysema. Knudson *et al*⁹ have analysed the effects of pack years of smoking (average number of cigarette packs of 20 smoked per day multiplied by the number of years of smoking) in current smokers and ex-smokers studied on a single occasion in a cross sectional study in Tucson. They concluded that the effects of smoking on TLCO and TLCO/VA were best expressed by using separate terms for the effects of current smoking and for the cumulative smoking exposure (expressed as pack years) in reference equations. In men their analysis suggested that smoking caused a decline in TLCO soon after the start of smoking and that this effect was reversed within three years of stopping smoking. Cumulative smoking history also had an irreversible effect: although ex-smokers on average always had a higher TLCO than continuing smokers, TLCO tended to be lower

in ex-smokers who had accumulated more pack years of smoking. Hence in the early years of smoking the predominant factor reducing TLCO in smokers is likely to be the reversible factor and to be found in a high proportion of smokers. Irreversible changes due to emphysema develop in a much smaller proportion of smokers and later in the smoking history. Since they did this analysis Knudson *et al*³¹ have attempted to detect emphysema by observing TLCO and TLCO/VA values lower than those predicted on the basis of standard factors (age, height, gender) plus factors expressing the average effects of cumulative cigarette consumption and current smoking. Because the factor indicating the effect of cumulative cigarette smoking is presumably itself influenced by the development of emphysema this approach indicates the development of more than the average amount of emphysema in an individual.

In summary, the present results imply that the reduction in TLCO and TLCO/VA found in many male cigarette smokers in early middle age is commonly reversible. These changes will tend to obscure irreversible changes due to emphysema, which develop in a minority of smokers. To detect emphysema it is necessary to allow not only for conventional factors (sex, age, height, haemoglobin, blood carbon monoxide) but also for the effects of current smoking on TLCO/VA.

This work was supported by Medical Research Council Grant 84040575 SA.

- Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, *et al*. Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. *Am Rev Respir Dis* 1989;139:1179-87.
- Martt JM. Pulmonary diffusing capacity in cigarette smokers. *Ann Intern Med* 1962;56:39-45.
- Krumholz RA, Chevalier RB, Ross JC. Cardiopulmonary function in young smokers. A comparison of pulmonary function measurements and some cardiopulmonary responses to exercise between a group of young smokers and a comparable group of nonsmokers. *Ann Intern Med* 1964;60:603-10.
- Rankin J, Gee JBL, Chosy LW. The influence of age and smoking on pulmonary diffusing capacity in healthy subjects. *Medicina Thoracalis* 1965;22:366-74.
- Krumholz RA, Hedrick ED. Pulmonary function differences in normal smoking and nonsmoking, middle-aged, white-collar workers. *Am Rev Respir Dis* 1973;107:225-30.
- Frans A, Stanescu DC, Veriter C, Clerbaux T, Brasseur L. Smoking and pulmonary diffusing capacity. *Scand J Respir Dis* 1975;56:165-83.
- Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state: predicted values, lower limits of normal, and frequencies of abnormality by smoking history. *Am Rev Respir Dis* 1983;127:270-7.
- Leech JA, Martz L, Liben A, Becklake MR. Diffusing capacity for carbon monoxide. The effects of different derivations of breathhold time and alveolar volume and of carbon monoxide back pressure on calculated results. *Am Rev Respir Dis* 1985;132:1127-9.
- Knudson RJ, Kaltenborn WT, Burrows B. The effects of cigarette smoking and smoking cessation on the carbon monoxide diffusing capacity of the lung in asymptomatic subjects. *Am Rev Respir Dis* 1989;140:645-51.
- Viegi G, Paoletti P, Prediletto R, Di Pede F, Carrozzi L, Carmignani G, *et al*. Carbon monoxide diffusing capacity, other indices of lung function, and respiratory symptoms in a general population sample. *Am Rev Respir Dis* 1990;141:1033-9.
- Bradley J, Bye C, Hayden SP, Hughes DTD. Normal values of transfer factor and transfer coefficients in healthy males and females. *Respiration* 1979;38:221-6.

- 12 Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123:185-9.
- 13 Paoletti P, Viegi G, Pistelli G, Di Pede F, Fazzi P, Polato R, et al. Reference equations for the single-breath diffusing capacity. A cross-sectional analysis and effect of body size and age. *Am Rev Respir Dis* 1985;132:806-13.
- 14 Knudson RJ, Kaltenborn WR, Knudson DE, Burrows B. The single-breath carbon monoxide diffusing capacity: reference equations derived from a healthy nonsmoking population and effects of hematocrit. *Am Rev Respir Dis* 1987;135:805-11.
- 15 Van Ganse WF, Ferris BG, Cotes JE. Cigarette smoking and pulmonary diffusing capacity (transfer factor). *Am Rev Respir Dis* 1972;105:30-41.
- 16 Krumholz RA, Chevalier RB, Ross JC. Changes in cardiopulmonary functions related to abstinence from smoking. Studies in young cigarette smokers at rest and exercise at 3 and 6 weeks of abstinence. *Ann Intern Med* 1965;62:197-207.
- 17 Tattersall SF, Benson MK, Hunter D, Mansell A, Pride NB, Fletcher CM, 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.
- 18 DuBois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH Jr. 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.
- 19 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.
- 20 Cotes JE. *Lung function: assessment and application in medicine*. 4th ed. Boston: Blackwell Scientific Publications, 1979: 239-43.
- 21 American Thoracic Society. Single breath carbon monoxide diffusing capacity (transfer factor): recommendations for a standard technique. *Am Rev Respir Dis* 1987;136:1299-307.
- 22 Jarvis MJ, Russell MAH, Saloojee Y. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *BMJ* 1980;281:484-5.
- 23 McDermott M, McDermott TJ, Collins MM. A portable bellows spirometer and timing unit for the measurement of respiratory function. *Med Biol Eng* 1968;6:291-3.
- 24 Quanjer PhH, ed. Standardized lung function testing. *Bull Eur Physiopathol Respir* 1983;19(suppl 5):39-44.
- 25 Gould GA, MacNee W, McLean A, Warren PM, Redpath A, Best JJK, et al. CT measurements of lung density in life can quantitate distal airspace enlargement—an essential defining feature of human emphysema. *Am Rev Respir Dis* 1988;137:380-92.
- 26 West WM, Nagel A, Hodgkin JE, Thurlbeck WM. The National Institutes of Health intermittent positive pressure breathing trial. Pathology studies III. The diagnosis of emphysema. *Am Rev Respir Dis* 1987;135:123-9.
- 27 Menkes HA, Permutt S, Cohen BH. Patterns of pulmonary function abnormalities in high risk groups. In: Macklem PT, Permutt S, eds. *The lungs in the transition between health and disease*. New York: Dekker, 1979: 301-12.
- 28 Teculescu DB, Stanescu DC. Lung diffusing capacity. Normal values in male smokers and nonsmokers using the breath-holding technique. *Scand J Respir* 1970;51:137-49.
- 29 Tockman M, Menkes H, Cohen B, Permutt S, Benjamin J, Ball WC. A comparison of pulmonary function in male smokers and nonsmokers. *Am Rev Respir Dis* 1976;114:711-22.
- 30 Fahey PJ, Utell MJ, Condemni JJ, Green R, Hyde RW. Raynaud's phenomenon of the lung. *Am J Med* 1984;76:263-9.
- 31 Knudson RJ, Kaltenborn WT, Burrows B. Single breath carbon monoxide transfer factor in different forms of chronic airflow obstruction in a general population sample. *Thorax* 1990;45:514-9.
- 32 Sansores RH, Paré P, Abboud RT. Effect of smoking cessation on pulmonary carbon monoxide diffusing capacity and capillary blood volume. *Am Rev Respir Dis* 1992;146:959-64.