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Prediction of peak oxygen uptake using the modified shuttle test in children and adolescents with cystic fibrosis

Fernanda M. Vendrusculo PT, PhD | João P. Heinzmann-Filho PT, PhD | Natália E. Campos PT | Mailise F. Gheller | Ingrid S. de Almeida | Márcio V. F. Donadio PT, PhD

Laboratory of Pediatric Physical Activity, Centro Infant, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Rio Grande do Sul, Brazil

Correspondence
Marcio V. F. Donadio, Laboratory of Pediatric Physical Activity, Centro Infant, Av. Ipiranga, 6690, 2° andar, Porto Alegre, Rio Grande do Sul, CEP 90610-000, Brazil.
Email: mdonadio@pucrs.br

Abstract

Background: Several tests may be used to assess exercise intolerance in cystic fibrosis (CF), including the gold standard cardiopulmonary exercise test (CPET) and the Modified Shuttle Test (MST).

Objective: To evaluate the use of the MST as a predictor of peak oxygen uptake (VO_2peak) and to compare VO_2peak and maximal heart rate (HRmax) obtained in both tests.

Methods: Cross-sectional study including individuals with CF aged between 6 and 20 years old. Participants who were unable to perform the tests and/or presented signs of pulmonary exacerbation were excluded. Demographic, anthropometric, clinical and spirometric values were collected. CPET and the MST were performed in two consecutive outpatient visits. HRmax, peripheral oxygen saturation, dyspnea, and VO_2peak measured and estimated were compared.

Results: Twenty-four patients, mean age 15.7 ± 4.2 years and FEV_1 (% predicted) 76.4 ± 23.8, were included. Mean values of HRmax (bpm) and HRmax in percent of predicted (HRmax%) were lower ($P = 0.01$) in the MST (171.6 ± 14.5 and 87.1 ± 7.5) compared to CPET (180.9 ± 10.0 and 91.9 ± 5.4). However, there was no significant differences between tests in the variation (delta) for HRmax and HRmax% ($P = 0.17$). A strong correlation ($r = 0.79$; $P < 0.0001$) was found between distance achieved (MST) and VO_2peak (CPET). The regression model to estimate VO_2peak resulted in the following equation: $VO_2(mL \cdot kg^{-1} \cdot min^{-1}) = 20.301 + 0.019 \times$ MST distance (meters). There was no difference ($P = 0.50$) between VO_2peak measured (CPET) and estimated by the equation.

Conclusion: The MST may be an alternative method to evaluate exercise capacity and to predict VO_2peak in children and adolescents with CF.

KEYWORDS
adolescent, child, cystic fibrosis, exercise testing, exercise tolerance

1 | INTRODUCTION

Cystic fibrosis (CF) is a multisystemic disease characterized by progressive loss of pulmonary function and consequent physical exercise intolerance.[1] Higher levels of physical activity have been associated with a lower decline in lung function, a greater participation in activities of daily living and a reduction in hospital admissions.[2,3] In addition, studies have shown that exercise capacity correlates with survival in patients with CF.[4–8] Thus, the evaluation of exercise tolerance may be a useful tool to help determining disease prognosis, accurately prescribing physical exercise[9] and evaluating response to treatment.[10]

The assessment of exercise capacity is recommended to be performed annually in patients with CF.[11] The main outcome of aerobic capacity is the peak oxygen uptake (VO_2peak), defined as the maximum amount of oxygen that can be absorbed during exercise.[9] Cardiopulmonary exercise testing (CPET) is considered the gold standard for the assessment of physical fitness, evaluating the interaction of cardiovascular, respiratory, and metabolic systems.[12–14] However, the performance of CPET is still not available in many CF centers due to the need of high cost equipment (treadmill or cycle ergometer and a gas analysis system) and highly trained staff.

Thus, the evaluation of exercise capacity through inexpensive and simple field tests, such as the Modified Shuttle Test (MST), may be an alternative method for measuring physical performance.[15,16] The MST consists of 15 levels, in a course of 10 m, where patients walk/run with increasing speeds following an audio signal that represents the level change. Exercise capacity assessment is based on the total distance covered in the end of the test.[10] It is considered a maximum test, since an incremental protocol with increasing speed is used, similar to common CPET protocols, leading subjects to levels close to exhaustion.[10]

Studies have shown a strong correlation between VO_2peak and the performance of children[17] and adults[10] with CF in shuttle tests. In addition, VO_2peak prediction formulas were proposed using the distance achieved on the tests. Previous studies in children and adolescents validated different shuttle tests as a sensitive and specific measure to assess exercise capacity, using both the 10-m shuttle walk with 12 levels and the 20-m shuttle run tests.[17] However, the MST is the mostly common version used, as it presents three extra levels and allow patients to run, contributing to elicit a maximal response.[10] Thus, considering that the MST was validated to assess exercise capacity only in adults,[10] it is still unknown whether VO_2peak can be estimated by the distance achieved on the MST (10 m and 15 levels) in children and adolescents with CF.

Thus, the objective of present study was to evaluate the use of the MST as a predictor of peak oxygen uptake and to compare VO_2peak and maximal heart rate (HRmax) obtained in both MST and CPET. Our working hypothesis was that the distance covered in the MST would be an accurate predictor of peak oxygen uptake measured by CPET in children and adolescents with CF.

2 | METHODS

A cross-sectional study was performed including patients with a confirmed diagnosis of CF, of both sexes, aged 6 years and older, who were regularly monitored at a CF outpatient clinic. Patients with osteoarticular and musculoskeletal abnormalities or unable to perform at least one of the tests were excluded. Moreover, children and adolescents were not recruited to the study at times of CF chest exacerbation, but could later be approached at a time of stability.

The sample size was estimated considering previous data[10] that showed a standard deviation of $10.36\,mL\cdot kg^{-1}\cdot min^{-1}$ for the VO_2peak and 335 m for the distance obtained on the MST. Thus, to identify a minimum correlation of 0.7, with a significance of 0.01 and a power of 0.90, a minimum sample size of 18 individuals was estimated. The study was approved by the Research Ethics Committee of the University under number 52583416.5.0000.5336. All legal guardians and patients over the age of 18 signed the Informed Consent Form. In addition, children and adolescents under the age of 18 signed an assent form. Data were collected from March 2016 to November 2017.

Data collection procedures were performed at the Laboratory of Pediatric Physical Activity (Infant Center—PUCRS). The CPET and MST were performed in two consecutive visits before the appointment, and spirometry was performed during the appointment following the outpatient clinic routine. In addition, clinical and genetic data including the type of mutation, presence of pancreatic insufficiency and chronic colonization by *Pseudomonas aeruginosa* (PA) were collected. Chronic colonization by PA was defined as the persistent presence of the bacterium in the oropharyngeal swab or sputum samples for at least 6 months or in three consecutive collections.[18]

2.1 | Anthropometric data

Weight and height measurements were performed in triplicate or until two identical values were obtained. The weight measurement was performed in orthostasis, with the minimum of clothing and without footwear, through a digital scale (G-tech, Glass 1 FW, Rio de Janeiro, Brazil) previously calibrated with 100 g precision. The height was obtained through a portable stadiometer (AlturaExata, TBW, São Paulo, Brazil) with a precision of 1 mm, with participants barefoot, feet parallel, ankles joined and arms extended along the body.[19] The absolute body mass index (BMI) was calculated by the relationship between the weight in kilograms and the height in meters raised to the square (Kg/m^2). The WHO Anthroplus program was used to calculate the *z*-score.[20]

2.2 | Cardiopulmonary exercise testing

The test was performed following the recommendations of the American Thoracic Society and American College of Chest Physicians.[21] The evaluation was performed in a computerized system (Aerograph, AeroSport®), coupled to a gas analyzer (VO2000, MedGraphics®) using an ergometric treadmill (KT-10400, Inbramed®, Brazil). The variables collected during the test included VO_2peak, carbon dioxide production (VCO_2), maximal ventilation (VEmax), respiratory exchange ratio (RER), ventilatory equivalents for oxygen consumption (VE/VO_2) and for carbon dioxide production (VE/VCO_2) and maximum heart rate (HRmax).

To perform the test, a ramp protocol was used, adapted according to a previous study.[22] Participants were asked to walk for 2 min to adapt to the treadmill, with a speed of 3 km/h and no inclination. After that, there were increments in the speed of 0.5 km/h every minute, with a fixed slope of 3% until the test was finished.[22] All patients were encouraged to keep pace until exhaustion or the onset of signs and/or limiting symptoms (dyspnea, leg pain, and/or dizziness). In order to consider the test as maximum, at least three of the following criteria should be observed: exhaustion or inability to maintain the required speed, respiratory exchange ratio >1.10, HRmax > 85% of the heart rate (HR) estimated by the formula 208 − 0.7 × age[23] and the presence of a plateau on VO_2.[24,25] Aerobic capacity was calculated as the VO_{2peak} over the last 30 s of the test and was expressed corrected for body weight ($mL \cdot kg^{-1} \cdot min^{-1}$).

At beginning and end of the test, HR and peripheral oxygen saturation (SpO_2) data were collected through a pulse oximeter (Nonin®, Minneapolis, MN), blood pressure was measured using a sphygmomanometer (BIC, Itupeva, Brazil) and the subjective perception of dyspnea and fatigue of legs were evaluated through the Modified Borg scale. HR and SpO_2 were monitored throughout the CPET protocol.

2.3 | Modified shuttle test

MST was performed as described by Bradley et al.[10] The modified test has 15 levels and patients should walk/run with increasing speeds, in a course of 10 m delimited by two cones that must be circumvented by the patient. An audio signal is an integral part of the test that represents the level change, as well as the increase of the patient's speed during the test. The test protocol begins with an average velocity of 0.5 m/s (level 1), followed by an increment of 0.17 m/s at each subsequent level and each level in the test lasts for 1 min. The patients were followed up by a physiotherapist during the first minute in order to adapt to the rhythm of the audio signal. At the end of each level, a standardized verbal incentive was offered ("good job, keep going, you are doing well"). The patients were also told to go a little faster and were reminded that they were permitted to run at any time during the test. The test was completed when participants stated that they were unable to continue the test, lost the rhythm of the audio signal for two consecutive times, or reached the maximum distance of 1500 m.

Before the start of the test and immediately at the end, HR and SpO_2 (Nonin®, Minneapolis, MN), blood pressure (BIC sphygmomanometer, Itupeva, Brazil) and the modified BORG score for dyspnea and fatigue of legs were measured. In addition, HR and SpO_2 were monitored throughout the test. The distance achieved was calculated by counting the total number of shuttles at the end of the test and expressed in meters.

2.4 | Lung function

Spirometry was performed following the recommendations of the American Thoracic Society—European Respiratory Society ATS/ERS.[26] The test was performed with patients in orthostatic position, without the use of a nasal clip,[27] using the KOKO spirometer (Louisville, CO). The spirometric parameters evaluated included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1) and forced expiratory flow between 25% and 75% of vital capacity ($FEF_{25-75\%}$). Data were expressed as *z*-score based on an international reference equation.[28]

TABLE 1 Characterization of the study sample

Variables evaluated	*n* = 24
Demographic characteristics	
Age (years)	15.7 ± 4.2
Male, *n* (%)	18 (75)
Anthropometry	
Height (cm)	158.8 ± 18.1
Weight (kg)	50.1 ± 14.8
BMI (absolute)	19.3 ± 2.9
BMI (*z* score)	−0.2 ± 1.0
Genotype	
F508del homozygous, *n* (%)	3 (12.5)
F508del heterozygous, *n* (%)	15 (62.5)
Other mutations, *n* (%)	6 (25)
Chronic colonization	
Pseudomonas aeruginosa, *n* (%)	6 (25)
Pancreatic insufficiency	
Yes, *n* (%)	9 (37.5)
Lung function	
FEV_1 (absolute)	2.4 ± 1.0
FEV_1 (% predicted)	76.4 ± 23.8
FEV_1 (*z* score)	−1.7 ± 2.2
FVC (absolute)	3.2 ± 1.2
FVC (% predicted)	84.8 ± 20.6
FVC (*z* score)	−1.3 ± 1.8
$FEF_{25-75\%}$ (absolute)	2.2 ± 1.3
$FEF_{25-75\%}$ (% predicted)	60.7 ± 32.3
$FEF_{25-75\%}$ (*z* score)	−2.1 ± 1.9

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of vital capacity.
Values expressed as mean ± standard deviation.

2.5 | Statistical analysis

The distribution of variables was evaluated using the Shapiro Wilk test and, as a normal distribution was demonstrated, continuous variables were presented as mean and standard deviation. Categorical variables were presented in absolute and relative frequency. Comparisons between MST and CPET variables were performed with the Student's *t*-test for paired samples. Correlations were assessed using a Pearson linear correlation test. The association between VO_2peak measured on CPET and the distance achieved on the MST was analyzed using a multiple linear regression model. The agreement between the VO_2peak measured on CPET and the VO_2 estimated by the distance obtained on the MST was graphically demonstrated using the Bland-

Altman plot. All analyzes and data processing were performed in SPSS version 18.0 (SPSS Inc.). In all cases, the level of significance adopted was $P < 0.05$.

3 | RESULTS

Twenty four CF patients (75% male) with a mean age of 15.7 ± 4.2 and 62.5% presenting a F508del heterozygous mutation were included. As to lung function, the mean FEV_1 (% predicted) was 76.4 ± 23.8 and FVC 84.8 ± 20.6. The characteristics of the sample are presented in Table 1.

Physiological responses during CPET and the MST were demonstrated in Table 2. The mean level achieved during the MST was 12.2 ± 1.7 and the average distance reached was 968.0 ± 251.7 m. Regarding the variables evaluated on CPET, the mean VO_2peak was 38.3 ± 5.9 $mL \cdot kg^{-1} \cdot min^{-1}$ and the VE was 47.1 ± 14.6 $L\,min^{-1}$. Although a difference of only 9.3 bpm for the HRmax reached and 4.8% for the HRmax as percentage of predicted (HRmax%) were found between tests, the student's *t*-test for paired samples showed significance ($P = 0.01$). The mean HRmax (bpm) achieved was 171.6 ± 14.5 for the MST and 180.9 ± 10.0 for CPET, whereas the mean HRmax% was 87.1 ± 7.5 for the MST and 91.9 ± 5.4 for CPET. On the other hand, no significant differences were found between the two tests in the variation (delta = peak − rest) of HRmax ($P = 0.17$), HRmax% ($P = 0.17$), Borg for dyspnea ($P = 0.22$), and Borg for leg discomfort ($P = 0.33$). These data are shown in Table 3.

A significant and moderate correlation was found between lung function (FEV_1 absolute) and both distance walked on the MST ($r = 0.62$; $P = 0.001$) and VO_2peak measured on CPET ($r = 0.47$; $P = 0.02$). The correlation ($r = 0.79$; $P < 0.0001$) between the distance achieved on the MST and the VO_2peak measured on CPET was significant and strong (Figure 1).

The use of a multiple linear regression model to estimate VO_2peak through the achieved distance on the MST resulted in the following equation, explaining 62.8% of the VO_2peak:

$$VO_2(mL \cdot kg^{-1} \cdot min^{-1}) = 20.301 + 0.019 \times \text{MST distance (m)}$$

$$R^2 = 0.628; \text{Standard error of the estimate} = 3.67$$

TABLE 2 Resting characteristics and physiological responses to exercise testing

Variables evaluated	MST	CPET	*P*-value
Resting			
Heart rate (beats/min)	85.6 ± 17.4	90.5 ± 19.4	0.13
SpO_2 (%)	97.1 ± 2.0	96.7 ± 1.9	0.25
Systolic blood pressure (mmHg)	106.1 ± 14.9	112.6 ± 11.4	0.06
Diastolic blood pressure (mmHg)	67.4 ± 9.5	68.3 ± 7.8	0.64
Borg dyspnea	0.1 ± 0.2	0.2 ± 0.5	0.26
Borg leg discomfort	0.2 ± 0.6	0.2 ± 0.5	0.88
Physiological responses			
MST level	12.2 ± 1.7	-	-
MST distance (m)	968.0 ± 251.7	-	-
VO_2 peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	-	38.3 ± 5.9	-
VE peak ($L\,min^{-1}$)	-	47.1 ± 14.6	-
VE/VO_2 peak ($L\,min^{-1}$)	-	23.2 ± 4.4	-
VE/VCO_2 peak ($L\,min^{-1}$)	-	22.5 ± 4.3	-
RER	-	1.1 ± 0.7	-
Max heart rate (beats/min)	171.6 ± 14.5	180.9 ± 10.0	0.01
Max heart rate (% predicted)	87.1 ± 7.5	91.9 ± 5.4	0.01
End SpO_2 (%)	93.7 ± 4.3	94.4 ± 3.9	0.3
End SpO_2 desaturation *n* (%)	5 (20.8)	3 (12.5)	-
End systolic blood pressure (mmHg)	130.2 ± 22.8	130.0 ± 14.1	0.96
End diastolic blood pressure (mmHg)	74.8 ± 7.5	71.9 ± 8.7	0.3
End Borg dyspnea	4.2 ± 2.8	3.7 ± 3.3	0.33
End Borg leg discomfort	4.0 ± 2.4	4.5 ± 3.0	0.30

CPET, cardiopulmonary exercise testing; MST, modified shuttle test; RER, respiratory exchange ratio VE, minute ventilation; VE/VO_2, ventilatory equivalent ratio for oxygen uptake; VE/VCO_2, ventilatory equivalent ratio for carbon dioxide production; VO_2, maximal oxygen uptake.
Values expressed as mean ± standard deviation.

TABLE 3 Comparison of the difference (delta) between peak and resting values of maximum heart rate and subjective perception of exhaustion

Variables evaluated	MST	CPET	*P*-value
Delta heart rate (beats/min)	85.1 ± 21.2	90.5 ± 13.7	0.17
Delta heart rate (% predicted)	43.2 ± 10.8	45.9 ± 7.1	0.17
Delta Borg dyspnea	4.1 ± 2.7	3.5 ± 3.2	0.22
Delta Borg leg discomfort	3.8 ± 2.2	4.3 ± 2.9	0.33

CPET, cardiopulmonary exercise testing; MST, modified shuttle test. Values expressed as mean ± standard deviation.

The agreement of VO_2peak measured on CPET with VO_2 estimated by the equation presented in this study was represented by the Bland-Altman plot (Figure 2). In addition, there was no significant difference ($P = 0.50$) between VO_2peak values measured on CPET and estimated by the equation (Figure 3).

4 | DISCUSSION

The results of present study confirm the hypothesis that the MST may be used as an alternative predictor of peak oxygen uptake in children and adolescents with CF, considering the strong correlation between the distance achieved on the MST and the VO_2peak measured on CPET, as well as the similarity between the measured and estimated VO_2peak using the MST. To the best of our knowledge, this is the first study to validate the use of the MST (15 levels/10 m) in children and adolescents with CF. Although CPET is considered the gold standard for the evaluation of exercise capacity, the test is not available in many CF reference centers. Thus, the MST is suggested as an alternative to assess physical fitness in this population.

Regarding physiological variables evaluated at the end of both MST and CPET, our data corroborate previous studies in children[17] and adults[10] with CF, using shuttle tests, which also did not demonstrate significant differences in blood pressure, SpO_2 and Borg for dyspnea and for leg discomfort, suggesting that shuttle tests present similar responses to the gold standard (CPET), and may be considered as maximum tests. However, in our study, we found a significant difference in HRmax and HRmax% compared to CPET. Nevertheless, the lower values achieved in the MST represent an absolute mean difference of only 9.3 bpm, which may not be a clinically relevant difference. In addition, the mean HRmax% reached in the MST was greater than 85%, which is usually the cut-off required to consider an exercise test as maximum.[29] Indeed, no differences were found between tests on the variation (delta) for HRmax and HRmax%. On the other hand, a recent study that evaluated physiological responses of the MST in adults with CF showed that the HRmax obtained in the MST was significantly higher than values achieved on CPET performed in a cycle ergometer.[30] The authors justify this finding by the fact that fast walking or running involves greater muscle mass than pedaling in a cycle ergometer. Anyway, in our study we have used an incremental treadmill protocol that is similar to the MST.

Our results also show a moderate correlation between lung function and both walked distance on the MST and VO_2peak reached on CPET, which was also demonstrated in the original MST study.[10] Doeleman et al[31] demonstrated a strong association between distance walked on the MST and lung function only in adult patients presenting a $FEV_1 < 67\%$ of predicted, suggesting that lung function may only be considered a good predictor of exercise capacity in patients with moderate to severe disease. Another study also showed that only 50% of the variation in VO_2peak is explained by FEV_1.[32] In addition, it is already known that the limitation of exercise capacity in CF patients may be influenced by several factors, including nutritional status, muscle mass, strength and resistance of respiratory muscles, as well as lung function.[33,34] In our study, patients presented a mild impairment of lung function, which may help to explain the absence of a strong correlation with exercise capacity variables.

Previous studies[10,17,35] have shown a strong correlation between the distance achieved on shuttle tests and VO_2peak measured by

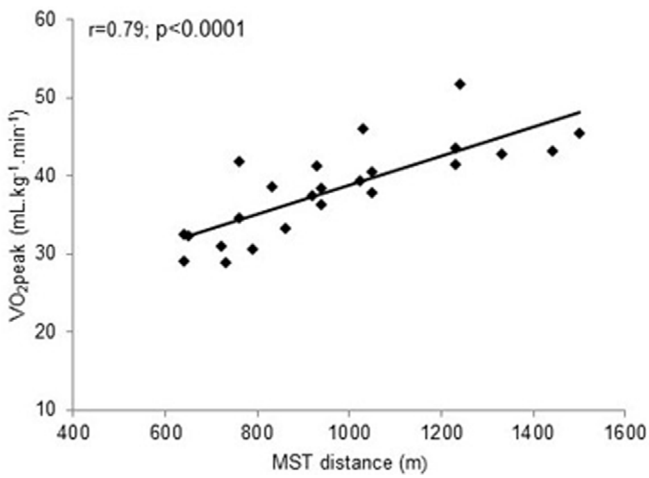

FIGURE 1 Correlation between the performance on the modified shuttle test (MST) and peak oxygen consumption (VO_2peak) measured during cardiopulmonary exercise testing

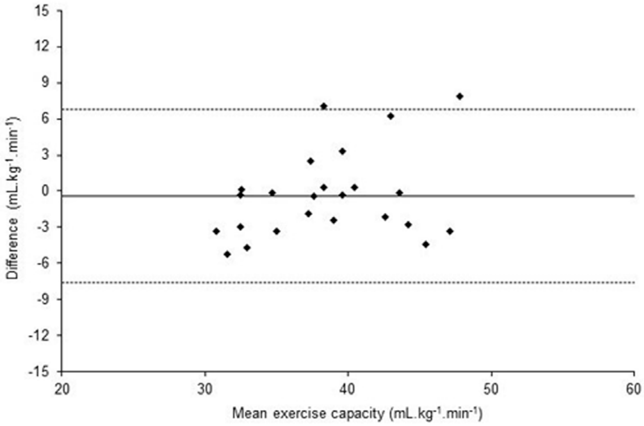

FIGURE 2 Comparison of measured and calculated methods of estimating exercise capacity for the modified shuttle test (Bland and Altman plot). Difference ($mL \cdot kg^{-1} \cdot min^{-1}$) = measured exercise capacity − calculated exercise capacity

CPET. Moreover, there are prediction equations available to estimate VO_2peak through the distance reached in the test, although there is a variation in the shuttle test used.[10,17,35] In children with CF, only the study by Selvadurai et al[17] evaluated this association, but the tests used were the 10-m shuttle walk with 12 levels and the 20-m shuttle run test. Thus, to the best of our knowledge, this is the first study to demonstrate the correlation between the distance achieved on the MST (10 m and 15 levels) and VO_2peak measured by CPET, besides generating a prediction equation for children and adolescents with FC using the distance achieved on the test.

The results found in this study have shown that there was no significant difference between VO_2peak estimated by the proposed equation and VO_2peak measured by CPET. Furthermore, a good agreement between both tests was observed, showing that the maximum difference between measured VO_2peak and estimated VO_2peak was $7.8\ mL \cdot kg^{-1} \cdot min^{-1}$. This agreement has already been demonstrated by Selvadurai et al,[17] although using the 20-m shuttle run, in which the maximum difference was approximately 5 mL/kg min.

One of the limitations of present study was the impossibility of direct measuring gases during the MST, which prevented the comparison of several variables between tests, including VO_2peak, minute ventilation, respiratory equivalents and respiratory exchange rate. However, the equation generated in our study was used to predict VO_2peak through the distance walked and demonstrated an agreement between estimated (MST) and measured (CPET) values.

In conclusion, results of present study demonstrate that it is possible to predict VO_2peak using the MST. Thus, considering the costs and logistics to perform CPET, the use of a simple and non-expensive field test such as the MST may be an alternative for the evaluation and monitoring of exercise capacity in children and adolescents with CF.

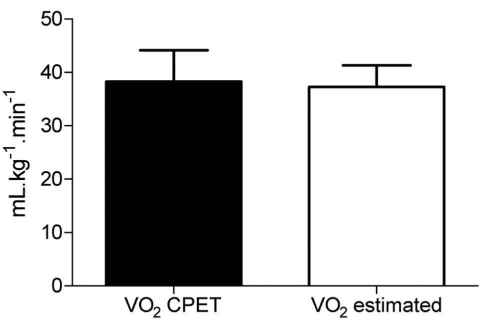

FIGURE 3 Comparison of peak oxygen consumption (VO_2peak) measured during cardiopulmonary exercise testing (CPET) and estimated by the modified shuttle test (MST) equation

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ORCID

Márcio V. F. Donadio http://orcid.org/0000-0001-8836-9109

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