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ORIGINAL ARTICLE

Reference values for the carbon monoxide diffusion (transfer factor) in a brazilian sample of white race

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Study carried out in six centers in Brazil, having as its coordinating center the Madre Teresa Hospital, Belo Horizonte, (MG) Brazil.

ABSTRACT

Objective: To derive reference values from white race adults, for DCO in a sample from different sites in Brazil, through the same equipment model (Sensormedics), and compare the results with the derivatives from Crapo, Miller, Neder equations and from the Global Lung Initiative (GLI) proposal. **Methods:** The tests were performed according to the norms suggested by ATS/ERS in 2005 in six Brazilian cities, with 120 adult volunteers of each gender, non-smokers, without referred anemia and without lung or cardio diseases. The expected values were derived from linear regressions and the differences between the values forecasted by some authors and the ones observed in the current study were calculated. **Results:** Among men, the age varied between 25 and 88 years old, and the height varied between 140 and 176 cm. DCO was correlated significantly and positively with the height and negatively with the age. The values forecasted by Crapo, Neder, and Miller equations were higher in comparison with the ones obtained by the current study ($p<0.01$) in both genders. Among men, the values did not differ when compared to the ones calculated by GLI ($p=0.29$); among women, the values derived by GLI were slightly higher: 0.99 ml/min/mmHg ($p<0.01$). **Conclusion:** new values forecasted for DCO were derived in a sample of white adults in Brazil. The forecasted values are similar to the ones complied by GLI equations and differ from the previously proposed equations.

Keywords: Transfer factor; Pulmonary diffusing capacity; Diffusion; Carbon monoxide; Reference values; Lung function tests.

INTRODUCTION

The measurement of the diffusion of carbon monoxide (DCO) or transfer factor for CO, by a single breath, is an essential test at the diagnostic assessment and at the functional follow up in several breathing conditions.[(1)] Reference values were derived and validated for the spirometry in Brazil.[(2,3)] The reference value selection for DCO is more difficult than the choice of the reference value for spirometry, due to the large variation among laboratories.[(4)] In 2005, the task force of ATS/ERS did not recommend the adoption of any specific equation for DCO. However, it suggested that the values forecasted for the alveolar volume (AV) for DCO and for the diffusion coefficient (kCO) should derive from the same source.[(4)]

In Brazil, Crapo proposed equations and the ones derived from Neder are used; however, the foreseen values are higher than other studies.[(5-7)] Yet, other equations, like the ones proposed by Miller, show lower forecast.[(5,8)]

In the last years, there was a great development in the lung function equipment, such as the advent of quick response gas analyzers, with excellent linearity and accuracy. This led to more precise results and most demanding proposals regarding the performance of single breath test for measuring DCO in comparison with the previously suggested guidelines.[(9,10)]

In 2017, the *Global Lung Initiative* (GLI) derived reference values for the DCO by compiling the obtained values in several studies made after the 2000, in more modern equipment. The foreseen values by this equation are lower in comparison with the ones previously published and must be validated.[(11)]

The objective of this study was to derive reference values from the white race to the DCO in a sample of different sites in Brazil by the same equipment model (Sensormedics) and to compare the results with the derived ones from Crapo, Miller, Neder equations and from GLI proposal.[(6-8,11)]

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METHODS

Data were obtained between 2015 and 2017 in six Brazilian cities by systems of the same brand (Sensormedics, Yorba Linda, California).

DCO was measured in all the sites according to the norms suggested by ATS/ERS in 2005, using the CO (0.30%) and CH4 (0.30%) as gases test.[9] FiO_2 was of 0.21. The lung volumes were simultaneously determined by plethysmography. The equipment measures the room temperature by electronic thermometer and the barometric pressure by internal gauge. It performs the conversion of the corrected exhaled gas volume for the corporal conditions of temperature and water vapor pressure into the barometric pressure (BTPS).

The equipment dead space and the valve volume, by *default,* are fixed, from 0.15 L and 0.08 L, respectively.

The individuals were selected by oral invitation, and they are more commonly family members or companions and, eventually, school staff, and of different socioeconomic levels. The volunteers that accepted and consented in participating initially answered a respiratory questionnaire translated from the American Thoracic Society/Division of Lung Diseases, validated in our country and signed the informed consent form.[12,13]

The devices were daily calibrated with a three-liter syringe and weekly submitted to biological controls by the lab employees. The exams were performed by technicians or doctors certified in lung function by the Brazilian Society of Pneumology and Tisiology (SBPT).

The study inclusion criteria were the same as the ones used in the study for the spirometry values derivation in 2007, added a question related to the presence of anemia, which should be absent.[2]

The weight and height were measured according to SBPT recommendations.[14] Obese people (BMI>30 kg/m^2) were excluded.

The DCO measures were performed after the spirometry measures.

They should meet the acceptance and reproducibility criteria suggested by SBPT.[14] The observed CVF values were compared to the ones forecasted for the Brazilian population derived in 2007.[2]

The volume inhaled in the maneuver should be ≥85% of the vital capacity and should be completed in less than 4s. At least two acceptable maneuvers with a difference of ±10% of the highest value and less than 3 ml/min/mmHg were obtained, with 4 min interval. The final registered value was derived from the average of the acceptable maneuver values.[9]

The inspiratory time, measured by Jones and Meade method, should be between 8-12s. As acceptance criteria, during the sustained respiration, there should not exist leaking, or excessive pressure variations in the mouth, exhibited in the monitor during the test performance, indicating Muller and Valsalva maneuver. The exhalation should last for less than 4s. The volume discarded at the exhalation before the alveolar gas sample collection was 0.75 L.[9]

The variables of numeric nature were analyzed by average and standard deviation and the amount of these variables were compared between the genders using the *t*-test of Student.

Linear regressions were used for reference values derivations, considering variables with p≤0.10 at the univariate analysis.

The differences between the values observed in the current study and the ones forecasted for CPT by Crapo, Miller, Neder equations and the ones suggested by GLI were calculated in the total sample and at representative ages and height of each gender. The average difference and its significance were calculated by the matched *t*-test.

All the tests were individually rechecked by one of the authors (CACP), and the ones that did not meet the acceptance and reproducibility criteria were excluded. The cases considered discrepant by distribution after graphs *blox plot* and the ones where the residues derived from the equations exceeded the acceptable values were also excluded.[15]

The statistical analysis was performed ofusing the statistics software SPSS-22. By the comparison multiplicity, the significant *p*-value was considered < 0.01.

With full documentation of all the involved sites, the project was approved by the Ethics and Research Committee of the Hospital Madre Teresa/Belo Horizonte, Minas Gerais, under register number 1617108.

RESULTS

Initially, 292 cases were evaluated; 45 were excluded for inadequate tests and 7 for discrepant values. In the end, 240 cases were included, 120 of each gender. In decreasing order, 153 (63.8%) were from São Paulo, 28 from Salvador, 25 from Criciúma, 25 from Belo Horizonte and 9 from other sites.

The distribution by age, height and BMI is separately shown by each gender in Table 1. Among men, the age varied from 25 to 88 years old, the average height was of 173cm, varying from 156 to 189cm. Among women, the age varied from 21 to 92 years old, the average height was 160cm, varying from 140 to 176cm.

The main functional parameters average, including values for DCO, kCO and alveolar volume (VA), are shown in Table 2. All the values were higher in the male gender, except for CVF in the percentage of the forecasted and kCO, that did not show a significant difference between the genders. CVF was 98.7% of the forecasted for both genders. The relation between the inspiratory vital ability of the diffusion maneuver and the slow vital ability, obtained separately, was 0.91 ± 0.04 in the total sample.

VA/CPT relation was in average 0.87 ± 0.07 among men and 0.86 ± 0.08 among women. In both genders the VA/CPT relation was directly correlated with the inspiratory vital ability (r = 0.44 among men and 0.43 among women, p<0.001) and inversely related

Table 1. Distribution of patients by gender, age, height, and body mass index.3

Variable	Female sex n = 120		Male sex n = 120	
	n	%	n	%
Age (years)				
20-24	4	3.3	----	----
25-34	30	25.0	24	20.0
35-44	18	15.0	20	16.7
45-54	18	15.0	26	21.7
55-64	24	20.0	17	14.2
65-74	13	10.8	25	20.8
≥75	13	10.8	8	6.7
Height (cm)				
140-154	28	23.3	---	----
155-164	62	51.7	13	10.8
165-174	29	24.2	62	51.7
175-184	1 (176 cm)	0.8	38	31.7
≥ 185	----	---	7	5.8
IMC (Kg/m^2)				
18-24	45	37.5	38	31.7
25-30	75	62.5	82	68.3

Table 2. Average of functional variables separated by gender.

Functional variable	Women (N = 120) X ± SD	Men (N = 120) X ± SD	P
CVF (L)	3.24 ± 0.62	4.59 ± 0.79	<0.01
CVF (% forecasted)	99.8 ± 12.3	97.5 ± 10.2	0.12
VEF1 (L)	2.63 ± 0.53	3.62 ± 0.63	<0.01
VEF1/CVF%	0.81 ± 0.05	0.79 ± 0.05	<0.01
CV (L)	3.30 ± 0.60	4.71 ± 0.82	<0.01
VR (L)	1.58 ± 0.46	2.00 ± 0.51	<0.01
CPT (L)	4.88 ± 0.63	6.71 ± 0.84	<0.01
DCO (ml/min/mmHg)	19.29 ± 3.86	27.90 ± 5.19	<0.01
kCO (ml. min^{-1}. mmHg^{-1}. L^{-1})	3.97 ± 0.58	4.09 ± 0.61	0.12
VA (L)	4.18 ± 0.64	5.92 ± 0.85	<0.01

to age (r = -0.31 among men, and -0.33 among women, p<0.001).

The correlation between DCO and age and height in both genders and the lower limits determined by the 5th percentile of residues are shown in the Figure 1.

The linear equations derived for the DCO, kCO, and VA are shown in Table 3. DCO significantly correlated with age and height in both genders, VA with height in both genders, kCO only with age in the male gender, and in a poor way only with height in the female gender. By considering the obtained average values, the lower limits, determined by the 5th residue percentile, they were less distant from the average among men (82%), in comparison with the women (78%). The same was observed with kCO: 80% among men and 74% among women.

The differences were calculated for men and women, between the forecasted values for individuals of the same age and height, by the selected authors, and the ones observed for DCO in this study. In the male gender, the differences were Neder = 7.7 (IC95% = 7.1-8.3); Crapo = 6.5 (IC95% = 5.8-7.2); Miller = 1.7 (IC95% = 1.0-2.3), all of them with p<0.01. The values did not significantly differ when compared to the derived by GLI: -0.32 (IC95% = -0.93 to 0.28).

In the female gender, the differences were also positive. For Crapo = 6.2 (IC95% = 5.7-6.7); Neder = 6.0 (IC95% = 5.5-6.4); Miller = 3.0 (IC95% = 2.5-3.5), all of them with p<0.01. The lower difference was observed with the valued derived by GLI, although in a significant way: 0.99 (IC95% = 0.52 -1.46), p<0.01.

Table 4 shows the comparisons among the average values and the lower limits calculated by the regression equations by the several authors and the values observed in this study, in individuals with representative age and height. The average values and limits closer

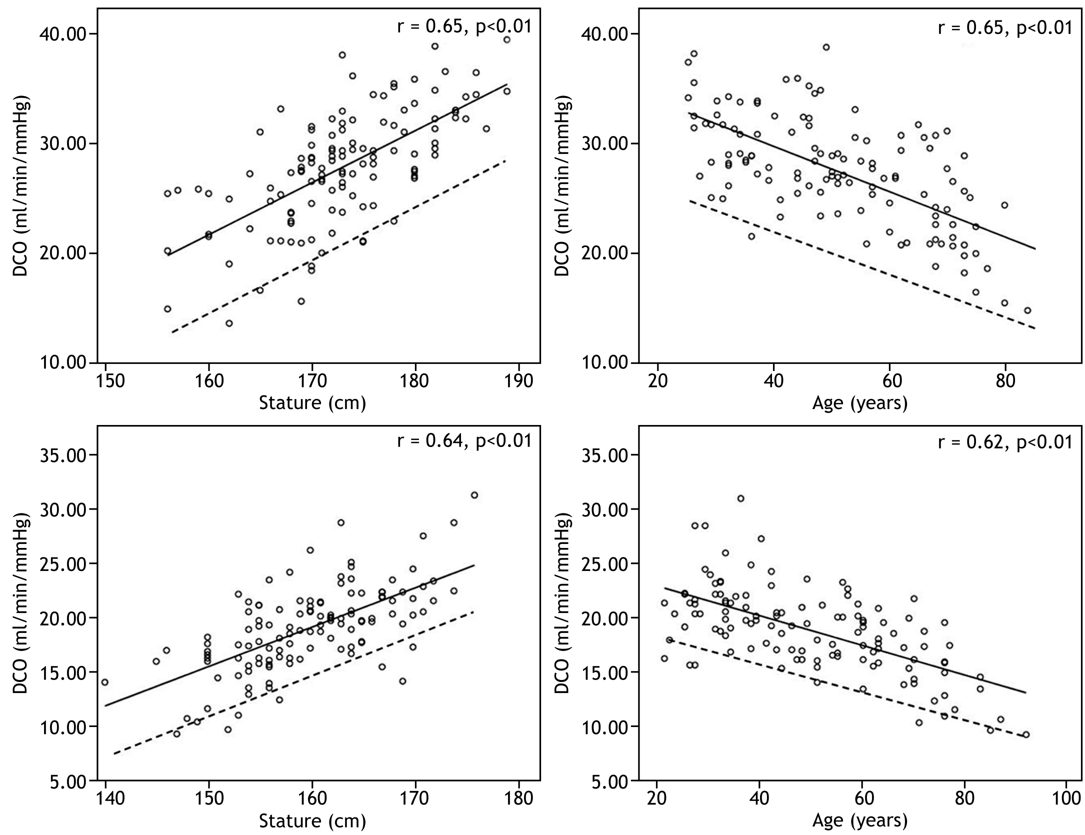

Figure 1. Dispersion of the values for the CO Diffusion with height and age of the reference population in the genders male (above) and female (below).

Table 3. Regression equations, explanation coefficient (r^2) and lower limits for CO diffusion, CO diffusion constant and alveolar volume in the reference population of the female and male genders.

Female, 21-92 years, 140-176 cm height, white race (n = 120)						
	Height coefficient	Age coefficient	Constant	r^2 adjusted	5th residue percentile	Lower limit
DCO (ml/min/mmHg)	0.244	- 0.087	- 15.32	0.53	4.18	P-4.18
VA (L)	0.058	---------	- 5.06	0.40	0.83	P-0.83
KCO (ml. min^{-1}. $mmHg^{-1}$. L^{-1})	0.019	---------	+ 0.98	0.05	1.05	P-1.05
Male, 25-88 years, 156-189 cm height, white race (n = 120)						
	Height coefficient	Age coefficient	Constant	r^2 adjusted	5th residue percentile	Lower limit
DCO (ml/min/mmHg)	0.335	- 0.148	- 22.48	0.60	5.00	P-5.00
VA (L)	0.091	---------	- 9.76	0.56	1.00	P-1.00
KCO (ml. min^{-1}. $mmHg^{-1}$. L^{-1})	-------	- 0.019	5.03	0.25	0.82	P-0.82

Table 4. Average values and lower limits calculated by the current equation compared to values calculated by the equations of other authors in individuals with representative age and height.

Male		Author, average forecasted value and lower limit				
Age	Height	Current	Crapo	Neder	Miller	GLI
26	177	32.97/27.97	41.60/33.4	40.19/30.31	35.99/28.05	32.73/25.84
50	173	28.08/23.08	34.68/26.48	35.79/25.91	29.83/21.89	27.71/21.17
75	168	22.70/17.70	27.12/18.92	30.94/21.06	23.29/15.35	22.26/16.26
Female		**Author, average forecasted value and lower limit**				
Age	Height	Current	Crapo	Neder	Miller	GLI
25	167	23.25/19.07	30.85/24.25	28.38/24.40	26.18/19.68	23.73/18.47
52	161	19.44/15.26	25.43/18.83	25.28/21.30	22.2/15.73	20.46/15.72
76	156	16.13/11.95	20.69/14.09	22.58/18.60	18.76/12.26	17.43/13.05

to the forecasted values and lower limits with the current equations were the ones proposed by GLI. The differences from Neder proposed equations are due to the higher values observed by this author for VA: in the male gender 7.50 L vs 5.92 L in this study ($p<0.001$) and in the female gender 4.88 L vs 4.18 L ($p<0.001$). By linear equations, the explanation coefficient (r^2) at Neder equation was of 0.24 in the male gender and 0.36 in the female gender, in comparison with the values of 0.60 and 0.53 among men and women, respectively, in this sample.

DISCUSSION

New forecasted values for the DCO measure by a single breath were derived in a multi-centric sample of the Brazilian population of the white race.

In this study, DCO values were expressed in traditional units (ml/min/mmHg). For the conversion into mmol/min/kPa, the values should be divided by 2.987.[11]

The forecasted values for DCO were influenced by gender, age, and height. Despite the weight does not affect the DCO average in obese individuals, VA can be lower and kCO higher, that is why the exclusion of obese individuals in the present study.[16]

At the linear equations, the lower limits should be calculated by the subtraction of the 5th residue percentile, a fixed value, of forecasted values.[2] Similar to other studies, the women had higher dispersion of the reference values; that is why the lower limits had been more distant from the median values.[11]

Among adults, DCO along with aging follows a decreasing curve, with relatively stable values in younger individuals and more markedly decline along with aging. This is due to a faster loss of the gas exchange surface, and worsening of the ventilation distribution with aging.[7,17]

The upper limit for DCO was not shown in this study. The meeting value of DCO above the upper limit is small.[11] kCO and VA values were also derived. DCO is the product of kCO x VA; however, the report of DCO/VA relation should be abandoned.[11] There is a great deal of controversy, within the literature, regarding the kCO value at DCO interpretation.[18,19] If a normal individual performs a submaximal inhalation, during the maneuver for measuring DCO, kCO will be high, and so the kCO can only be valued when the VA falls in the forecasted range.[11] In these cases, when kCO is reduced, in general, DCO will be equally reduced.

DCO is measured during a maneuver sustained in plenary inspiration. The inhalation of tracer gas, non-absorbable, allows estimating the lung volume ("a single maneuver CPT") and the dilution occurred to CO. VA calculation represents an estimate of the lung gas volume in which CO is distributed through the alveolar-capillary membrane. Therefore, it is essential to measuring DCO. In normal individuals, the adding of VA and the dead space gets close to the CPT measured by plethysmography.[9]

In the present study, the relation between VA/CPT observed, on average 0.87 ± 0.08, was lower than the reported of 0.94 ± 0.07.[18] Also, different from what has been reported, there was an inverse correlation of this relation with age, suggesting that even in normal individuals, the ventilation distribution, which worsens at aging, can influence VA measure VA.[18]

In this study, it was not done DCO correction for altitude. The barometric pressure (Pb) decreases with attitude, resulting in lower O_2 (PiO_2) inhaled pressure, lower O_2 (PaO_2) alveolar pressure and increase of DCO, for lower "competition" of O_2 with CO at the connection with hemoglobin (Hb). It has been suggested, that the reference values for DCO be adjusted to Pb at sea level (760 mmHg). In a study performed in 4 cities in Latin America, the altitude has influenced DCO measures, with higher values observed in the cities of Mexico (2240m) and Bogota (2640 m) in comparison with the ones observed in Santiago (650m) and Caracas (900m).[20] In this study, the altitude of the evaluated sites varied from 8 m (Salvador) to 852 m (Belo-Horizonte). When the several altitudes were included in the analyses for DCO prediction in this study, they did not havesignificant influence. The relation between DCO and Pb was not confirmed with the new systems that use fast action analyzers.[10] The DCO correction to Pb in altitudes below 1500m is based in scarce data and should be better evaluated.[10]

Ideally, DCO measures should be corrected for the individual level of Hb, but rare laboratories routinely do this correction. In the present study, patients who referred anemia through the questionnaire were excluded. Most of the studies published for the derivation of the reference value did not use correction for Hb level.[11]

The dead space must be considered at VA calculation. In 1995, ATS suggested that fixed value of 0.15 L was used. However, in 2005 the estimated value by the equation weight × 2.2 in ml was suggested in non-obese individuals.[9,21] By this equation, in the present sample, the average ± SD of the dead space would be among men 0.17 ± 0.02 L and among women 0.14 ± 0.02 L, values very close to the fixed amount used by default, of 0.15 L.

In this study, the tests were obtained in Sensormedics equipment.

Several equipment were used in GLI study and 29.5% of Sensormedics brand and the average values obtained did not differ among the different equipment.

The derived values in this study were lower thanthe suggested values by Miller, Neder, and Crapo.[6-8] Crapo evaluated 122 individuals of the female gender and 123 of the male gender in Salt Lake City (altitude 1400m).[6] The sample selection method was not described. DCO was corrected to Hb. The authors used FiO_2 of 0.25, to simulate FIO_2 observed at sea level.

Miller and cols derived values for DCO in a randomized and stratified sample of the state of Michigan.[8]

Values for non-smokers were derived in 74 men and in 130 women. The values were corrected to Hb.

Neder and cols derived reference values in 50 individuals of each gender, from 20-80 years old, selected at random among the staff od a large hospital in São Paulo.[7] Racial profiling was variable. Hb was not measured. Linear equations were used; however, the explanation coefficient was low, indicating large variability of the forecasted values.

At the system used by Neder (MedGraphics), the exhaled gases are analyzed by chromatography, what results in a hyper estimate of the lung volumes, as demonstrated by the VA values compared with the ones observed in the present study.[22,23]

GLI project has recently published reference values for DCO in white children and adults, by data compilation derived from 18 sites, obtained after 2000.[11] The amounts were derived by LMS (lambda, mu, sigma) methods. The most outstanding result was the meeting of lower values than the suggested by elder equations; however, similar to the ones observed in this study.

Limitations should be recognized in the current study. The most obvious limitation is the uncertainty of data extension to the black race, prevailing in Brazil. Volunteers were invited to attend. Reference value derivation for the lung function should only include non-smoking individuals, without symptoms or cardiorespiratory diseases. For this purpose, a validated breathing epidemiologic questionnaire must be applied. After meeting the above-mentioned conditions, the use of volunteers for establishing the reference value is considered valid.[24,25]

Diabetic patients were not excluded from the sample. Diabetic white people have lower values for DCO. In a study, when diabetic white people were paired with non-diabetic controls, the DCO was 1.44 ml/min/mmHg lower in the diabetic ones.[26]

In coclusion, new forecasted values for DCO were derived in a significant sample of white adults in Brazil. The forecasted values are similar to the ones obtained from more modern systems, compiled by GLI, and differ from previously proposed equations.

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