International equations overestimate the respiratory muscle strength in children and adolescents with Cystic Fibrosis

Equações internacionais superestimam a força muscular ventilatória em crianças e adolescentes com Fibrose Cística

Ecuaciones internacionales sobreestiman la fuerza muscular ventilatoria en niños y adolescentes con Fibrosis Quística

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ABSTRACT | The aim of the present study was to compare the results of standardization of ventilatory muscle strength data using three international reference values and one Brazilian reference in children and adolescents with cystic fibrosis (CF). This was a retrospective study, which included patients with CF aged 8 to 12 years and in regular follow-up at an outpatient facility. Demographic and anthropometric data were collected. All patients included in the sample should have had ventilatory muscle strength and lung function measured in the past 12 months. The standardization of the results was made using predicted values from each equation. Data were compared using one-way ANOVA. We included 24 patients, 62.5% males, with mean age of 10.5±1.53 years, height 138.0±0.08 cm, weight 34.6±7.9 kg, FEV1 93.29±29.02% and FVC 103.78±26.12%. The maximum inspiratory (MIP) and expiratory (MEP) pressures (cmH2O) observed were 92.1±22.8 and 98.9±24.5, respectively. After standardization by the different equations, we found that the international reference tend to overestimate the findings. The Brazilian equation showed values significantly lower (p<0.05) for MIP and MEP compared to international reference equations, and these would consider MIP values above normal (>100%) in 91.6, 79.1, and 75.0% of the subjects and MEP in 66.6, 87.5 and 50% of them, while using the national equation only 50.0 and 37.5% of subjects were above 100%, respectively. The results of standardization of ventilatory muscle strength in children and adolescents with CF aged 8 to 12 years using international equations overestimate the values of maximal respiratory pressures.

Keywords | Muscle Strenghth; Respiratory Muscles; Cystic Fibrosis.

RESUMO | O objetivo deste estudo foi comparar os resultados da normalização dos dados de força muscular ventilatória utilizando-se três equações de referência internacionais e uma nacional em crianças e adolescentes com fibrose cística (FC). Estudo retrospectivo, no qual foram incluídos pacientes com FC, idade entre 8 e 12 anos e acompanhamento ambulatorial regular. Foram coletados dados demográficos e variáveis antropométricas. Todos os pacientes incluídos deveriam ter realizado teste de força muscular ventilatória e espirometria nos últimos 12 meses. A normalização dos resultados foi realizada utilizando-se as variáveis preditoras requeridas em cada equação estudada. Os dados foram comparados utilizando-se uma ANOVA de uma via. Foram incluídos 24 pacientes, 62,5% masculinos, média de idade 10,5±1,53 anos, estatura 138,0±0,08 cm, massa corporal 34,6±9,07 kg, VEF_1 93,29±29,02% e CVF 103,78±26,12%. As pressões (cmH_2O) inspiratória (PIMAX) e expiratória (PEMAX) máximas encontradas foram 92,1±22,8 e 98,9±24,5, respectivamente. Após a normalização pelas diferentes equações, demonstrou-se que as internacionais tendem a superestimar os achados para a nossa população. A equação nacional apresentou valores médios previstos significativamente (p<0,05) menores para PIMAX e PEMAX em comparação com as equações internacionais, sendo que estas classificariam a PIMAX como acima do normal (>100%) em 91,6, 79,1, e 75,0% dos sujeitos e a PEMAX em 66,6, 87,5 e 50%, enquanto a equação nacional estimaria apenas 50,0 e 37,5% dos indivíduos, respectivamente. A normalização dos resultados de força muscular ventilatória em crianças e adolescentes entre 8 e 12 anos

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com FC utilizando-se equações internacionais superestimam os valores das pressões respiratórias máximas.

Descritores | Força Muscular; Músculos Respiratórios; Fibrose Cística.

RESUMEN | El objetivo de este estudio fue comparar los resultados de la normalización de los datos de fuerza muscular ventilatoria utilizando tres ecuaciones de referencia internacionales y una nacional en niños y adolescentes con fibrosis quística (FC). Estudio retrospectivo, en el cual fueron incluidos pacientes con FC, edad entre 8 y 12 años y control ambulatorio regular. Fueron colectados datos demográficos y variables antropométricas. Todos los pacientes incluidos deberían haber realizado test de fuerza muscular ventilatoria y espirometría en los últimos 12 meses. La normalización de los resultados fue realizada utilizando las variables predictoras requeridas en cada ecuación estudiada. Los datos fueron comparados utilizando una ANOVA de una vía. Fueron incluidos 24 pacientes, 62,5% masculinos, media de edad 10,5±1,53 años, estatura 138,0±0,08 cm, masa corporal 34,6±9,07 kg, VEF_1 93,29±29,02% y CVF 103,78±26,12%. Las presiones (cmH_2O) inspiratoria (PIMAX) y expiratoria (PEMAX) máximas encontradas fueron 92,1±22,8 y 98,9±24,5, respectivamente. Después de la normalización por las diferentes ecuaciones, se demostró que las internacionales tienden a sobreestimar los hallazgos para nuestra población. La ecuación nacional presentó valores medios previstos significativamente (p<0,05) menores para PIMAX y PEMAX en comparación con las ecuaciones internacionales, siendo que estas clasificarían la PIMAX como encima de lo normal (>100%) en 91,6, 79,1, y 75,0% de los sujetos y la PEMAX en 66,6, 87,5 y 50%, mientras la ecuación nacional estimaría apenas 50,0 y 37,5% de los individuos, respectivamente. La normalización de los resultados de fuerza muscular ventilatoria en niños y adolescentes entre 8 y 12 años con FC utilizando ecuaciones internacionales sobreestiman los valores de las presiones respiratorias máximas.

Palabras clave | Fuerza Muscular; Músculos Respiratorios; Fibrosis Quísticas.

INTRODUCTION

Cystic fibrosis (CF) is a genetic progressive disease associated with impairment of the respiratory function[1]. The course of the disease is influenced by chronic inflammation of the airways and recurrent bacterial infections that predispose the patient to airflow limitation and change their respiratory system compliance, causing ventilatory muscle weakness[2].

Many studies conducted with pediatric samples have shown contradictions in the assessment of ventilatory muscle strength, with results varying from decrease[3,4] to increase[1,5] in strength. Some papers report that hyperinflation combined with malnutrition may be a factor predisposing to ventilatory muscle weakening[4,6,7]. On the other hand, chronic cough and increase in ventilatory effort seem to favor muscle strength[5,8]. In the last decade, some national studies assessing ventilatory muscle strength in CF patients[1,9,10] also showed conflicting results.

Currently there are three international equations used for standardization of results in evaluations of ventilatory muscle strength of children under the age of 12[11-13]; however, the use of such equations may not reflect the actual ventilatory condition of patients, for they under- or overestimate the findings. Our study group has recently published reference values for ventilatory muscle strength in healthy preschool Brazilian children[14]. This study showed that international equations compared to local reference values overestimate the ventilatory muscle strength of healthy children and adolescents, suggesting that the standardization of findings in subjects with changes in the respiratory system may not reflect the actual conditions of these muscles.

Considering the wide range of differences in evidence regarding ventilatory muscle strength in CF patients and the usual use of international reference values for standardization of findings, we raised the hypothesis that the appliance of a national equation could show the behavior of these muscles more accurately. The purpose of this paper was, therefore, to compare results of data standardization regarding ventilatory muscle strength using one national and three international reference equations in children and adolescents with CF.

METHODOLOGY

This was a retrospective observational study based on a secondary database research. Patients diagnosed with CF by sweat or genetic test, aging from 8 to 12 years old, in outpatient follow-up at Hospital São Lucas (Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS) were included in the sample. All subjects should have been submitted to ventilatory muscle strength and spirometry tests in the 12 months prior to the study. Patients whose data were not available on the database were excluded from the sample. The research

was approved by the Ethics Committee of the institution (08/04102).

Data regarding identification (such as name, birth date, genre), body mass index, height, spirometry and ventilatory muscle strength were collected. The spirometric features assessed (KOKO spirometer, Louisville, CO, EUA) included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and mid-breath forced expiratory flow in measurements of FVC (FEF 25–70%). All procedures were performed in compliance with pre-established guidelines[15], and values expressed were absolute and predicted. Manovacuometry test was made using a digital manovacuometer (MVD500, Globalmed, Porto Alegre, RS, Brazil). The maximum inspiratory (MIP) and expiratory (MEP) pressures[15] were measured with patients sitting down, wearing a nose clip, and holding firmly the equipment in their lips to prevent escaping air. MIP was measured by residual volumes, and MEP by total lung capacity (TLC).

During the last maneuver, patients were supposed to put their hands on their cheeks to avoid air accumulation inside their mouth. All measures were taken at maximum effort and sustained for at least 1 second. Patients should perform at least three and at most nine maneuvers, being three acceptable (without air escape) and two reproducible (variance <10% between two measures). The value could not be higher than the precedent[13,15], so the final result would be the highest measure obtained.

Standardization of the results was made by using different reference equations (one national and three international) according to the predictor factors required by each of them. Reference equations were named after the first letter of the study author's name, being the national equation (2012)[14] named H, and the international ones (1984, 2002 and 2003) W, T and D, respectively[11-13] (Chart 1).

After data standardization, three cut off points were established: muscle strength above normality (100% of predicted values), values between 80 and 100% of prediction, and values below 80% of the prediction. To define the sample size, MIP was the variable of choice. Considering a 5% alpha error and 80% power, and aiming at detecting a variation of two standard deviations, the sample size was estimated in roughly 20 individuals.

The variables were assessed by the Shapiro-Wilk test and expressed as mean and standard deviation. Spirometric data and results of the ventilatory muscle strength were expressed as absolute and predicted values. Comparisons between equations were made by one-way ANOVA (Bonferroni post-test). All analyzes were made in the software SPSS 18.0 (SPSS Inc., EUA), with significance level set at 5%.

RESULTS

Twenty-four patients were included in the samples, being 9 females. Spirometry values, maximal respiratory pressures and sample characterization are shown in Table 1.

After data standardization, it was shown that international equations tend to overestimate the findings in our sample. Considering that there were no significant differences regarding gender, data are presented in group. The national equation (H) had mean predicted values for MIP significantly lower (p=0.0003) compared to equations W and T (Figure 1A). On the other hand, predicted MEP in equation H was significantly lower (p<0.0001) compared to equation T (Figure 1B).

Using 100% of the prediction as cut off point, international equations would classify MIP as above normality (>100%) in 91.6, 79.1, and 75% of subjects (in W, T and D, respectively), and MEP in 66.6, 87.5 and 50% of subjects, while the national equation would only overestimate 50 and 77.5% of individuals, respectively. When data below 80% of the prediction were assessed, only 4.1, 8.3 and 12.5% (MIP) and 12.5, 4.1 and 29.1% (MEP) of the patients were classified in this range, while the national equation estimated a higher percentage, 16.6 and 29.1%, respectively. Finally, 4.1, 12.5, 12.5% (MIP) and 20.8, 8.3 e 20.8% (MEP) of patients had values between 80 and 100% of the international equations' prediction, while the national equation estimated 33.3% for both respiratory pressures. These findings are shown in Figure 2.

DISCUSSION

Our findings show that the standardization of ventilatory muscle strength data by the use of international equations tend to overestimate values of maximal pressures in children and adolescents with CF. This may be justified by social, environmental and ethnical differences between peoples, which makes hard to extrapolate and to apply international equations, for the use of reference values from other environments may not

Wilson et al.[11] 1984 United Kingdom	MIP	*Females* 40 + (0.57 x Weight)	*Males* 44.5 + (0.75 x Weight)
	MEP	*Females* 24 + (4.8 x Age)	*Males* 35 + (5.5 x Age)
Tomalak et al.[12] 2002 Poland	MIP	*Females* -3.142 + (0.300 x Age)	*Males* -1.939 + (0.554 x Age)
	MEP	*Females* 4.131 + (0.230 x Age)	*Males* 2.839 + (0.451 x Age)
Domenèch-Clar et al.[13] 2003 Spain	MIP	*Females* -33.854 - (1.814 x Age) -(0.004 x Height x Weight)	*Males* -27.020 - (4.132 x Age) -(0.003 x Height x Weight)
	MEP	*Females* 17.066 + (7.22 x Age)	*Males* 7.619 + (7.806 x Age) + (0.004 x Height x Weight)
Heinzmann et al.[14] 2012 Brazil	MIP	*Females* 14.226 - (0.551 x Height) - (0.638 x Weight)	*Males* 17.879 - (0.674 x Height) - (0.604 x Weight)
	MEP	*Females* 30.045 + (0.749 x Weight) + (4.213 x Age)	*Males* 47.417 + (0.898 x Weight) + (3.166 x Age)

MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure.

Chart 1. Reference equations used for standardization

Table 1. Sample characteristics

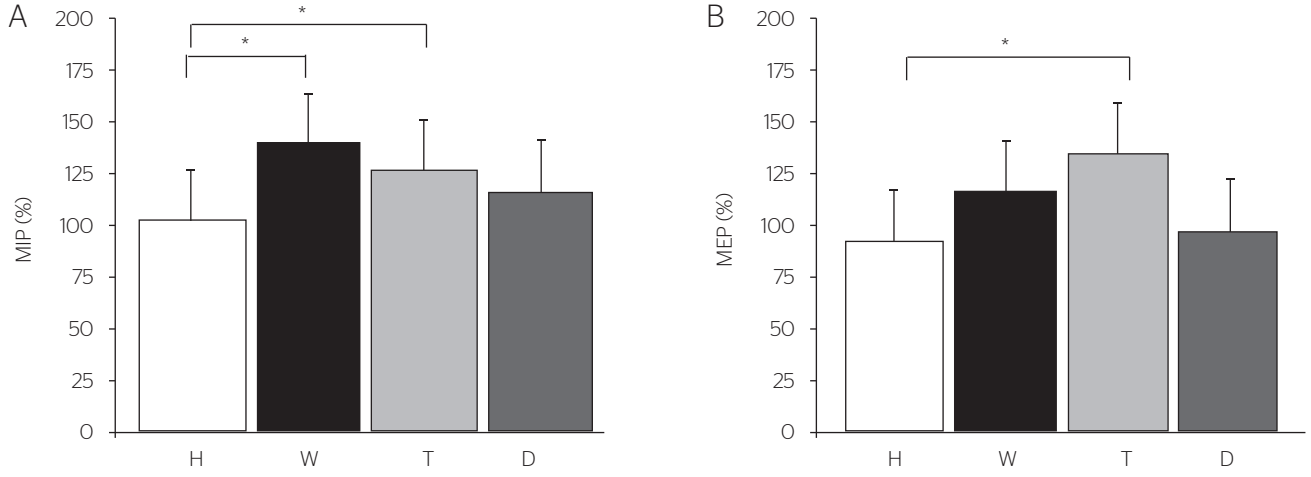
Variables	Mean±SD n=24
Gender	
Male (%)	15 (62.5)
Anthropometric variables	
Age (years)	10.5±1.53
Height (cm)	138.0±0.08
Body mass (kg)	34.6±9.07
BMI Absolute	17.92±2.84
Percentile	54.25±31.14
Spirometry	
FEV_1 (L)	1.80±0.62
(%)	93.29±29.02
FVC (L)	2.19±0.65
(%)	103.78±26.12
FEV_1/FVC	0.81±0.11
$FEF_{25-75\%}$ (L)	1.94±1.07
(%)	78.04±39.63
Manovacuometry (cmH_2O)	
MIP	92.1±22.8
MEP	98.9±24.5

BMI: Body Mass Index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FEF: force expiratory volumen; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; SD: standard deviation

represent the actual conditions of ventilatory muscles in our population.

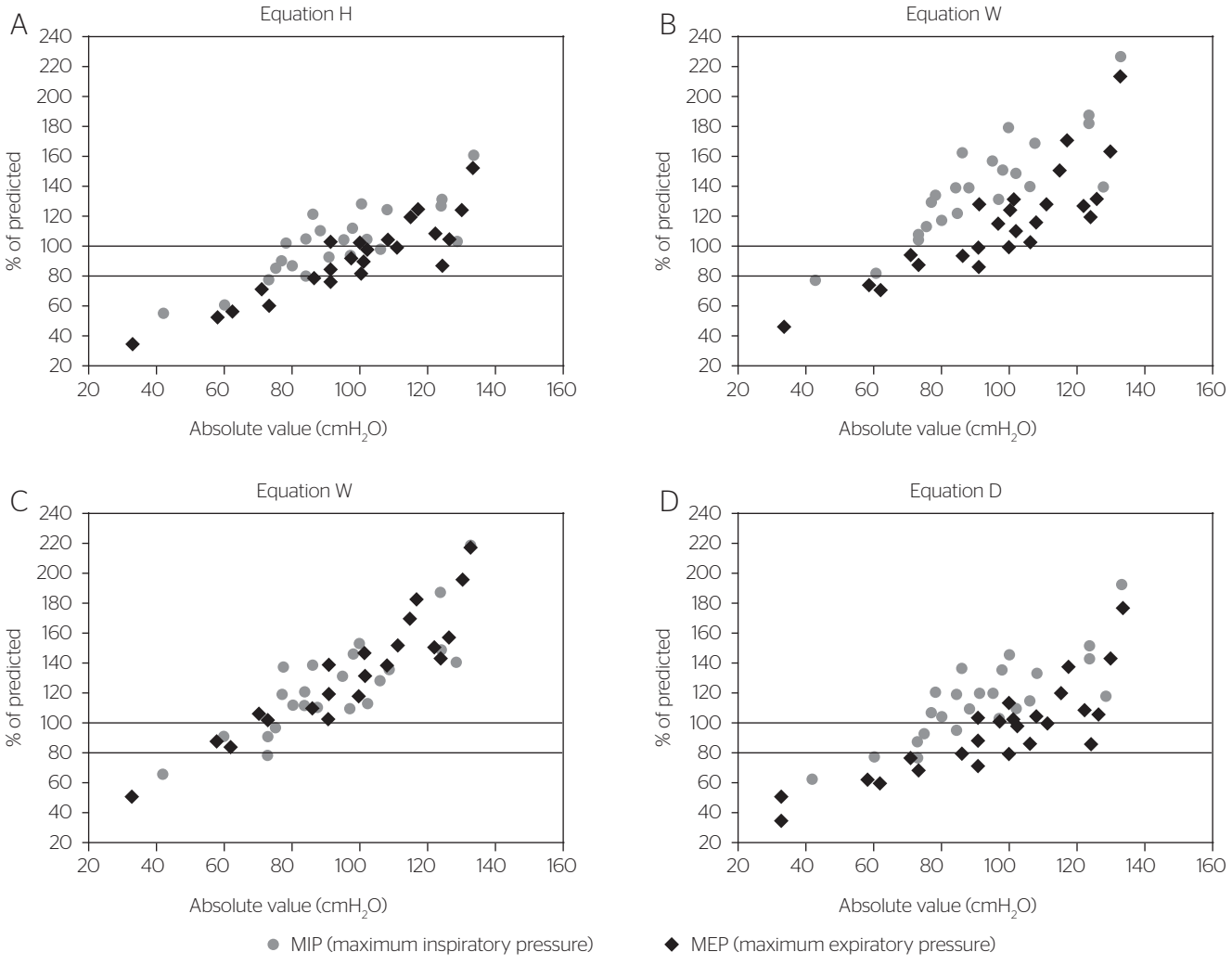
A previous study[16] assessed healthy Brazilian children and showed significant differences between mean values obtained by them in the tests compared to MIP and MEP means values established in international equations[17], rather than other equations[11,13]. However, it is worth noting the small sample for a study with healthy individuals and the comparison between mean values without normalization for each equation. ATS recommends the generation of reference values for the spirometric patterns of each region[18]. Ventilatory muscle strength can also be influenced by demographic differences, supporting the hypothesis that a distinct equation for each population is the ideal.

Moreover, studies about lung function also showed significant differences in the prediction of spirometric variables when using reference equations[19,20] and attributed them to many factors, including sample selection criteria, use of different equipment and techniques, and biological differences between populations[16,19,20]. Overestimation of



MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure;
*p<0.05. H: Heinzmann *et al.*[14]; W: Wilson *et al.*[11] ;T: Tomalak *et al.*[12]; D: Domenèch-Clar *et al.*[13]

Figure 1. Comparison between prediction values by different reference equations for maximum inspiratory pressure (A) and maximum expiratory pressure (B).



MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure;
H: Heinzmann *et al.*[14]; W: Wilson *et al.*[11]; T: Tomalak *et al.*[12]; D: Domenèch-Clar *et al.*[13]. For a better visualization, the results of MIP (absolute) were expressed as positive values in a range of 80 to 100% of the prediction.

Figure 2. Absolute values and percentual of predicted values for maximum inspiratory pressure and maximum expiratory pressure obtained by standardization with different equations

ventilatory muscle strength using international equations may also be related to the distinct prediction variables used in each study for maximal respiratory pressures, once the way they influence results may also vary. Wilson *et al.*[11] showed that body mass and age, for MIP and MEP respectively, were the only variables presenting predicted values for both genders. Tomalak *et al.*[12], on the other hand, attested that age was the only variable that could influence results. Domènech-Clar *et al.*[13] used age, height and body mass to establish MIP in both genders and MEP among males, while among females only age was considered for MEP.

In contrast, a study conducted with Brazilian children considered height and body mass to predict MIP, and body mass and age to predict MEP[14]. Besides that, international studies have shown a lower prediction power (R^2) (9–51%) when compared to the national equation (46–58%).

Another important factor to justify differences in value estimative is that ethnics and skin color have not been considered in the evaluation of some studies because samples were homogeneous, including only Caucasian[11] or same-origin[13] individuals. Ethnic origin has been cited in previous studies as a potential factor influencing results of ventilatory muscle strength[21,22]. Although our study included Brazilian children from various ethnic origins, it did not influence the results of maximal pressure significantly[14]. On the other hand and despite ethnics, different social, economic and cultural contexts involving the subjects may also interfere in results, which mean that equations from other countries do not represent global characteristics of children and adolescents, especially considering the interracial and heterogeneous features of the Brazilian people.

Although the inclusion of malnourished patients in our sample may have influenced results, most subjects presented normal nutritional values. In addition, the study of equation H[14] showed that even with healthy children and adolescents, or those presenting preserved nutritional profile, international equations tend to overestimate maximal respiratory pressures, which means that this factor is not likely to be relevant. Therefore, the use of a national and current equation can better represent and quantify the conditions of ventilator muscles in children and adolescents with different clinical pictures, avoiding overestimation of results.

Despite the constant use of such method in the assessment and follow-up of CF patients, there is no consensus regarding the expected results of ventilatory muscle strength[1,4,5]. In our study, the use of international equations led to the classification of MEP and MIP above normality in 30% more children compared to the standardization using the national one. Also, international equations pointed out maximal respiratory pressures as decreased in 50% less patients, for they would identify 8% for MIP and 15% for MEP, on average, while the national equation would classify as 16.6 and 29.1%, respectively.

These findings show that international equations may show a lower rate of children presenting weakening in ventilatory muscles, which delays the diagnosis of potential changes and, consequently, the establishment of treatment, thereby causing patients to be referred to muscle strengthening programs too late, when degrees of muscle weakening are advanced. It is worth emphasizing that the sample with CF patients was relatively healthy as to lung function and nutritional status probably due to the low mean age and periodical follow-up.

CONCLUSION

The standardization of ventilatory muscle strength values in CF children and adolescents by international equations tend to overestimate maximal pressure values. We recommend caution by health professionals when standardizing and interpreting results based on different reference values, being necessary an individual assessment of each equation to be used. National and current equation may help to reflect actual conditions of ventilatory muscles in Brazilian patients, helping to identify clinical pictures of ventilatory muscle weakening more accurately.

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