Original Article

Prediction equations for diffusing capacity (transfer factor) of lung for North Indians

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ABSTRACT

Background: Prediction equations for diffusing capacity of lung for carbon monoxide (DLCO), alveolar volume (VA), and DLCO/VA using the current standardization guidelines are not available for Indian population. The present study was carried out to develop equations for these parameters for North Indian adults and examine the ethnic diversity in predictions. **Materials and Methods:** DLCO was measured by single-breath technique and VA by single-breath helium dilution using standardized methodology in 357 (258 males, 99 females) normal nonsmoker adult North Indians and DLCO/VA was computed. The subjects were randomized into training and test datasets for development of prediction equations by multiple linear regressions and for validation, respectively. **Results:** For males, the following equations were developed: DLCO, $-7.813 + 0.318 \times ht - 0.624 \times age + 0.00552 \times age^2$; VA, $-8.152 + 0.087 \times ht - 0.019 \times wt$; DLCO/VA, $7.315 - 0.037 \times age$. For females, the equations were: DLCO, $-44.15 + 0.449 \times ht - 0.099 \times age$; VA, $-6.893 + 0.068 \times ht$. A statistically acceptable prediction equation was not obtained for DLCO/VA in females. It was therefore computed from predicted DLCO and predicted VA. All equations were internally valid. Predictions of DLCO by Indian equations were lower than most Caucasian predictions in both males and females and greater than the Chinese predictions for males. **Conclusion:** This study has developed validated prediction equations for DLCO, VA, and DLCO/VA in North Indians. Substantial ethnic diversity exists in predictions for DLCO and VA with Caucasian equations generally yielding higher values than the Indian or Chinese equations. However, DLCO/VA predicted by the Indian equations is slightly higher than that by other equations.

KEY WORDS: Diffusing capacity, lung function tests, prediction equations, transfer factor

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INTRODUCTION

The diffusing capacity of lung for carbon monoxide (DLCO) or transfer factor of lung measures the integrity of the alveolocapillary structure and is most commonly measured by the single breath technique at total lung capacity using a gas mixture containing carbon monoxide. It is a product of the rate constant of CO uptake, i.e., fall in concentration of alveolar CO per unit time per unit driving pressure (also called the Krogh's constant [KCO]) and the alveolar volume (VA) at full lung inflation.[1] Normally, DLCO and VA are measured and KCO is calculated as DLCO/VA. DLCO and DLCO/VA are considered together for interpretation of the measurements. The measurement of DLCO is technically complex with wide variability between laboratories.[1] The methodology has been standardized in an attempt to ensure quality control and reduce between laboratory variability.[2,3] It was revised recently by a joint task force of the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[4]

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Substantial variations, ascribed to differences in methodology, exist in prediction equations for DLCO even among similar populations such as Caucasians.[3,5-13] Therefore, use of standardized methodology is strongly recommended and equations developed in local populations should be used to interpret data.[4] Lack of prediction equations for DLCO using current standardized methodology for Indian population is a major limitation in clinical practice and research. Application of Caucasian equations as is necessitated currently for Indians in lung function laboratories may result in errors in interpretation. Little is known about ethnic differences in DLCO due to a paucity of equations for nonwhite populations.[14,15] The only available Indian equations for DLCO were developed three decades ago and that too only in a restricted age group limiting their wider application.[16] The present study was carried out to develop prediction equations for DLCO, VA, and DLCO/VA for Indians and examine the ethnic diversity in these parameters.

MATERIALS AND METHODS

Study design and subjects

The study was approved by the Institutional Ethics Committee (vide letter date November 29, 2004). The details of the sampling methodology were published recently in the report on prediction equations for spirometry parameters in the same population.[17] Subjects aged 18 years and above with parentage of Northern Indian plains around Delhi were drawn from a wide social and economic background from healthy and willing attendants of patients, volunteers from employees from institutions, general public, private, and public sector offices. As is common with studies of this nature, a convenient sample was taken after rigorous screening for inclusion and exclusion criteria described below. A written informed consent was taken. These regions are ethnically homogenous with a near sea-level altitude and a tropical climate.

For multiple linear regression, the recommended minimum sample size is [50 + (8xm)] where m = number of independent variables.[18] Based on previous studies[3,5-14] we identified age, height, and weight as possible predictors of DLCO giving a sample size of 74. We targeted an age distribution matching the adult population of India.[19]

"Normal" health was defined using the criteria proposed by the ATS[20] and employed by Hankinson *et al.*[21] A standardized respiratory symptoms questionnaire[22] was administered besides a complete historical review and examination by one of the coauthors (UAG) to confirm normal health. Those with any acute or chronic chest or other systemic disease, thoracic cage abnormality, pregnancy, body mass index <18.5 or >30, and smokers, except occasional ones, were excluded. Age in completed years, height to the nearest centimeter, and weight to the nearest kilogram were recorded.

Measurements

Spirometry was carried out[23] using a nonheated Fleisch pneumotach spirometer (KOKO, nSpire, UK). DLCO was measured by single-breath technique using standardized methodology[4] on benchmark lung function equipment (PK Morgan, Kent, United Kingdom). It has an automated valve box with inspiratory and expiratory bags and measures Helium by thermal conductivity and CO by infrared absorption. Gas analyzer calibration was performed weekly, volume calibration was performed daily, and moisture and carbon dioxide absorbers were replaced regularly. All measurements were made by the same technician.

A light meal was allowed but exercise and caffeinated drinks were not permitted in the morning. The subject rested for 2 h before the test. After exhaling to the residual volume, the subject inhaled maximally a gas mixture containing 0.3% CO, 12–14% helium, and 18% oxygen from the inspiratory bag of the diffusion apparatus, followed by breath-holding at full lung inflation and then performed a rapid exhalation, washing out dead space air followed by collection of the alveolar sample in the expiratory bag. The concentrations of CO and helium in the inspired and expired gas were analyzed. Inspired volume was required to be more than 85–90% of the previously measured vital capacity and inspiration was completed within 2–3 s. Breath holding time was set at 9 s and the subject was instructed to voluntarily maintain full inspiration using only the minimal effort necessary to avoid Valsalva or Müller maneuvers. Effective breath-holding time was calculated by the method of Jones and Mead[24] and kept between 10 ± 1 s. Expiratory maneuver was smooth, unforced, and without hesitation or interruption. The total exhalation time was <4 s with a sample collection time of <3 s. The washout and alveolar sample volume were set at 900 ml if forced vital capacity exceeded 2 l and 600–800 ml for smaller lungs. The DLCO was calculated as described below:[2]

$$DLCO = VA\ (STPD) \times (1/t) \times (1/[PB - 47]) \times Ln\ (F_ACO_O/F_ACO_t) \times 60{,}000$$

$$F_ACO_O = F_ICO \times (F_AHe/F_IHe)$$

$$VA = (V_I - V_D) \times (F_IHe/F_AHe)$$

Volumes are in liters. PB is the barometric pressure in mmHg, 47 mmHg is the water vapor pressure at 37°C, t is the effective breath-holding time and, F_ACO_t and F_ACO_O are the fraction of CO in the alveolar gas at the end and beginning of the breath-hold, respectively. F_ICO is the fraction of CO in the inspired gas, and F_AHe and F_IHe the fractions of the tracer gas (helium) in the alveolar and inspired gas samples, respectively. VA is alveolar volume, V_I is inspired volume, and V_D is dead-space volume (anatomic and instrument). The factor 60,000 converts l/s to ml/min.

DLCO was expressed in milliliters CO/min mm/Hg at standard temperature and pressure dry (STPD). It was corrected for dead space (both instrumental and anatomic) and for hemoglobin, 14.6 g/dL for males and 13.4 g/dL for females, according to Cotes.[25] No correction was required for carboxyhemoglobin, assuming it to be negligible as the subjects were nonsmokers. Correction for altitude was not required as Delhi is almost at sea level. VA was expressed in liters at body temperature 37°C atmospheric pressure fully saturated conditions.

Statistical analysis

Statistical analysis was carried out using SPSS 20.0 (IBM Corporation, New York, USA) and GraphPad Prism 6.05 (GraphPad, Inc., California, USA) software. Data are presented as mean ± standard deviation with 95% confidence intervals (CI). The sample was randomized into a training dataset (70% of sample) with 182 males and 70 females for development of prediction equations and a test dataset (30% of sample) for validation, with 76 males and 29 females. Anthropometric characteristics and lung function data of the training and test datasets were compared using unpaired *t*-test. Pearson's correlation analysis and univariate regression were carried out to identify significant predictor variables for DLCO, DLCO/VA, and VA. Multiple linear and nonlinear regression models with different transformations of the dependent and/or independent variables were examined. Complex transformations offered no advantage over linear equations for most of the final models. Analysis of variance (ANOVA) was carried out to evaluate the significance of the equations. Final models were selected considering simplicity, highest predictive capability (by coefficient of determination, R^2), and compliance with the assumptions of regression analysis, i.e., independence, homoscedasticity, and normal distribution of residuals.

The equations were validated on the test dataset by comparing observed and predicted values using the paired *t*-test. Comparisons of predictions of DLCO, VA, and DLCO/VA by current equations with predictions by Caucasians[2,5-11] and Chinese[14] equations were carried in the test dataset with repeated measures ANOVA (RM-ANOVA) with *post hoc* Dunnet *t*-test to evaluate the significance of differences between the current and other equations. Age- and height-related changes in DLCO values in subjects of constant height and age were represented graphically.

RESULTS

In all 357 subjects, 258 males and 99 females, provided acceptable test maneuvers. The anthropometric characteristics and spirometry data of these subjects are shown in Table 1. Nearly three-fourths of the subjects were aged 40 years or less while about 5% were aged above 50 years, the oldest being 71 years in males and 65 years in females. This age distribution is consistent with the Indian national demographic profile.[18] The anthropometric characteristics and lung function data of the training and test datasets were matched and are presented in Table 2. As these characteristics of the training and test datasets were matched, validation of the equations developed in the former could be done on the latter.

Univariate analysis showed that DLCO was negatively correlated with age ($r = -0.38$, $P < 0.0001$ in males and $r = -0.29$, $P = 0.014$ in females) and positively with height ($r = 0.38$, $P < 0.0001$ in males and $r = 0.63$, $P < 0.0001$ in females). Correlation with weight was not significant. The developed prediction equations are presented in Table 3.

In the test dataset in males, the observed and predicted DLCO were 32.13 ± 7.21 and 32.85 ± 3.48, respectively; the difference of −0.71 (95% CI: −1.95, 0.51) was not significant ($P = 0.249$). For VA, the observed and predicted values were, respectively, 5.21 ± 0.89 and 5.24 ± 0.53; the difference −0.03 (95% CI: −0.20, 0.13) was not significant ($P = 0.71$). In females, the observed and predicted DLCO were 23.82 ± 4.50 and 22.38 ± 2.92, respectively; the difference of 1.45 (95% CI: 0.01, 2.88) though small was statistically significant ($P = 0.048$). However, all the observed values were within ± 1.645 × standard error of estimate (SEE) of the predicted and thus were interpreted as normal. For VA, the measured and predicted values were, respectively, 3.75 ± 0.62 and 3.68 ± 0.40; the difference 0.08 (95% CI: −0.09, 0.24) was not significant ($P = 0.344$).

Differences in predictions of DLCO by current and other equations were significant in both males and females (RM-ANOVA, $P < 0.0001$). In males, the Indian equations predicted significantly lower DLCO than most Caucasian equations [Table 4] but higher values compared

Table 1: Anthropometric characteristics and spirometry data

	Males (*n*=258)		Females (*n*=99)	
	Range	Mean±SD (95% CI)	Range	Mean±SD (95% CI)
Age (years)	18-71	31.9±10.3^{NS} (30.60-33.11)	18-65	33.8±10.3 (31.72-35.81)
Height (cm)	153-193	169.2±7.1*** (168.3-170.0)	141-170	155.6±6.2 (154.4-156.8)
Weight (kg)	40-94	69.4±10.0*** (68.12-70.58)	37-76	57.2±9.1 (55.39-59.03)
FVC (L)	2.20-5.77	4.11±0.63*** (4.03-4.19)	1.81-3.98	2.78±0.44 (2.69-2.86)
FEV_1 (L)	1.83-4.76	3.30±0.58*** (3.23-3.37)	1.28-3.54	2.29±0.42 (2.20-2.37)
FEV_1/FVC	63.2-97.3	80.3±6.3** (79.55-81.09)	63.1-99.0	82.4±7.2 (80.94-83.79)

Unpaired *t*-test $^{**}P<0.01$, $^{***}P<0.001$, ^{NS}Not significant $P>0.05$. SD: Standard deviation, CI: Confidence interval in parenthesis, FVC: Forced vital capacity, FEV_1: Forced expiratory volume in the 1 s

Table 2: Anthropometric characteristics and lung function of the training and test datasets

	Training set		Test set	
	Males (*n*=182)	Females (*n*=70)	Males (*n*=76)	Females (*n*=29)
Age (years)	32.9±10.6* (31.38-34.48)	34.1±10.3NS (31.64-36.54)	29.4±8.9 (27.47-31.57)	33.0±10.4 (29.06-36.94)
Height (cm)	169.2±7.1NS (168.02-170.12)	155.7±6.3NS (154.15-157.17)	169.2±6.9 (167.58-170.81)	155.4±5.9 (153.18-157.70)
Weight (kg)	69.3±9.8NS (67.76-70.67)	57.4±9.1NS (55.26-59.59)	69.5±10.6 (67.34-72.15)	56.7±9.4 (53.12-60.25)
FVC (L)	4.11±0.65NS (4.02-4.21)	2.78±0.44NS (2.67-2.89)	4.10±0.60 (3.97-4.24)	2.77±0.44 (2.60-2.93)
FEV_1 (L)	3.31±0.59NS (3.22-3.39)	2.27±0.45NS (2.17-2.38)	3.29±0.56 (3.16-3.42)	2.33±0.36 (2.19-2.46)
FEV_1/FVC	80.4±6.5NS (79.44-81.35)	81.5±7.1NS (79.83-83.20)	80.2±5.9 (78.76-81.46)	84.4±7.0 (81.73-87.08)
DLCO	32.00±6.44NS (31.01-32.90)	22.44±4.91NS (21.27-23.61)	32.13±7.21 (30.42-33.75)	23.82±4.51 (22.11-25.54)
VA	5.27±0.83NS (5.15-5.39)	3.67±0.62NS (3.52-3.81)	5.21±0.89 (5.02-5.43)	3.75±0.62 (3.52-3.99)
DLCO/VA	6.11±1.12NS (5.93-6.27)	6.17±1.01NS (5.90-6.39)	6.13±0.82 (5.92-6.34)	6.36±0.71 (6.09-6.63)

Comparison of training and test datasets in respective genders by unpaired *t*-test: *$P<0.05$, NSNot significant, $P>0.05$. Data presented as mean±SD, 95% CI: Confidence interval in parenthesis; FVC: Forced vital capacity, FEV_1: Forced expiratory volume in the 1 s, DLCO: Diffusing capacity of lung for carbon monoxide, VA: Alveolar volume, SD: Standard deviation

Table 3: Regression equations developed in the training dataset

Parameter	Equation	Adjusted R^2	SEE
Males			
DLCO	−7.813+0.318 × ht −0.624 × age +0.00552 × age²	0.28	5.37
VA	−8.152+0.087 × ht −0.019 × wt	0.45	0.59
DLCO/VA	7.315−0.037 × age	0.13	0.99
Females			
DLCO	−44.15+0.449 × ht −0.099 × age	0.41	3.81
VA	−6.893+0.068 × ht	0.48	0.44
DLCO/VA†	No significant predictor found	-	5th percentile: 5.38
	Mean±SD: 6.04±0.31		95th percentile: 6.47
	95% CI of mean: 5.97-6.12		

†No acceptable model was developed for DLCO/VA in females. Mean predicted and upper and lower limits of normal (5th and 95th percentile values) for DLCO/VA in females are derived from descriptive statistics of predicted DLCO/predicted VA. DLCO: Diffusing capacity of lung for carbon monoxide, VA: Alveolar volume, Adjusted R^2: Coefficient of determination in multiple linear regression, SEE: Standard error of estimate, Age in years, Height in cm, Weight in kg, SD: Standard deviation, CI: Confidence interval

to Chinese equations. For females, all Caucasian equations predicted higher DLCO than the Indian equations but the Chinese predictions were not significantly different. Comparison of Indian equation with Caucasian and Chinese equations in subjects with a constant age, height, and weight confirmed these differences [Figures 1-4].

Tables 5 and 6 show the predicted values of VA and DLCO/VA by the current Indian and other equations. The Indian equations predicted a lower VA than all the Caucasian equations and the Chinese equations, though the difference with the latter was much smaller. The DLCO/VA predicted by Indian equations was significantly greater than the predictions by all Caucasian and Chinese equations in both males and females, except the Knudson *et al.*[8]

DISCUSSION

We have presented internally validated prediction equations for DLCO, VA, and DLCO/VA for adult North Indians, measured using the recent standardized methodology.[4] Age had a negative and height had a positive association with DLCO, in both males and females. Height was a significant positive predictor for VA in both genders with weight also included with a negative coefficient in the equation for males. DLCO/VA was predicted negatively by age in males but no statistically valid prediction model was developed in females. Therefore, it was computed by dividing the predicted DLCO by predicted VA as recommended by the ERS- European Community for Steel and Coal (ECSC) standardization guidelines.[3] The upper and lower limits of normal (ULN and LLN) range for these parameters can be calculated by the formula: Predicted ± 1.645 × SEE. For DLCO/VA in females, the 5th and 95th percentile values obtained from descriptive statistics of the predicted DLCO/VA computed as above represent the LLN and the ULN, respectively.

Predictions of DLCO in males by Indian equations were lower than most Caucasian predictions by 3.4 to 19.2% but greater than the predictions for Caucasians by Roberts *et al.*[10] and the ECSC equations[4] by 1.6–2.6%, and also greater than the Chinese predictions by 8%. In females, all Caucasian equations predicted higher DLCO than the Indian equations ranging from 3.4% to 20.6%, whereas the latter and the Chinese predictions were not different. The VA predicted by Indian equations was significantly lower than the Caucasian equations by 10.2–24.3% in males and 11.5–42.2% in females, and also slightly lower than the Chinese predictions by 2.4–3.4% in males and females, respectively. On the other, the Indian equations predicted a higher DLCO/VA than all the Caucasian equations in females by 1–21.6%, and also all Caucasian equations in males by 4.5–15.8%, except the Knudson *et al.*[8] equations that predicted slightly higher values by 2.8%. Indian predictions for DLCO/VA were also higher than the Chinese predictions by 7.4% in males and 9.9% in females.

It is well established that Caucasians have higher lung volumes per unit height compared to Asians, including Indians and the Chinese.[26] In contrast, information on ethnic differences in DLCO, VA and DLCO/VA is limited because of lack of sufficient studies in nonwhite

Table 4: Comparison of predicted diffusing capacity of lung for carbon monoxide by current and other equations in the test dataset

Authors and population	Males				Females			
	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)
ECSC, Caucasians[3]	32.34±3.12	0.51****	0.30-0.73	1.6	24.97±2.17	−2.59****	−3.25-−1.93	−10.4
Crapo and Morris, Caucasians[5]	37.60±3.74	−4.75****	−4.99-−4.50	−12.6	27.76±2.41	−5.39****	−5.97-−4.87	−19.4
Miller *et al.*, Caucasians[6]	34.02±2.49	−1.17****	−1.58-−0.76	−3.4	23.47±1.54	−1.10*	−1.98-−0.21	−4.7
Paoletti *et al.*, Caucasians[7]	37.55±3.76	−4.7****	−5.02-−4.38	−12.5	27.23±1.20	−4.85****	−5.81-−3.90	−17.8
Knudson *et al.*, Caucasians[8]	40.66±3.74	−7.82****	−8.00-−7.63	−19.2	28.16±1.94	−5.79****	−6.64-−4.93	−20.6
Roca *et al.*, Caucasians[9]	34.49±3.32	−1.64****	−1.87-−1.42	−4.8	24.30±1.50	−1.92****	−2.88-−0.96	−7.9
Roberts *et al.*, Caucasians[10]	32.00±3.77	0.85****	0.59-1.10	2.6	23.15±1.80	−0.78*	−1.48-−0.08	−3.4
Neder *et al.*, Caucasians[11]	37.24±2.67	−4.39****	−4.76-−4.03	−11.8	25.70±1.36	−3.33****	−4.17-−2.48	−12.9
Yang *et al.*, Chinese[14]	30.39±3.65	2.46****	2.06-2.86	8	21.41±1.85	0.96NS	0.03-1.95	4.5

†Comparisons with predictions by Indian equations (males: 32.85±3.48; females: 22.42±2.86) using repeated measures analysis of variance and *post hoc* Dunnet *t*-test, $*P<0.05$, $****P<0.0001$; NSNot significant: $P>0.05$. SD: Standard deviation, CI: Confidence interval, ECSC: European Community for Steel and Coal

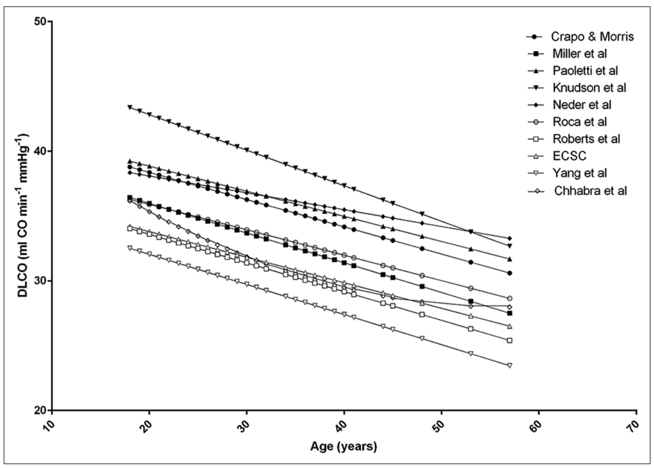

Figure 1: Comparison of the current prediction equation for diffusing capacity of lung for carbon monoxide with those of other investigators for males with a constant height (168 cm) and weight (68 kg); equations: Crapo and Morris,[5] Miller *et al.*,[6] Paoletti *et al.*,[7] Knudson *et al.*,[8] Roca *et al.*,[9] Roberts *et al.*,[10] Neder *et al.*,[11] Yang *et al.*,[14] Chhabra *et al.* (present study)

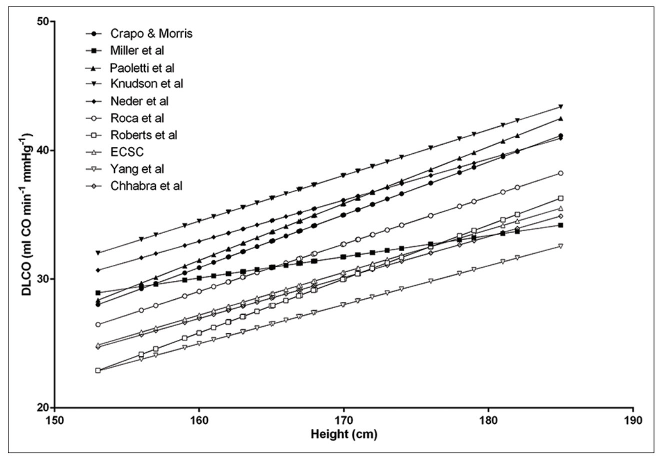

Figure 2: Comparison of the current prediction equation for diffusing capacity of lung for carbon monoxide with those of other investigators for males with a constant age (40 years) and weight (68 kg); equations: Crapo and Morris,[5] Miller *et al.*,[6] Paoletti *et al.*,[7] Knudson *et al.*,[8] Roca *et al.*,[9] Roberts *et al.*,[10] Neder *et al.*,[11] Yang *et al.*,[14] Chhabra *et al.* (present study)

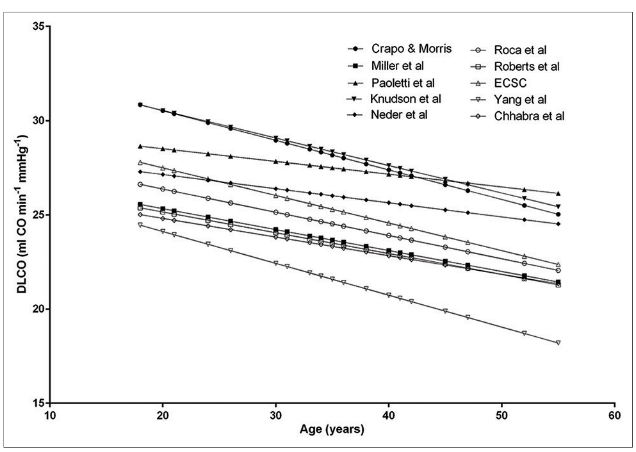

Figure 3: Comparison of the current prediction equation for diffusing capacity of lung for carbon monoxide with those of other investigators for females with a constant height (158 cm) and weight (58 kg); equations: Crapo and Morris,[5] Miller *et al.*,[6] Paoletti *et al.*,[7] Knudson *et al.*,[8] Roca *et al.*,[9] Roberts *et al.*,[10] Neder *et al.*,[11] Yang *et al.*,[14] Chhabra *et al.* (present study)

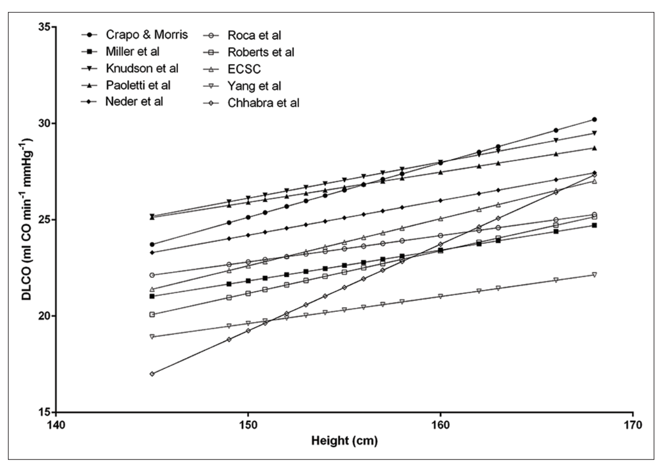

Figure 4: Comparison of the current prediction equation for diffusing capacity of lung for carbon monoxide with those of other investigators for females with a constant age (40 years) and weight (68 kg); equations: Crapo and Morris,[5] Miller *et al.*,[6] Paoletti *et al.*,[7] Knudson *et al.*,[8] Roca *et al.*,[9] Roberts *et al.*,[10] Neder *et al.*,[11] Yang *et al.*,[14] Chhabra *et al.* (present study)

Table 5: Comparison of predicted alveolar volume by current and other equations in the test dataset

Authors and population	Males				Females			
	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)
Miller *et al.*, Caucasians[6]	6.16±0.53	−0.92****	−0.97-−0.87	−14.9	6.37±0.45	−2.69****	−2.72-−2.67	−42.2
Paoletti *et al.*, Caucasians[7]	6.93±0.69	−1.69****	−1.76-−1.61	−24.3	4.99±0.34	−1.32****	−1.35-−1.29	−26.4
Knudson *et al.*, Caucasians[8]	6.39±0.62	−1.14****	−1.20-−1.08	−17.8	4.59±0.43	−0.92****	−0.93-−0.91	−20.0
Roca *et al.*, Caucasians[9]	5.85±0.59	−0.60****	−0.62-−0.58	−10.2	4.16±0.29	−0.48****	−0.53-−0.42	−11.5
Yang *et al.*, Chinese[14]	5.38±0.61	−0.13***	−0.22-−0.052	−2.4	3.80±0.20	−0.13*	−0.23-−0.02	−3.4

†Comparisons with predictions by Indian equations (males: 5.25±0.54, females: 3.68±0.40) using repeated measures analysis of variance and *post hoc* Dunnet *t*-test; *$P<0.05$, ***$P<0.001$, ****$P<0.0001$. SD: Standard deviation, CI: Confidence interval in parenthesis

Table 6: Comparison of predicted diffusing capacity of lung for carbon monoxide/alveolar volume by current and other equations in the test dataset

Authors and population	Males				Females			
	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)	Predicted mean±SD	Mean difference†	95% CI of difference	Difference (%)
Crapo and Morris, Caucasians[5]	5.96±0.29	0.27****	0.26-0.28	4.5	6.02±0.29	0.06****	0.03-0.09	1
Miller *et al.*, Caucasians[6]	5.38±0.30	0.84****	0.79-0.89	15.6	5.00±0.19	1.08****	0.97-1.19	21.6
Paoletti *et al.*, Caucasians[7]	5.38±0.21	0.85****	0.81-0.89	15.8	5.30±0.23	0.78****	0.66-0.90	14.7
Knudson *et al.*, Caucasians[8]	6.41±0.38	−0.18****	−0.23-−0.13	−2.8	5.93±0.30	0.15**	0.03-0.27	2.5
Roca *et al.*, Caucasians[9]	5.94±0.31	0.28****	0.22-0.36	4.7	5.81±0.32	0.27**	0.07-0.46	4.6
Roberts *et al.*, Caucasians[10]	5.44±0.24	0.79****	0.76-0.82	14.5	5.19±0.19	0.88****	0.82-0.94	17
Neder *et al.*, Caucasians[11]	5.67±0.43	0.55****	0.44-0.67	9.7	5.51±0.19	0.57****	0.44-0.69	10.3
Yang *et al.*, Chinese[14]	5.79±0.36	0.43****	0.38-0.49	7.4	5.44±0.31	0.64****	0.54-0.74	9.9

†Comparisons with predictions by Indian equations (males: 6.23±0.33; females: 6.08±0.29) using repeated measures analysis of variance and *post hoc* Dunnet *t*-test; **$P<0.01$, ****$P<0.0001$. SD: Standard deviation, CI: Confidence interval

populations. Yang *et al.*[14] showed that predicted values for DLCO and VA in the Chinese were significantly lower than the Caucasian predictions but DLCO/VA did not differ. Pesola *et al.*[27] observed that Caucasian-derived prediction equation estimates of DLCO resulted in healthy Chinese subjects being labeled as abnormal. The wide differences in predictions of DLCO, VA and DLCO/VA among the Caucasian equations[3,5-11] preclude any comment on the magnitude of differences with the Indian predictions. Nevertheless, our observations in Indians are in agreement with those of Yang *et al.*[14] for the Chinese, both populations showing lower DLCO and VA than the Caucasians. The two major Asian populations are closer between themselves though with small differences, the Indian equations predicting a higher DLCO than the Chinese for males but not for females, and a slightly lower VA than the Chinese predictions for both males and females.

All reported equations for DLCO have included age and height with negative and positive coefficients, respectively.[3,5-16] Three studies have also included weight as a significant predictor.[9,12,14] The explained variance for DLCO has varied from more than 50% in males[5,8-10,14] and females[5,6,8,9] to <50% in some other studies in males[6,7,11] and females,[7,10,11,14] the lowest being only 9% for the equation by Paoletti *et al.*[7] In the present study, the explained variance for DLCO was 28% and 41% in males and females, respectively, and comparable to that reported in several other studies.[6,10,11,14] There is a lack of agreement over the predictors of DLCO/VA with some studies including only age[5,7,10] others including both age and height with negative coefficients[6-8,11] and still others, also including weight with a positive coefficient.[9,14] We found age as the only determinant of DLCO/VA in males with a negative coefficient whereas no model satisfied the requirements of a valid regression analysis in females. It is remarkable that the explained variance for DLCO/VA in all the studies has been <50%, ranging from a low of 10%[7] to a maximum of 46%[8] in males and from 7%[7] to 48%[9] in females. Being an indirectly computed entity and a ratio, DLCO/VA estimates are susceptible to errors in the measurement of either component leading to greater uncertainty in its estimation.

The higher DLCO in Caucasians compared to the Chinese and the Indians is likely due to a larger lung size (larger VA) as surface area of the gas exchange zone is a major determinant of diffusion. If both DLCO and VA increase proportionately, their ratio would remain the same explaining the observations in the Chinese population where DLCO and VA were both lower compared to Caucasians whereas DLCO/VA was similar.[14] However, the relationship between DLCO and VA is not linear and therefore a proportionately greater reduction in the latter would result in a somewhat higher DLCO/VA as observed in Indians by us. The small difference in DLCO/VA predicted by ours and the Caucasian or Chinese equations may be due to the inherent uncertainty in its estimation[28] rather than being a true difference. Ethnic differences are not known for arterial oxygenation and neither are there any known structural or physiological differences, including pulmonary capillary blood flow and ventilation-perfusion matching in the alveolar unit among populations. Anatomic and physiologic rationale therefore dictates that gas exchange in lungs per unit volume should be essentially similar in all humans and the observed differences in DLCO arise mainly from differences in the lung sizes. As gas exchange in individual lung units cannot be measured directly, it is not possible to substantiate this hypothesis experimentally. Nevertheless, our results and those of Yang *et al*.[14] for the Chinese population do raise the possibility that DLCO/VA may be similar or differ only marginally across populations irrespective of gender and ethnicity.

Strengths and limitations

This is the first study to provide prediction equations for DLCO, VA, and DLCO/VA for Indians using the recent standardized methodology and fulfills a long unmet need. Lack of Indian equations for diffusing capacity parameters has been a major limitation in clinical practice and research. These equations should bridge this gap in information. The study also establishes the substantial ethnic diversity in these prediction equations besides the wide within Caucasian differences, reinforcing the need to follow a standardized methodology and locally appropriate equations. While the number of female subjects was lower than males, the sample size was statistically adequate in both genders. The sampling strategy was similar to that used in several other studies cited above. The joint task force of the ATS and ERS has suggested that for development of regression equations, a convenient sample is acceptable as an alternative to random sampling if the selection criteria and the distribution of anthropometric characteristics remain adequate.[23] This was ensured. Further, Van Ganse *et al*.[29] observed that for lung function measurements, the method of selection does not impact the mean values or their ranges. Lack of availability of sufficient number of normal elderly subjects who could perform acceptable test maneuvers limited the maximum age in our study to 71 years in males and 65 years in females. Thus, caution is required in extrapolating these equations to elderly patients beyond these ages. It is however pointed out that according to Census 2011 data,[18] only 1.5% of males and 3.4% of female population of India is above these ages. Thus, the present equations would be valid for all except a very small fraction of the population. The age distribution of our sample matched the age distribution of the population in India.

We and other authors have earlier documented that regional variations exist in lung function within India.[30,31] Therefore, we restricted our sample to North Indians. Similar equations would have to be developed for other regions or these would require validation in other populations.

CONCLUSIONS

Validated prediction equations for DLCO, VA and DLCO/VA for North Indians have been developed. Predictions of DLCO in Indians are generally lower compared to Caucasians but greater than in the Chinese population, at least in males. Predictions for DLCO/VA in Indian males and females are greater by a variable extent than the predictions for both Caucasians and the Chinese. With populations in several countries increasingly becoming multi-ethnic, laboratories should be able to select ethnically appropriate equations to avoid errors in interpretation. Development of these equations is a step in this direction.

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Conflicts of interest

There are no conflicts of interest.

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