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PREDICTION EQUATIONS FOR SINGLE BREATH DIFFUSING CAPACITY D_LCO (T_LCO) IN A MIDDLE AGED CAUCASIAN POPULATION

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Abstract

Rationale: There are many reference equations for the measurement of D_LCO. However the testing methodologies vary and there are no well-documented studies that develop reference equations for D_LCO and alveolar volume (V_A) in middle aged and older populations.
Objectives: 1. Develop reference equations for D_LCO in a middle aged population using the current ATS/ERS guidelines; 2. Compare the equations with those commonly used in laboratories around the world.
Methods: Healthy subjects (498 male and 474 female) aged 45 to 71 years were recruited as part of a larger epidemiological study. All participants completed a respiratory questionnaire and had spirometry and single breath D_LCO (corrected for haemoglobin) measurements following ATS/ERS guidelines.
Results: The mean age was 58 years for males and 57 years for females. For males, factors that predicted D_LCO were: Height, Age and Age * Height interaction and being an ex-smoker. For females, factors that predicted D_LCO were: Height, Age, Weight and an Age * Height interaction.
Conclusion: We have described new prediction equations for D_LCO in a middle-aged population that require validation in other populations.

Number of Words: 175

Key words: Diffusion capacity, Transfer factor, Carbon monoxide, Reference equations, Middle age, Epidemiology

INTRODUCTION

There are many studies describing prediction equations for the measurement of single breath carbon monoxide diffusing capacity of the lung (D_LCO) (1-6). These studies have demonstrated that the main predictors of D_LCO are height, gender and age. Significant limitations of the previous studies include small sample sizes (3, 7), non-standardised equipment (1, 3, 5), and different concentrations of inspired oxygen (1, 3-7). Importantly, previous prediction equations have been based on populations that included only relatively few subjects older than 55 years. However in clinical practice, D_LCO is most likely to be measured in this age group as many respiratory diseases such as chronic obstructive pulmonary disease (COPD) are predominantly confined to older patients.

Despite evidence of increasing morbidity in older people with respiratory disease, knowledge of normal respiratory function in older people is limited. Diffusing capacity along with spirometry is the cornerstone of the clinical guidelines for the diagnoses of COPD and other pulmonary conditions (8, 9). Current measurements are compared with "normal" values which have been calculated using algorithms derived from population studies of healthy volunteers. Only relatively recently have publications reported normal values for spirometry in those aged over 70 years in European (10) and American (11) populations, which show departures of 20% or more obtained in predictive values compared to those obtained from extrapolations of equations derived in younger people. Neither of these studies included D_LCO measurements.

The existing studies on D_LCO normative values have a number of methodological differences. All existing studies have used manual or semi-automated D_LCO measurement equipment (1-7). However currently used testing systems are fully computerised and depending on the manufacturer, differ in the methodology of the gas analysers, flow measuring devices, analogue to digital converters and sample rates. All these factors can affect the measured D_LCO (12, 13, 15).

Finally, the population sampled has a significant effect on the outcomes of the study. In a recent study (1), weight was shown to be a significant predictor of D_LCO and D_LCO/V_A (Kco) in the female population. However in this Spanish study, the distribution of weight was limited, again making the equations susceptible to extrapolation errors in broader clinical populations.

To address the above methodological issues, we set out to develop a set of prediction equations for D_LCO and alveolar volume (V_A) in a large "normal" middle aged and older population using modern computerised equipment, specifically following guidelines produced by the ERS/ATS (9).

METHODS

Subject selection

D_LCO and V_A were obtained in Caucasian subjects with no history of lung disease based on questionnaires, who either never smoked or were former smokers. Lung function was not used to define normality, as it can become a circular argument when creating new prediction equations for "normal" subjects. The subjects were recruited as part of another larger epidemiological study of COPD (16). All patients had D_LCO and spirometry measured, and were administered the European Community Respiratory Health Study (ECRHS) questionnaire (17 - 19) – see on line repository for further details. Smoking status was based

on standard Australian smoking questions (20). Anyone with serum cotinine > 100 μmol/L was reclassified as a current smoker and excluded from the analysis. We further excluded any subject who met Global Obstructive Lung Disease (GOLD) (21) criteria for COPD stage 2 or greater. The study was approved by the Ethics Committee at The Alfred, Melbourne. All participants gave written informed consent.

Measurement of D_LCO and Alveolar Volume

Single breath D_LCO was measured in duplicate on a fully computerised system (Medgraphics Profiler, Minnesota, USA, software version 4a) according to ATS/ERS guidelines (9). This testing system uses gas chromatography for the measurement of gas concentrations and a pitot tube for measurement of flow. The inspired gas mixture contained 0.3% carbon monoxide, 0.5% neon, 20.6% oxygen with the balance, nitrogen. Breath-hold time was calculated as described by Jones-Meade (22), washout and sample volumes were set to 0.9 L, and an interval between repeat tests was at least 4 minutes. At least two measurements were performed which had to agree to within 1 mmol/min/kPa or 10%, whichever was greater, otherwise further measurements were made until repeatable results were obtained. All D_LCO results were corrected to a standard haemoglobin concentration of 14.6 g/dL using the method described by Cotes (13). Standing height (metres) and body weight (kilograms) were measured without shoes.

Quality control of equipment

The quality control of the flow and volume signals was performed using a pulmonary waveform generator initially, an explosion decompression device monthly and biological control weekly. The flow sensor was also calibrated prior to each testing session using a 3 litre certified syringe. The accuracy of the D_LCO and V_A measurements was determined monthly using a custom built validator. The D_LCO and V_A validator consisted of a 3L certified syringe and two accurately known concentrations of inspired and expired CO and Ne to simulate typical inspired and expired gas concentrations. With the two gas mixtures it was possible to simulate a measured D_LCO and V_A value with known limits of agreement (7.20 – 7.43 mmol/min/kPa for D_LCO and 3.15 - 3.25 L for V_A). D_LCO measurements were taken at ATPS and subject dead space correction was not included (30). Further detail of the methods is supplied in the on-line repository including the results of the quality assurance program for the testing equipment.

Statistical analysis

All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) or SPSS version 15.0 (SPSS Inc, Chicago, IL 2006). Multivariate linear regression models were constructed using a stepwise selection technique and validated using a backwards elimination technique. Each model was then assessed for clinical and biological plausibility. A two-sided p-value of 0.05 was considered statistically significant.

RESULTS

We recruited 1201 subjects in to the study; 147 were excluded as current smokers, 41 had doctor diagnosed COPD, 1 was excluded for dwarfism. We then excluded a further 4 subjects with incomplete smoking data, and 36 with undiagnosed COPD (GOLD stage 2 or greater) leaving a total of 972 subjects (498 male and 474 female)

Table 1 shows the demographic details of the sample. All subjects were aged between 45 and 71 years with a relatively even distribution across the ages up to 70 years. Of the 498 males,

248(50%) were ex-smokers, and of the 491 females, 159 (34%) were ex-smokers. The mean pack year history of the ex-smokers was 13 and the range was 5 - 28.

	Males median (5-95%le)	Females median (5-95%le)
N	498	474
FEV_1 (L)	3.75 (2.57 – 4.84)	2.71 (1.96 – 3.61)
FVC (L)	4.92 (3.61 – 6.33)	3.48 (2.60 – 4.57)
FER (%)	77.0 (65 – 85)	78.0 (68 – 85.3)
Height (m)	1.75 (1.64 – 1.87)	1.62 (1.52 – 1.71)
Weight (kg)	83.0 (66 – 109)	69.0 (53.8 – 92.3)
BMI (kg/m^2)	27 (22.5 –34.6)	26 (20.9 – 36)
Age (yrs)	57.0 (47 – 70)	57.0 (47 -70)
Haemoglobin	15.2 (13.7 – 16.9)	13.7 (12.1 – 15.5)
D_LCO (mmol/min/KPa)	9.17 (6.80 - 12.0)	6.63 (4.97 – 8.61)
VA (L)	6.71 (5.06 – 8.29)	4.88 (3.82 – 6.09)

Table 1. Anthropometric and respiratory measurements of the study sample. Abbreviations: FEV_1 = Forced expired volume in one second (L), FVC = Forced vital capacity (L), FER = Forced expired ratio (%), BMI = Body Mass Index (Kg/m^2), D_LCO = Carbon monoxide transfer factor (mmol/min/kPa), VA = Alveolar volume (L).

Prediction equations for D_LCO and VA in males

Both linear and more complex higher order models and interactions between variables were explored. The model that gave the best fit was one in which the height was cubed, age squared and included an interaction between age and being an ex-smoker (Table 2). This model explained over a third of the variance in D_LCO. Predicted V_A was a simpler linear equation which included the terms height and weight which described nearly half of the variance in V_A.

Prediction equations for D_LCO and VA in females

The model that gave the best fit for D_LCO in the female population was one that included height, height cubed, age, weight and an age-height interaction (Table 2). Similar to the equations for males this model explained 36% of the variance. The equation for V_A was also similar to the male equation including height and weight, however it also included an age-height interaction term and explained a third of the variance.

Age-Height Interaction

In our sample, there was an interaction between age and height that was a significant predictor for all outcomes in females. The effect of an age height interaction was a greater rate of decline in age-related D_LCO with increasing height. That is, the taller the subject the more rapid the decline in D_LCO with age (see Figure 1 in on line repository). This interaction is a novel finding which significantly increases the total explanatory power of the model.

	Prediction equation	**R^2**	**SD**
Males			
D_LCO	$1.109*Ht^3 - 0.000402*A^2 - 0.035*A*ExSm + 1.805*ExSm +4.696$	36.0%	3.71
D_LCO^{95th}	$1.109*Ht^3 - 0.000402*A^2 - 0.035*A*ExSm + 1.805*ExSm +6.741$		
D_LCO^{5th}	$1.109*Ht^3 - 0.000402*A^2 - 0.035*A*ExSm + 1.805*ExSm +2.651$		
V_A	$10.155*Ht - 0.013*Wt - 0.0000943*A^2 - 9.628$	47.8%	0.69
V_A^{95th}	$10.155*Ht - 0.013*Wt - 0.0000943*A^2 – 8.501$		

V_A^{5th}	10.155*Ht - 0.013*Wt - 0.0000943*A^2 – 10.755		
Females			
D_LCO	51.900*Ht-3.901*Ht^3+0.375*Age+0.012*Wt - 0.273*A*Ht – 57.703	36.2%	2.73
D_LCO^{95th}	51.900*Ht-3.901*Ht^3+0.375*Age+0.012*Wt - 0.273*A*Ht – 56.200		
D_LCO^{5th}	51.900*Ht-3.901*Ht^3+0.375*Age+0.012*Wt - 0.273*A*Ht – 59.207		
V_A	7.206*Ht - 0.0041*Wt - 0.0073*Age*Ht - 5.77	35.6%	0.56
V_A^{95th}	7.206*Ht - 0.0041*Wt - 0.0073*Age*Ht – 4.856		
V_A^{5th}	7.206*Ht - 0.0041*Wt - 0.0073*Age*Ht – 6.684		

Table 2. Abbreviations: Ht = Height (metres), A = Age (years), ExSm = Ex Smoker. Ex-smoker is a binary term in which ex-smoker is one and never-smoker is zero, BMI = Body Mass Index (Kg/m^2).

Comparison with other equations

Table 3 gives the mean predicted D_LCO for other published prediction equations using our data set. In our sample, D_LCO expressed as a percent predicted was systematically lower using all the previous commonly used prediction equations. This is highly likely to reflect the older population included in our study. The previous prediction equations that best fitted our sample were those of Miller (5). Conversely, the equations of Knudson (7) substantially overestimated the observed mean D_LCO in both males and females.

DISCUSSION

We have developed a new set of prediction equations for the measurement of D_LCO and V_A for a middle aged and older population using current computerised equipment and methods. We have shown that there are major differences in our equations compared with previous studies that were mainly developed in younger populations (Table 3). The importance is that a significant proportion of patients seen in a clinical lung function laboratory are in this particular age group, making our new equations more clinically relevant.

	Mean D_LCO %predicted		**R^2**	
	Males	**Females**	**Males**	**Females**
Present Study	100	100	0.36	0.36
Roca et al (1)	90	85	0.44	0.37
Crapo and Morris (4)	82.5	80.3	0.6	0.6
Miller et al (5)	96.3	91.3	0.46	0.54
Paoletti et al (6)	79.4	74.8		
Knudson et al (7)	78.6	77.1		

Table 3. Comparison of mean percent predicted D_LCO in this sample using other published equations.

Many of the respiratory disorders that use D_LCO to help diagnosis, such as parenchymal and pulmonary vascular lung diseases, occur predominantly in an older population. Previous equations (1, 3, 4, 5, 7) have had relatively few subjects (eg, 8 males (3)) in older age groups (>60 years) compared with younger (<40 years) age groups. The inclusion of relatively few older subjects has led to the equations being susceptible to error in this group. Moreover extrapolating the equations to patients with an age greater than those included in a specific study can lead to considerable error, especially if the data are biased to a younger population.

Previous studies looking at spirometric prediction equations in an older population have shown differences of up to 20% when compared with extrapolating equations generated from a younger population (10, 11). The mean age of the subjects in our study was substantially older than other recent studies of normal D_LCO ranges, where the mean age has been as young as 35 years (1). Over half the subjects in our sample were more than 55 years of age.

Smoking status

A substantial minority of the subjects included in our study were classified as ex-smokers which improves the generalisability of our prediction equations. Although most of these subjects had only a limited smoking history, separate analyses to develop separate prediction equations for D_LCO based on the never smokers and ex-smokers were performed. Whilst the regression curves were slightly different (figure 2 on-line repository), especially in the older subjects, this was not statistically significant. Nonetheless, being an ex-smoker was a significant predictor of D_LCO in our male population. There may have been some under-reporting of previous smoking in this population, or there may have been some other confounding factor such as passive smoking/occupational exposures to explain the results. Furthermore, there was an interaction between age and being an ex-smoker. Ex-smoker status was only a significant predictor for D_LCO in the males and not the females, who may have smoked less.

Comparison with other equations

This is the first study to describe a set of prediction equations for the measurement of D_LCO and V_A in a middle aged and older population. Moreover we have shown a number of interactions between predictors that had significant effects on the outcome. Previous studies have mainly confined predictors to Height and Age (1, 3, 4, 5, 7). However some other authors have used terms including weight (1). Previous studies have also tested for non-linear effects and also performed various transformations, which have added little to the strength of the models (1, 5). We confirmed that the improvement in R^2 using complex higher order terms was small compared to the use of simple linear equations. However, we believe it makes little difference to the end user as most equations are now incorporated within the software of the measuring device.

The subjects studied were sampled randomly for another larger epidemiological study (17). There is much controversy in the literature regarding the inclusion of ex-smokers. Some studies have found statistically different measurements of D_LCO in smokers versus non-smokers, but we did not find this in our group. Ex-smokers would be expected to have a lower D_LCO than never smokers. As a high proportion of patients presenting to a pulmonary function laboratory are former smokers, the ability to adjust for this factor improves the likelihood of detecting pulmonary disease.

One methodological difference between various prediction equation studies is the FiO_2 of the inspired mixture. It is well known that higher the FiO_2 the lower the measured D_LCO (29). The various published studies have used a FiO_2 ranging from 18% (1) to 25% (4). For the study that used 25% the reason for the higher FiO_2 was to counteract the effect of that study being performed at an altitude of 1520m. However the majority of the studies have used a FiO_2 of approximately 21%. Nevertheless, there are still large differences in measured D_LCO across the various equations that use the same FiO_2 (figures 1a and b). One exception is the equations published by Roca (1), if these were corrected to an FiO_2 of 21% this would reduce the overall D_LCO, leading to similar results obtained in the current study and the equations published by Miller (5).

An important consideration when using prediction equations is the cross over age from one set of equations to another. Although rarely a problem in an adult population, this issue is highlighted when changing from equations based on children to equations from an adult population as an individual patient reaches adulthood. From Figures 1a and b the issue is highlighted at an age of 45years where the equations for the current study start. The equations that minimise the difference in D_LCO at an age of 45years are those published by Miller (5), Quanjer (31), Crapo (4) and Roca(1).

Weight term

Weight was first demonstrated by Roca et al (1) to be a significant predictor of D_LCO in females. However the weight term may falsely elevate the predicted D_LCO especially in overweight and obese subjects. Part of this is likely due to the narrow weight range that was included in the population studied (60 – 75Kg (1)). Therefore previously published equations need to be extrapolated on a relatively frequent basis making the predicted value unreliable. This is especially the case with the documented increase in obesity in the population (32) . Not including the weight term would lead to increase numbers of people with reduced D_LCO relative to their predicted values solely based on their weight.

Further analysis of BMI demonstrated that 1.9% of the subjects were classified as underweight (BMI < 20kg/m^2), 29.2% were of ideal weight (BMI 20 – 25), 47.3 % were classified as overweight (BMI 26 – 30) and 21.6 % subjects were classified as obese (BMI>30). There was a positive relationship between weight and D_LCO. However the maximum difference in mean D_LCO between the groups was only 0.60 mmol/min/KPa. Furthermore it was the overweight not the obese group that lead to the significant weight term in the equation. The mean D_LCO for the overweight group was 0.60 mmol/min/KPa higher than the ideal weight ($p<0.001$) whereas in the obese subjects the D_LCO was only 0.35 higher than the ideal weight group.

Effect of equipment and testing methodology on the measurement.

There are relatively few studies that have entirely complied with the ATS/ERS criteria (9) for the measurement of D_LCO. Importantly, existing studies have significant methodological differences in the measurement of D_LCO relating to the calculation of breath-hold time, FiO_2 and dead space correction. Moreover there have not been any published prediction equations using fully computerised equipment. The type of analyser used for the CO analysis, the type of insoluble inert marker gas used for the calculation of V_A and estimating the initial alveolar CO concentration may all play a part in contributing to the variability of the measurement of D_LCO. Our study is up to date, using modern equipment and methods.

Calculation of breath hold time has also shown to be important leading to differences of up 6.8% in measured D_LCO (23) between the method described by the Epidemiology Standardisation Project (24) and Ogilvie et al (25). Using the breath-hold time calculation as described by Jones and Meade (22) gives a similar measured D_LCO to that of Ogilvie et al (25). The ATS criteria stipulate the Jones-Meade calculation, which is what was used in the current study.

The Medgraphics system uses gas chromatography for the analysis of tracer gases. Also peculiar to this system is the use of Neon as the insoluble inert tracer gas. Neon has a relatively low diffusivity and therefore likely to distribute further throughout the lung leading a higher measured alveolar volume than Helium (26). Even though the latest ATS/ERS (9)

document states that the tracer should have a diffusivity closer to that of Helium, there are now large numbers of computerised devices that use different gases such Methane and Helium.

Conclusion

We have developed a set of prediction equations for an older population using modern computerised equipment. The equations generated gave a significantly higher predicted D_LCO than most of those previously published (1, 3, 6, 7). Most of the differences are likely to be explained by the older population, but methodological differences cannot be excluded. The latest ATS/ ERS guidelines for the performance of D_LCO state that prediction equations need to be selected carefully taking into account important methodological differences. This is one of the few studies using fully computerised equipment, gas chromatography for the gas analysis and Neon as the tracer gas. Furthermore we have developed a set of predictions equations more specific to an older population which are therefore, likely to be the most clinically relevant available.

Acknowledgments

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Legends

Figure 1a and b.
D_LCO vs Age for males (a) and females. Height for the males was assumed to be the mean height in our sample (1.75meters for the males and 1.62meters for the females). The weight in the females was assumed to be the mean measured weight of the sample 70.4Kgs. The Miller equations were those of the non-smoking group.

Figure 1a

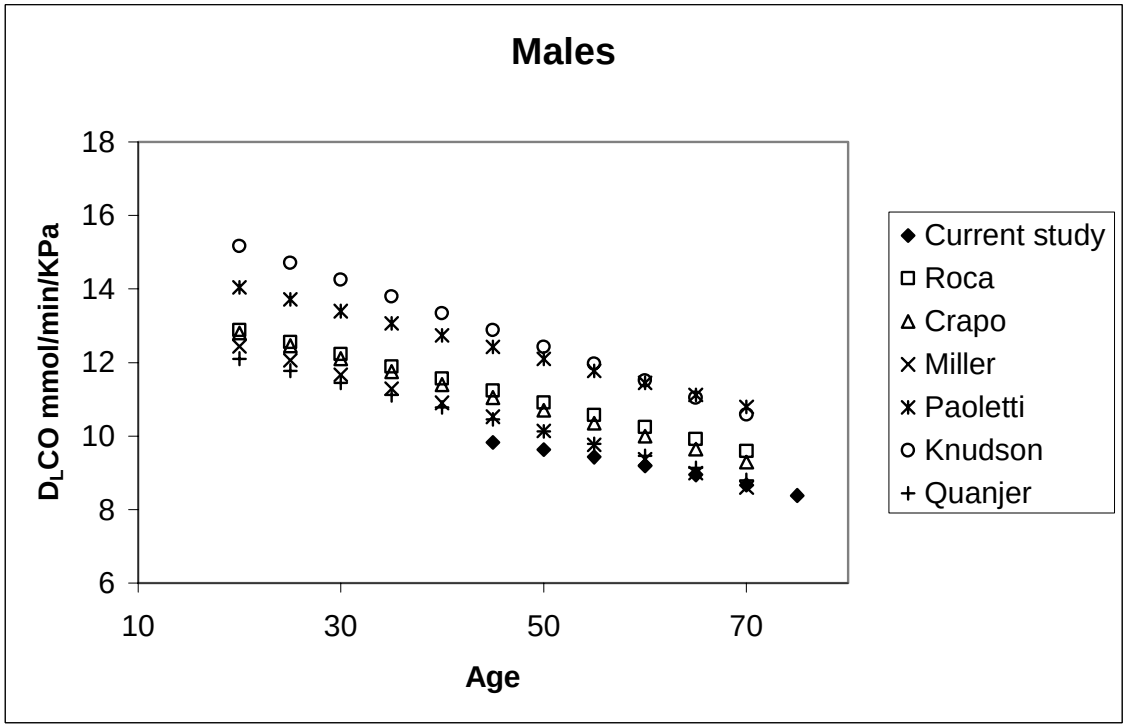
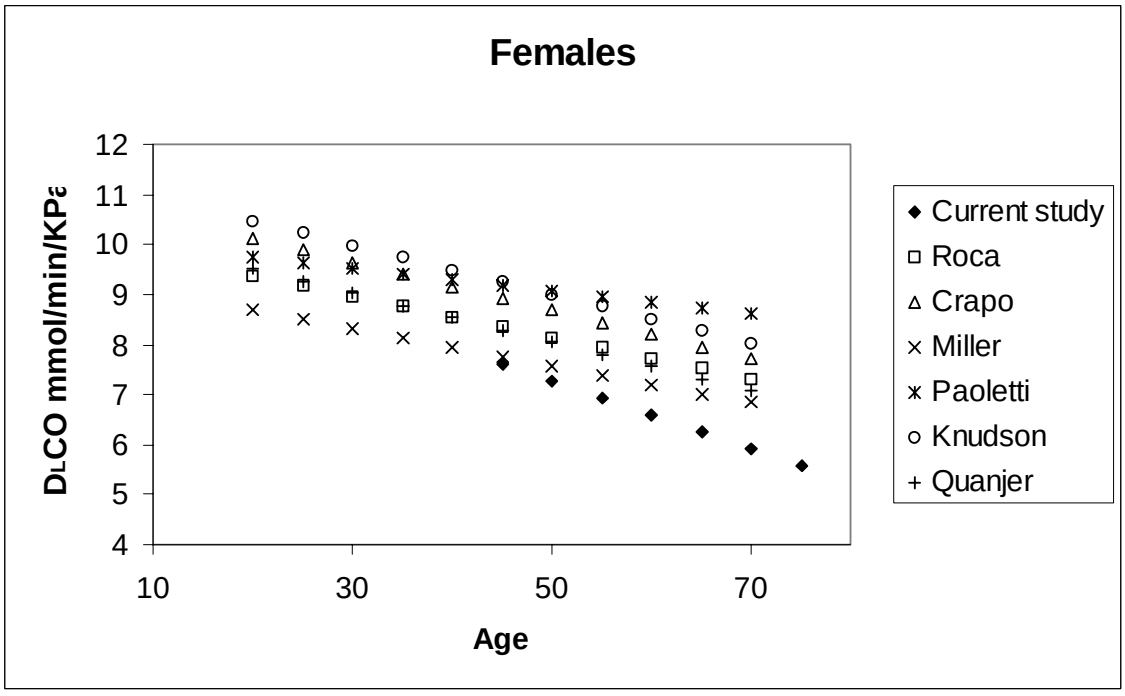


Figure 1b



ON-LINE DATA REPOSITORY

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METHODS

Subject selection

D_LCO and V_A were obtained in Caucasian subjects with no history of lung disease who either never smoked or were minimal ex-smokers. The subjects were recruited as part of another larger epidemiological study of COPD (1). All patients had D_LCO and spirometry measured, and were administered a respiratory health questionnaire (2). The interviewer-administered questionnaire comprised validated items on bronchial symptoms from the IUATLD questionnaire (3), British Medical Research Council items on cough, sputum and shortness of breath (4), demographics, past and family history and environmental risk factors from the main ECRHS questionnaire. Smoking status was based on standard Australian smoking questions (5). Only subjects in two categories were included: Firstly ex-smokers who did not smoke at all now, but have smoked at least 100 cigarettes or a similar amount of other tobacco products in their lifetimes. Secondly never smokers were defined as people who did not smoke now and have smoked fewer than 100 cigarettes or similar amount of other tobacco products in their lifetimes. Subject with a serum cotinine > 100 μmol/L were reclassified as current smokers and excluded from the analysis. To avoid including any subjects with undiagnosed COPD based on their lung function tests, we further excluded any subject who met Global Obstructive Lung Disease (GOLD) (6) criteria for stage 2 or greater. The study was approved by the Ethics Committee at The Alfred, Melbourne. All participants gave written informed consent.

Measurement of D_LCO and Alveolar Volume

Single breath D_LCO was measured in duplicate on a fully computerised system (Medgraphics Profiler, Minnesota, U.S.A) according to ATS/ERS guidelines (7). This testing system uses gas chromatography for the measurement of gas concentrations and a pitot tube for measurement of flow. The inspired gas mixture contained 0.3% carbon monoxide, 0.5% neon, 20.6% oxygen with the balance, nitrogen. Breath-hold time was calculated as described by Jones-Meade (8), washout and sample volumes were set to 0.9 L, and an interval between repeat tests was at least 4 minutes. At least two measurements were performed which had to agree to within 1 mmol/min/kPa or 10%, whichever was greater, otherwise a further measurement was made until repeatable results were obtained. All D_LCO results were corrected to a standard haemoglobin concentration of 14.6 g/dl using the method described by Cotes (9). Standing height (meters) and body weight (kilograms) were measured without shoes.

Quality control of equipment

The quality control of the flow and volume signals was performed using a pulmonary waveform generator initially, an explosion decompression device monthly and biological control performed weekly. The flow sensor was also calibrated prior to each testing session using a 3 litre certified syringe. The accuracy of the D_LCO and V_A measurements was determined monthly using a custom built validator. The D_LCO and V_A validator consisted of a 3L certified syringe and two accurately known concentrations of inspired and expired CO and Ne to simulate typical inspired and expired gas concentrations. With the two gas mixtures it was possible to simulate a measured D_LCO and V_A value with known limits of agreement (7.20 – 7.43 mmol/min/kPa for D_LCO and 3.15 - 3.25 L for V_A). All measurements were reported at ATPS and subject dead space correction was not included.

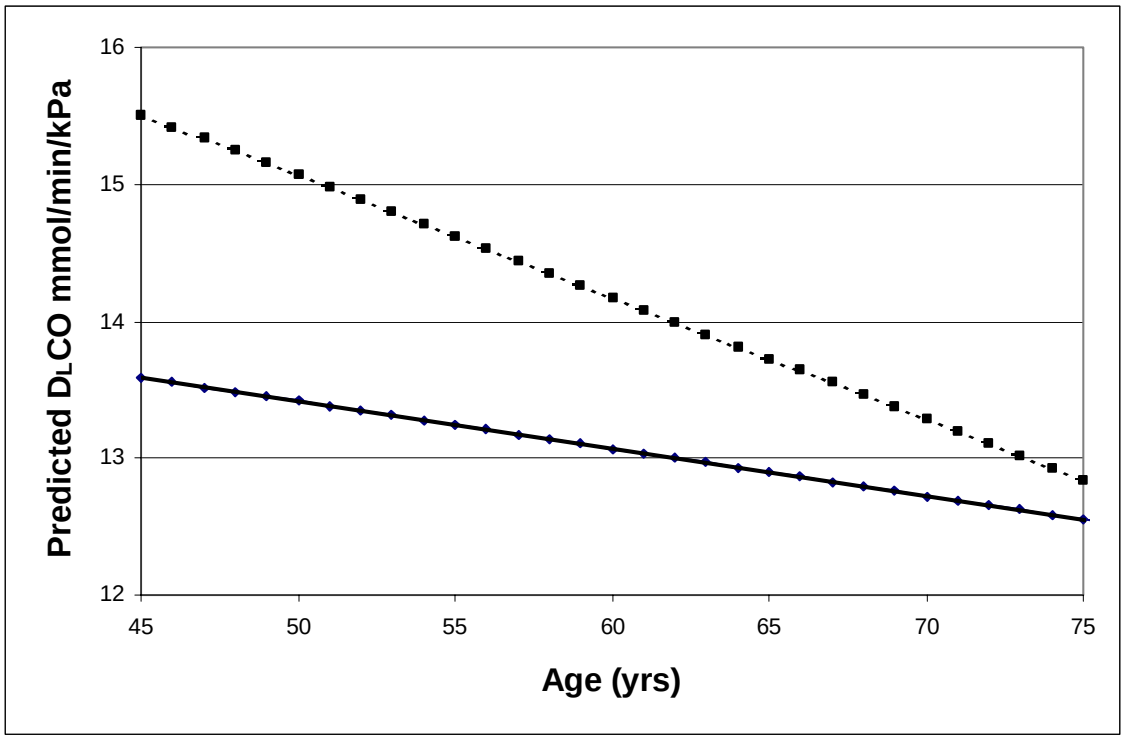
Results of the quality assurance program

The equipment remained within specification throughout the study and at no stage were any faults identified. There was no evidence of drift during the study. Based on the custom built validator, the inspiratory vital capacity, D_LCO and V_A were all within specification. The coefficient of variation for D_LCO and V_A from the custom built validator was 3.08% and 2.13% respectively. The coefficient of variation for D_LCO and V_A for the biological controls was 3.81% and 1.14% respectively.

Statistical analysis

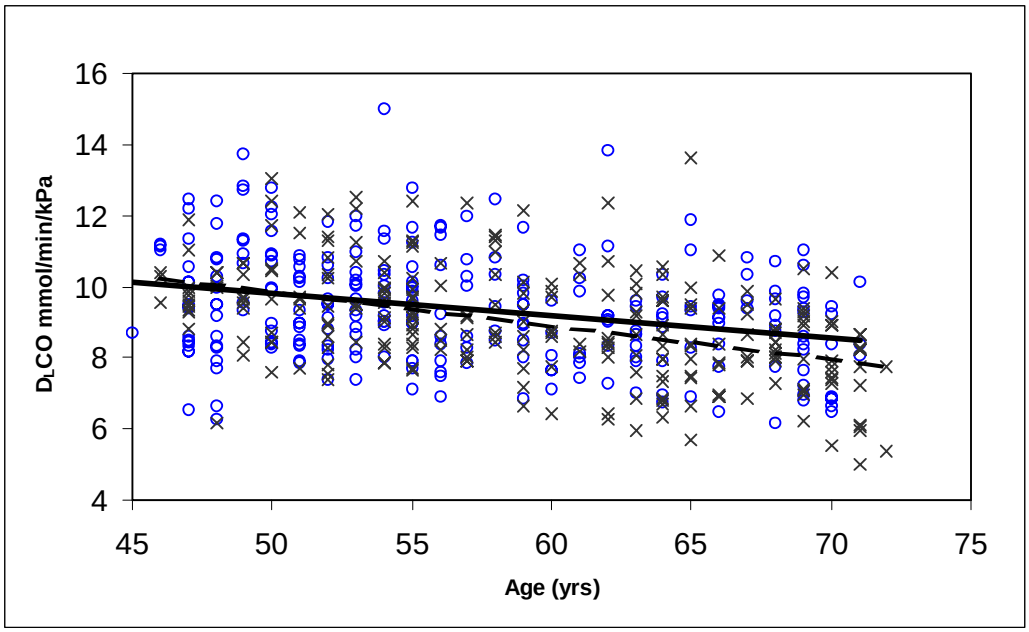
All analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) or SPSS version 15.0 (SPSS Inc, Chicago, IL 2006). Multivariate linear regression models were constructed using a stepwise selection technique and validated using a backwards elimination technique. Each model was then assessed for clinical and biological plausibility. A two-sided p-value of 0.05 was considered statistically significant.

Figure 1



Predicted D_LCO vs Age for 2 fixed heights within the female sample. Solid line is for a subject whose height is 1.5 meters, and the dotted line is for a subject whose height is 1.7 meters.

Figure 2



Measured D_LCO vs Age for men. Subjects who never smoked are represented by dots (….) and subjects classified as ex-smokers are represented by xxx. The regression curve for the never smokers is represented by the dashed line and the regression curve for the ex-smokers is represented by the solid line.

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