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ORIGINAL ARTICLE

Agreement of different reference equations to classify patients with COPD as having reduced or preserved 6MWD

F.V.C. Machado[a], G.W. Bisca[a,b], A.A. Morita[a], A. Rodrigues[a], V.S. Probst[a], K.C. Furlanetto[a,c], F. Pitta[a], N.A. Hernandes[a,*]

[a] *Laboratory of Research in Respiratory Physiotherapy (LFIP), Department of Physiotherapy, State University of Londrina (UEL), Londrina, Paraná, Brazil*
[b] *Centro Universitário Filadélfia (UniFil), Av. Juscelino Kubitscheck, 1626, 86020-000 Londrina, Paraná, Brazil*
[c] *Research Centre in Health Sciences (CPCS), University of Northern Paraná (UNOPAR), Londrina, Paraná, Brazil*

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Abstract
Background: Interpretation of the six-minute walk distance (6MWD) is enhanced by using recommended reference equations. Whenever possible, the choice of equation should be region-specific. A potential problem is that different equations for the 6MWD may have been developed for the same population, and it may be complicated to choose the most suitable.
Objective: To verify the agreement of different reference equations in classifying patients with Chronic Obstructive Pulmonary Disease (COPD) as having reduced or preserved 6MWD.
Methods: 159 patients with COPD performed the six-minute walk test according to international standardization. They were classified as having reduced 6MWD if it was below the lower limit of normal. Five Brazilian equations (Iwama; Britto1; Britto2; Dourado; Soares) and the two non-Brazilian equations most cited worldwide (Troosters; Enright) were used. The agreement for patients classified as reduced or preserved 6MWD was verified by Cohen's Kappa (pair-to-pair) analysis. The proportion of patients classified as having reduced walked distance was compared by the Chi-squared test.
Results: Agreement between equations varied largely in classifying subjects as having reduced or preserved 6MWD (Kappa: 0.10–0.82). Brazilian equations with the highest agreement were Iwama, Britto1 and Britto2 (Kappa > 0.75). The proportion of patients classified as having reduced 6MWD was statistically similar only between equations in which the agreement was higher than 0.70.

* Corresponding author.
E-mail address: nyhernandes@gmail.com (N.A. Hernandes).

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Conclusion: Even reference equations from the same country vary considerably in the classification of reduced or preserved 6MWD, and it is recommended that the region-specific ones be used as they give with higher agreement for similar and comparable interpretation of the patients' functional exercise capacity.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1] as ''*a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases*''. A consequence of these abnormalities is air trapping, which leads to dyspnea and lung hyperinflation.[1,2] Thus, patients are thrust into a vicious cycle of COPD symptoms and are liable to decrease their level of physical activity in daily life, adopting a predominantly sedentary lifestyle.[3,4] Furthermore, physical inactivity may lead to deconditioning as well as to systemic consequences, such as peripheral muscle weakness, impaired quality of life and functional status, body composition abnormalities, and poor exercise capacity,[1,5] resulting in an increase in the intensity of symptoms.

Exercise intolerance is a common finding in patients with COPD and is known to be multifactorial.[1,6] Hence, its evaluation is essential in research and clinical settings, since it plays an important role in disease progression.[7] Field tests, such as the six-minute walk test (6MWT), are available and have been widely used to assess functional exercise performance in these patients,[7,8] the 6MWT is easy to perform, inexpensive and highly reproducible.[7,9] Moreover, it provides the most comprehensive prognostic information available in the majority of chronic respiratory diseases.[7] In addition, it is used to prescribe training intensity[10] and to verify the effectiveness of interventions,[8] besides being a predictor of morbidity and mortality in COPD.[11]

Interpretation of the 6MWT is enhanced if reference values are obtained through the use of equations which consider anthropometric, demographic and/or physiological variables of a population. These equations predict the expected ''normal'' distance to be walked during the test for a given patient. Different authors have proposed reference values for the six-minute walk distance (6MWD, *i.e.*, the distance achieved in the test).[12–17] It is worth noting that there is a large number of available equations in Brazil[14–17] and these equations are composed of similar predictors, despite having quite variable coefficients of determination. Some related aspects still remain unknown, such as whether or not these equations agree in classifying patients as having reduced or preserved 6MWD. This information would be valuable and could help avoid differences in the clinicians and researchers' interpretation of the patient's functional exercise capacity. Thus, the aim of this study was to verify the agreement of different reference equations (five from Brazil and two from other countries) in classifying COPD patients as having reduced or preserved 6MWD.

Methods

Design and sample

A cross-sectional study was conducted with a convenience sample of patients with stable COPD enrolled at the Pulmonary Outpatient Clinic and Rehabilitation Center at the University Hospital of the State University of Londrina (HU/UEL), Londrina, Brazil. The study was approved by the Research Ethics Committee of the institution (number 123/09), and all participants gave written informed consent.

Inclusion criteria were: diagnosis of COPD according to the GOLD[1]; no exacerbation in the last three months, or any severe comorbidity which could interfere with the performance of the tests; not having attended to any formal exercise program in the preceding year. Subjects were excluded if they could not complete the research protocol due to any physical hindrance to their performance.

Assessments

Demographic (gender and age) and anthropometric (height [cm], body weight [kg] and body mass index [kg/m^2]) data were collected. Pulmonary function was evaluated by spirometry using a portable spirometer (Spirobank G®; MIR, Italy). The test procedures were performed according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standardization.[18] Reference values used were proposed by Pereira et al.[19] for the Brazilian population.

The 6MWT, used to evaluate the functional exercise capacity, was performed according to international recommendations.[8] Heart rate, blood pressure, oxygen saturation, dyspnea and fatigue perception according to the modified Borg scale (0–10)[20] were recorded before and immediately after finishing the test. The predicted values for the 6MWD were calculated according to five reference equations[14–17] developed specifically for the Brazilian population (Iwama; Britto1; Britto2; Dourado; Soares) and two non-Brazilian equations[12,13] which are the most frequently cited worldwide, according to Web of Science™ as of January 2017 (Troosters; Enright) (Table 1). The lower limit of normal (LLN) for each reference equation (one-tailed) was

Table 1 Reference equations to predict the walked distance in the six-minute walk test used in the study.

Study	Reference equation	r^2	SEE or equivalent	LLN determination
Enright and Sherrill[12]	♂ 6MWD = (7.57*height) − (5.02*age) − (1.76*weight) − 309	0.42	NRA	♂6MWD − 153#
	♀ 6MWD = (2.11* height) − (5.78* age) − (2.29*weight) + 667	0.38	NRA	♀6MWD − 139#
Troosters et al.[13]	6MWD = 218 + (5.14*height) − (5.32*age) − (1.80*weight) + (51.31*gender)	0.66	56	6MWD − (1.645 * 56)
Iwama et al.[14]	6MWD = 622.461 − (1.846*age) + (61.503*gender)	0.30	70.992	6MWD − (1.645 * 70.992)
Dourado et al.[15]	6MWD = 299.296 − (2.728*age) − (2.160*weight) + (361.731*height) + (56.386*gender)	0.55	57.7	6MWD − (1.645 * 57.7)
Soares and Pereira[16]	6MWD = 511 + (0.0066*height^2) − (0.03*age^2) − (0.068*BMI^2)	0.55	NRA	6MWD = 81%#
Britto et al. 1[17]	6MWD = 890.46 − (6.11*age) + (0.0345*age^2) + (48.87*gender) − (4.87*BMI)	0.46	77.2	6MWD − (1.645 * 77.2)
Britto et al. 2[17]	6MWD = 356.658 − (2.303*age) + (36.648*gender) + (1.704*height) + (1.365*ΔHR)	0.62	64.3	6MWD − (1.645 * 64.3)

BMI: body mass index; gender: Male = 1/Female = 0; HR: heart rate; LLN: lower limit of normality; NRA: not reported by the authors; SEE: standard error of the estimate; 6MWD: six minute walk distance; Δ: delta; r^2: coefficient of determination #LLN as reported by the authors.

established as mean − 1.645 X standard error of the estimate (SEE), or its equivalent as described in the original reference.[21] For the equations where neither SEE nor its equivalent were available, the LLN was established as proposed by the respective authors.[12,16] Subjects who walked any distance equal or above the LLN were classified as ''functional exercise capacity – preserved'' (FEC – P group) according to each equation, while those who did not were classified as ''functional exercise capacity – reduced'' (FEC – R group). We considered the one-tailed LLN calculation, that is equal to the 5th percentile of a healthy population,[21] because the major concern is the reduction of the 6MWD, since it is strongly associated with increased risk of hospitalization and mortality in people with respiratory disease.[8]

Statistical analysis

The statistical analysis was performed using SPSS Version 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and Epidat 3.1 (Dirección Xeral de Innovación e Xestión da Saúde Pública, A Corunã, Spain). The normality of data distribution was evaluated using the Shapiro–Wilk test, and according to data normality, results were described as mean ± standard deviation or median [interquartile range 25–75%]. In order to achieve an agreement value among the seven reference equations, the Global Kappa was calculated. In addition, the Cohen's kappa (pair-to-pair)[22,23] was used to verify the level of agreement between the equations. For the comparison between the proportion of patients classified as belonging to groups FEC – P or FEC – R according to each equation, the Chi-squared test was performed. The Friedman test (Dunn *post hoc* test) was used to compare the percentage of predicted values of 6MWD according to each reference equation. Cross-sectional comparisons were performed by either unpaired *t*-test or Mann–Whitney *U* test. The level of statistical significance was considered as $P < 0.05$.

Results

One hundred fifty-nine subjects were recruited for the study; their general characteristics can be found in Table 2. The median [IQR] walked distance in the 6MWT was 456 [403–510] m. Furthermore, there were differences in the comparison of the walked distance in percentage of the predicted according to the seven reference equations, which are presented in Fig. 1A.

The Global Kappa value considering all the equations was 0.29 (CI 95%: 0.27–0.31) ($P < 0.05$). When only the Brazilian reference equations[14–17] were considered, the Global Kappa was 0.57 (CI 95%: 0.54–0.60) ($P < 0.05$). The pair-to-pair Kappa analysis showed an agreement ranging from 0.10–0.82 (Table 3). Brazilian equations with the highest agreement were Iwama, Britto_1 and Britto_2.[14,17] (Kappa > 0.75). The Global Kappa of the equations by Iwama, Britto_1 and Britto_2 was 0.80 (CI 95%: 0.74–0.85) with no statistical differences between Kappa values ($P > 0.70$). These equations agreed on the classification of 137 patients. Those equations with Kappa value above 0.70 did not differ in the proportion of subjects classified as having preserved or reduced functional exercise capacity (Table 3 and Fig. 1B).

Out of the 137 patients, 95 were classified as belonging to FEC – P group and 42 as belonging to FEC – R group according to the equations by Iwama, Britto_1 and Britto_2, simultaneously. Table 2 displays the main characteristics of these two groups of patients with COPD according to these three equations. The analysis showed that patients from FEC – R group were older, mostly males and classified mainly as GOLD 3 and 4. They had lower 6MWD (FEC – R: 358 [290–390] *vs.* FEC – P: 496 [456–525] m) height, change [delta] of heart

Table 2 Clinical, anthropometric, demographic data and exercise capacity characteristics of patients with chronic obstructive pulmonary disease according to classification in functional exercise capacity - preserved (FEC - P group) or functional exercise capacity - reduced (FEC - R group) by the equations by Iwama, Britto_1 and Britto_2.

Variables	All patients $n = 159$	FEC-P $n = 95$	FEC-R $n = 42$	*P*-value
Demographic				
Gender (M/F) (*n*)	87/72	41/54	29/13	<0.01
Age (years)	66 ± 8	64 [60–71]	71 [63–72]	<0.01
Antrhopometric				
Weight (kg)	67 [55–79]	63 [53–77]	71 [57–81]	0.11
Height (cm)	160 ± 9	158 [152–163]	165 [155–168]	<0.01
BMI ($kg\,m^{-2}$)	26 [22–31]	26 [22–31]	27 [21–31]	0.84
Lung function				
FEV_1 (% predicted)	44 [31–55]	48 ± 15	35 ± 14	<0.0001
FVC (% predicted)	67 ± 16	71 [59–84]	59 [48–65]	<0.0001
FEV_1/FVC	53 [42–60]	54 ± 13	47 ± 15	<0.01
GOLD (1/2/3/4) (n)	(1/58/66/34)	(1/45/37/12)	(0/5/20/17)	<0.0001
6MWT outcomes				
6MWD (m)	456 [403–510]	496 [456–525]	358 [290–390]	<0.0001
$HR_{baseline}$ (bpm)	87 [78–97]	88 ± 14	88 ± 11	0.78
HR_{end} (bpm)	115 [106–127]	120 [111–129]	110 [101–119]	<0.01
$SpO_{2baseline}$ (%)	95 ± 2	95 ± 2	95 ± 2	0.45
SpO_{2end} (%)	91 ± 4	92 ± 4	92 ± 4	0.97
Borg $D_{baseline}$ (pts)	0.9 ± 3	0.6 ± 1	1.4 ± 2	<0.01
Borg D_{end} (pts)	3.7 ± 3	3.7 ± 3	4.1 ± 2	0.28
Borg $F_{baseline}$ (pts)	0.85 ± 1	0.64 ± 1	1.2 ± 2	<0.05
Borg F_{end} (pts)	2.7 ± 3	2.8 ± 3	2.7 ± 2	0.89

BMI: body mass index; Borg D: dyspnea sensation; Borg F: lower limb fatigue sensation; F: Female; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HR: heart rate; M: Male; SpO_2: peripheral capillary oxygen saturation; 6MWD: six minute walk distance.

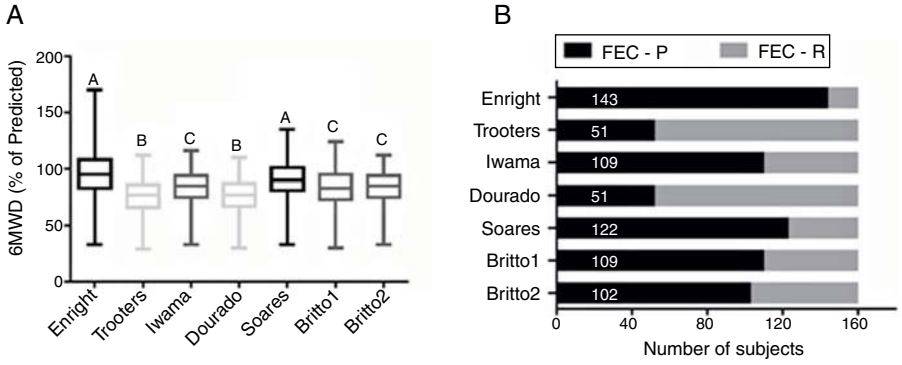

Figure 1 (A) Comparison of the 6MWD in percentage of predicted according to each equation. (B) Number of subjects classified as ''functional exercise capacity – preserved'' (FEC – P) or ''functional exercise capacity – reduced'' (FEC – R), according to lower limit of normal (LLN) of each equation. *Equal letters represent absence of statistical significance ($P > 0.05$).

rate during the test, and worse pulmonary function ($P < 0.05$ for all).

Discussion

The present study analyzed the agreement of equations commonly used in Brazil in classifying patients' functional exercise capacity as preserved or reduced according to the LLN of each equation, the agreement among the equations varied substantially. The set of equations by Iwama, Britto_1 and Britto_2 presented higher Global Kappa and higher pair-to-pair Kappa (*i.e.*, above 0.75). Patients from FEC-R group of these equations had more severe disease and, as expected, lower 6MWD compared to those who walked above the LLN of these same equations.

Previous studies aimed to compare different 6MWD reference equations applying it to the same population.[14,17,24–27].

Table 3 Agreement (pair-to-pair analysis) between the reference equations and pair-to-pair differences in the proportion of patients classified as functional exercise capacity preserved (FEC − P group) or functional exercise capacity reduced (FEC − R group).

Reference equation	Kappa
Enright *vs.* Troosters	0.10
Enright *vs.* Iwama	0.39
Enright *vs.* Dourado	0.10
Enright *vs.* Soares&Pereira	0.54
Enright *vs.* Britto_1	0.39
Enright *vs.* Britto_2	0.33
Troosters *vs.* Iwama	0.36
Troosters *vs.* Dourado*	0.77
Troosters *vs.* Soares&Pereira	0.25
Troosters *vs.* Britto_1	0.36
Troosters *vs.* Britto_2	0.42
Iwama *vs.* Dourado	0.36
Iwama *vs.* Soares&Pereira*	0.70
Iwama *vs.* Britto_1*	0.80
Iwama *vs.* Britto_2*	0.82
Dourado *vs.* Soares&Pereira	0.25
Dourado *vs.* Britto_1	0.36
Dourado *vs.* Britto_2	0.42
Soares&Pereira *vs.* Britto_1*	0.73
Soares&Pereira *vs.* Britto_2	0.62
Britto_1 *vs.* Britto_2*	0.76

* Chi-squared test $P < 0.05$.

These studies focused on comparing the values of the predicted 6MWD (m) or on percentage of the predicted by each equation. To the best of our knowledge, this is the first study that aimed to compare the agreement of Brazilian equations in classifying a relatively large sample of patients as reduced or preserved walking distance using the LLN.

Considering the international equations analyzed in this study, the equation by Enright and Sherrill[12] estimated lower values for the 6MWD in the present sample. Consequently, subjects covered on average 95% of the predicted distance (Fig. 1B); and the great majority was classified as having preserved walked distance (FEC − P group). This result was similar to previous studies[14,17,24–27] which showed that this is one of the equations that underestimates the distance to be walked by patients to a greater extent. The agreement between Enright and Sherrill's equation and the others varied from 0.10 to 0.54 (Table 3).

On the other hand, the international equation proposed by Troosters et al.[13] predicted higher values to be walked during the 6MWT; thus, the percentage of predicted covered by the subjects was lower in comparison to the majority of other equations (except Dourado's equation as shown in Fig. 1B) and consequently the number of individuals in the FEC − R group was higher. This result also corroborates with findings of previous studies[14,17,24–27] and possibly occurred because the study by Troosters et al.[13] was developed with a relatively small convenience sample, and with individuals ethnically and socioeconomically different from the Brazilian population.

Regarding the Brazilian equations studied, the one described by Iwama et al.[14] was the first equation developed for Brazilians. That study recruited 134 healthy subjects aged 13–84 years from students, employees and residents of surrounding the studied university and hospital. Although height significantly influenced the 6MWD in that study, after multiple regression analysis only age and gender remained as determinants of the 6MWD.[14] The median of age of this equation was slightly lower than the others (31 [22–37] years for males and 35 [24–52] years for females).

The equation suggested by Dourado et al.[15] was similar to that by Troosters et al.[13] when classifying subjects as FEC − P or FEC − R groups. In both formulas, the predicted values were higher than the others, thus the walked distance was considered lower in percentage of predict by the equations, leading to a larger number of subjects in the FEC − R group. As the equations above mentioned presented a very good agreement and were developed in different countries, it could be expected that Dourado's equation would lead to different interpretation of patient's functional exercise capacity in comparison with the other Brazilian equations. Besides the agreement between this equation and the other Brazilian ones varied from 0.25 to 0.42.

The equation developed by Soares and Pereira,[16] among the Brazilian equations analyzed, was the one that predicted the lowest values for the 6MWT. Thus, according to this equation, the majority of patients were classified with preserved exercise capacity. The observed pair-to-pair agreement between this equation and the other ones was fair (Kappa > 0.62), except with the equation by Dourado (Kappa = 0.25) (Table 3).

Finally, the study developed by Britto et al.,[17] is unique, with its multicenter design and inclusion of a large sample of healthy subjects ($n = 629$) from different regions of the country. This is a positive feature of the study since Brazil is a country of continental proportions. Looking specifically at the two equations from this study and the equation by the Iwama, the pair-to-pair Kappa values were higher (Kappa > 0.75), all of them predicted similar values for the 6MWD and presented no differences in the proportion of subjects classified as FEC − P or FEC − R group (Fig. 1A and B). Moreover, the Global Kappa of these equations showed no differences between the pair-to-pair Kappa values and was higher than the Global Kappa when the other two Brazilian equations were included in the analysis (0.80 [CI 95%: 0.74–0.85] *vs.* 0.57 [CI 95%: 0.54–0.60]).

In addition to the equations analyzed in this study, there is other Brazilian equation available in the literature that was developed including individuals with the age of COPD patients. The alternative equation proposed by Dourado et al.[15] was not studied because it used handgrip strength as an independent variable and this evaluation method was, unfortunately, not available in our research setting. Additionally, in their study, Dourado et al.[15] state that the values of handgrip strength did not increase significantly the equation's coefficient of determination.

The main limitation of this study was the small number of subjects with mild COPD (GOLD 1) which are expected to have better functional exercise capacity, so the results could not be the same for a sample with patients with less severe disease. However, the majority of the patients studied presented preserved functional exercise capacity and this might

reflect a characteristic of the Brazilians pulmonary rehabilitation centers such as the one in which this study was developed in.

The findings of this study suggest that even reference equations for the 6MWD developed for the same population vary considerably in classifying individuals as having reduced or preserved functional exercise capacity. The equation by Dourado et al.[15] was the one which presented lower agreement with the other Brazilian ones; the equation of Soares et al.[16] presented a fair to good agreement with the other Brazilian ones and the equations by Britto et al. and Iwama presented the higher agreement among all Brazilian equations. In conclusion, the use of region-specific reference equations with higher agreement iis recommended, such as the ones by Britto et al.[17] and Iwama et al.,[14] for similar and comparable interpretation of the patient's functional exercise capacity.

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Authors' contributions

FVC Machado was responsible for the literature review, conception and design of the study, acquisition of data, statistical analysis and writing of the paper. GW Bisca and AA Morita contributed for the conception and design of the study. A Rodrigues was responsible for the statistical analysis and interpretation of data, as well as for intellectual input. VS Probst, KC Furlanetto, F Pitta and NA Hernandes were responsible for critically advising the study and for intellectual input, as well as for the final approval of the version to be published.

Conflicts of interest

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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