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Peripheral muscle strength is associated with aerobic fitness and use of antibiotics in patients with cystic fibrosis

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Abstract

Aims: Individuals with cystic fibrosis (CF) may develop muscle abnormalities, although little is known on its clinical and functional impact. This study aimed to evaluate the association of peripheral muscle strength with aerobic fitness, habitual physical activity, lung function and the use of antibiotics (ATB) in patients with CF.

Methods: A cross-sectional study where individuals aged ≥6 years underwent peripheral muscle strength evaluation (biceps, quadriceps and hamstrings) and performed a cardiopulmonary exercise test. Demographic, anthropometric, genetic, lung function and total days of ATB use within 1 year of tests were also collected.

Results: Correlation was found for biceps ($r = .45$; $P = .002$) strength with the peak oxygen consumption (VO_2peak). Muscle strength (biceps and quadriceps) also correlated with the ventilatory equivalent for oxygen consumption (V_E/VO_2) at anaerobic threshold (AT) and with the ventilatory equivalent for carbon dioxide production (V_E/VCO_2) both at AT and peak exercise. Negative correlations were found for quadriceps ($r = -.39$) and hamstrings ($r = -.42$) with the total days of ATB use in the following year. Patients needing to use ATB presented lower biceps strength ($P = .05$) and individuals with VO_2peak lower than 37 $mL \cdot kg^{-1} \cdot min^{-1}$ presented lower muscle strength for both biceps ($P = .01$) and quadriceps ($P = .02$).

Conclusions: The results have shown that peripheral muscle strength is associated with aerobic fitness and the use of antibiotics in patients with CF.

1 | INTRODUCTION

Cystic fibrosis (CF) is a disease caused by a defect in the CF transmembrane conductance regulator gene (CFTR), characterised by progressive loss of lung function and exercise intolerance, mainly as a consequence of airway obstruction, caused by abnormal production of mucus, and the presence of chronic inflammation and recurrent infections.[1,2] Several factors have been associated with a worse prognosis in CF individuals, including malnutrition, female sex, increased number of exacerbations and presence of chronic airway colonisation.[3-6] Moreover, lung function decline, in addition to exercise intolerance, are identified as determinants of mortality.[7,8]

The progressive decrease in aerobic fitness, combined with physical inactivity and sedentary lifestyle, starts a vicious cycle in which worsening dyspnoea is associated with increasingly less physical efforts, also compromising peripheral muscle strength and leading to plain myopathy.[9,10] Evidence shows that individuals with CF do not express the CFTR protein in the muscles, leading to metabolic and contractile cellular changes.[11,12] In addition, studies show that patients with CF, when compared with healthy individuals, have

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reduced strength[9,13,14] and oxidative capacity[15] in the peripheral muscles, as well as reduced muscle mass.[16] Other factors (eg, systemic inflammation, oxidative stress, frequent exacerbations, use of systemic corticosteroids and malnutrition) also contribute to skeletal muscle atrophy and weakness in CF patients.[10] The strength of peripheral muscles is an important determinant of physical capacity, as data indicate that subjects with CF presenting reduced muscle mass and nutritional depletion show a decline in lung function, which may further accentuate exercise intolerance.[17-19]

Although there are few evidence showing an association between peripheral muscle strength and exercise capacity, both evaluated through oxygen consumption[20] and the distance covered in the 6-minute walk test (6MWT),[9,21] no study has assessed the association of muscle strength with important physical fitness variables, including cardiorespiratory parameters at the anaerobic threshold (AT) and peak exercise, as measured by cardiopulmonary exercise testing (CPET). Furthermore, to date, there are no studies showing whether there is an association between peripheral muscle strength and morbidity indicators, such as the use of antibiotics (ATB). Thus, the aim of this study was to assess the association of peripheral muscle strength with aerobic fitness, habitual physical activity, lung function and the use of ATB in patients with CF.

What's known

- The strength of peripheral muscles may influence physical capacity, and the lack of expression of the CFTR protein in the muscles leads to metabolic and contractile cellular changes in patients with cystic fibrosis.
- However, the association of peripheral muscle function with exercise capacity and morbidity in patients with cystic fibrosis is not fully understood to date.

What's new

- This study shows that peripheral muscle strength (biceps, quadriceps and hamstrings) is associated with aerobic fitness and use of antibiotics in patients with cystic fibrosis.
- Results highlight the importance of monitoring muscle strength in patients with cystic fibrosis.

2 | METHODS

A cross-sectional study was carried out. Patients with a genetic diagnosis of CF, of both sexes, aged ≥6 years and undergoing regular follow-up at a CF referral centre at Hospital São Lucas (PUCRS) were included. Individuals with haemodynamic instability, exacerbation of respiratory symptoms on the day of the tests and presenting any osteoarticular or musculoskeletal abnormalities interfering in the performance of tests were excluded. The sample size calculation was performed considering peak oxygen consumption (VO_2peak) as the main variable of interest and its relationship with peripheral muscle strength. Thus, adopting a significance index of 0.05, a power of 90% and aiming to detect a minimum correlation of 0.45 between variables, a sample size of approximately 45 participants was estimated.

Patients were recruited on the same day of the outpatient clinic visit and underwent peripheral muscle strength evaluation (biceps, quadriceps and hamstrings) and CPET. Demographic, anthropometric, genetic and clinical data were also collected, in addition to lung function, habitual physical activity and the total number of days of ATB use in the period of 1 year following the tests.

Anthropometric data were measured in triplicate. The weight measurement was performed in orthostasis using a digital scale (G-tech, Glass 1 FW, Rio de Janeiro, Brazil) previously calibrated with 100 grams precision. The height was obtained through a portable stadiometer (AlturaExata, TBW, São Paulo, Brazil) with a precision of 1 mm, and participants were barefoot.[22] The body mass index (BMI) was calculated and expressed as absolute (kg/m^2) and z-score values.

The evaluation of peripheral muscle strength was performed by measuring the maximum isometric strength of the biceps, quadriceps and hamstrings, using a manual dynamometer push/pull (Baseline®, Fabrication Enterprises, United States). Individuals were positioned seated, with the hip and knee angled at 90°.[23,24] Measurements were taken on the dominant limb and subjects were always instructed to perform the maximum strength possible against the tension meter positioned just above the respective joint. The best of three repetitions was considered as the peak muscle strength. Data were normalised by dividing the final measurement by the total body weight of each patient and expressed as kilogram force per kilogram of body weight (kgf·kg^{-1}).

CPET was performed according to the recommendations of the American Thoracic Society and American College of Chest Physicians.[25] The evaluation was performed using a computerised system (Aerograph, AeroSport®, United States) coupled to a gas analyser (VO_{2000}, MedGraphics®, United States) and using an ergometric treadmill (KT-10400, Inbramed®, Brazil). The variables collected included VO_2peak, carbon dioxide production (VCO_2), minute ventilation (V_E), respiratory exchange rate (RER), ventilatory equivalents for oxygen consumption (V_E/VO_2) and for carbon dioxide production (V_E/VCO_2) and maximum heart rate (HRmax). The test was performed using an adapted ramp protocol based on a previous study.[26] The subjects were instructed to walk for 2 minutes to adapt to the treadmill, with a speed of 3 km/h and without inclination. Afterwards, there were increments in speed of 0.5 km/h every minute, with a fixed slope of 3% until the end of the test.[26] All subjects were encouraged to keep pace until exhaustion or the onset of signs and/or limiting symptoms (dyspnoea, leg pain and/or dizziness). Subjective perception of dyspnoea was evaluated using the Modified Borg Scale. The AT was determined using the criteria of an increase in V_E/VO_2 with no correspondent increase in V_E/VCO_2. Breathing reserve was calculated as the difference between the maximum voluntary ventilation (MVV) at rest and the peak V_E, and was reported as a percentage of MVV

[1 − (V_E/MVV) × 100]. To consider the test as maximum, at least three of the following criteria should be observed: inability to maintain the required speed, RER > 1.05, HRmax > 85% of the HR estimated by the formula 208 − 0.7 × age[27] and the presence of a plateau in VO_2.[28,29]

The habitual physical activity was assessed using the Physical Activity Questionnaire (PAQ), in the short version.[30] Participants up to 15 years old completed the PAQ-C and were classified as active (score ≥3) or sedentary (score <3). This score represents an average of points, which takes into account physical activity practiced at different times, including children's free time, school holidays, physical education class and the type of activity performed on each day of the last week. Participants over 15 years old completed the PAQ-A, which addresses questions about the past 7 days, assessing the frequency and time spent on moderate and vigorous activities, as well as walking and the time spent sitting. The outcome of this instrument is based on the time spent (minutes) in these respective activities. Individuals who practiced at least 150 minutes of moderate intensity physical activity were classified as active.

Lung function was assessed using a KOKO spirometer (Louisville, CO, United States). The parameters evaluated were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio and forced expiratory flow between 25% and 75% of FVC ($FEF_{25\text{-}75\%}$). All procedures were performed following the criteria established by the American Thoracic Society/European Respiratory Society - ATS/ERS.[31] Data were expressed in absolute values and as a percentage of the predicted, based on an international reference equation.[32]

The study was performed following the Helsinki Declaration and approved by the Research Ethics Committee of the University (number 52583416.5.0000.5336). All legal guardians and participants over the age of 18 signed an informed consent form. In addition, children and adolescents up to 18 years of age signed an assent form.

The normality of the data was assessed using the Kolmogorov-Smirnoff test. Continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on its symmetry. Categorical data were presented in absolute and relative frequency. Spearman's correlation test was used to assess the relationship between peripheral muscle strength, CPET data and the use of ATB (patients who needed ATB in the following year). The coefficient of correlation (r) was used to classify correlations as weak (between 0 and 0.4), moderate (≥0.4 and <0.7) and strong (≥0.7). The comparisons of peripheral muscle strength (biceps, quadriceps and hamstrings) between individuals separated according to ATB use, lung function (FEV_1 < 80 or ≥80% of predicted), aerobic fitness (the median value of VO_2peak in the sample was used: <37 or ≥37 mL·kg^{-1}·min^{-1}) and habitual physical activity (sedentary or active) were performed using the independent Student's *t* test. In addition, a forward stepwise multivariate linear regression model was used to test the influence of muscle strength and clinically relevant variables (age, sex, genetic mutation, BMI, chronic colonisation by *Pseudomonas aeruginosa*, FEV_1 and muscle strength) on aerobic fitness (VO_2peak). All analyses and data processing were performed using the SPSS version 18.0 program (SPSS Inc, USA). In all cases, the level of significance adopted was $P \le .05$.

3 | RESULTS

Forty-seven CF patients with a mean age of 15.9 ± 6.5 years were included (Figure S1). Regarding lung function, the majority of the sample presented mild-to-moderate lung function impairment (mean FEV_1 80.6 ± 25.2% of predicted). As for habitual physical activity, data from both PAQ-A and PAQ-C indicated that 71.4% of patients were classified as sedentary. The characteristics of the sample are shown in Table 1.

Regarding the assessment of exercise capacity (CPET), data indicated a maximum effort, and a mean VO_2 of 36.6 ± 7.0 mL·kg^{-1}·min^{-1} at peak exercise was found. Both CPET variables and peripheral muscle strength evaluation (kgf·kg^{-1}) for biceps, quadriceps and hamstrings are presented in Table 2. When peripheral muscle strength values were correlated with exercise capacity variables, a significant (P = .002) moderate correlation (r = .45) was found between biceps strength and VO_2 at peak exercise. In addition, biceps and quadriceps strength levels presented significant correlations with V_E/VO_2 at the AT and with V_E/VCO_2 at the AT and peak exercise. The correlations between peripheral muscle strength values and CPET variables are shown in Figure 1. Furthermore, significant negative correlations were found between quadriceps (r = −.39) and hamstring (r = −.42) strength with the total days of ATB use in patients who needed antibiotics in the year following the assessments (Figure 2).

Peripheral muscle strength levels were also compared according to the use of ATB and results have shown that patients using ATB in the following year presented a significantly lower biceps strength (Figure 3). In addition, when separating patients by the median value of VO_2peak, individuals with VO_2peak lower than 37 mL·kg^{-1}·min^{-1} have shown a significant decrease in both biceps and quadriceps muscle strength. However, no significant differences were found for peripheral muscle strength when comparing active and sedentary patients (Figure 3), as well as individuals with different lung function values, both using a 80% of predicted FEV_1 cut-off value or separating patients in three (FEV_1 < 60%, between 60%-80%, and >80%) categories (data not shown). In addition, a multivariate linear regression model showed that biceps strength (β = 50.68; SE = 10.8; 95% CI = 28.79-72.57; P < .001) and FEV_1 (β = 0.11; SE = 0.03; 95% CI = 0.046-0.182; P = .002) were the variables that most explained (r^2 = .43) aerobic fitness (VO_2peak).

4 | DISCUSSION

This study sought to assess the association of peripheral muscle strength with exercise capacity, habitual physical activity, lung function and the use of ATB in patients with CF. The results showed that there is an association of peripheral muscle strength with physical

TABLE 1 Characteristics of the study sample

Variables evaluated	n = 47
Demographics	
Age (y)	15.9 ± 6.5
Male, n (%)	33 (70.2)
Anthropometry	
Weight (kg)	47.1 ± 16.3
Height (cm)	154.0 ± 19.2
BMI (kg/m^2)	19.1 ± 3.3
BMI (z-score)	−0.1 ± 0.9
Genotyping	
At least one allele F508del, n (%)[a]	32 (80.0)
Pancreatic insufficiency	
Yes, n (%)	41 (87.2)
Chronic airway colonisation	
Pseudomonas aeruginosa, n (%)	7 (14.9)
Lung function	
FEV_1 (L)	2.3 ± 0.9
FEV_1 (% predicted)	80.6 ± 25.2
FVC (L)	3.0 ± 1.2
FVC (% predicted)	88.9 ± 21.7
FEV_1/FVC (absolute)	0.9 ± 0.1
FEV_1/FVC (% predicted)	89.5 ± 12.7
$FEF_{25-75\%}$ (L·min^{-1})	2.3 ± 1.2
$FEF_{25-75\%}$ (% predicted)	69.7 ± 34.6
Habitual physical activity (min·wk^{-1})[b]	
PAQ-A	
Sitting/lying	930.0 (600.0-1200.0)
Walking	87.5 (0.0-262.5)
Moderate activity	30.0 (0.0-240.0)
Vigorous activity	75.0 (0.0-247.5)
PAQ-C	2.4 (2.0-3.0)

Abbreviations: BMI, body mass index; $FEF_{25-75\%}$, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

[a]n = 40. Values expressed as mean ± standard deviation.

[b]Values expressed as median (interquartile range).

TABLE 2 Cardiopulmonary exercise testing and peripheral muscle strength evaluations

Variables evaluated	n = 47
Cardiopulmonary exercise testing	
Resting	
HR (beats·min^{-1})	90.0 ± 17.9
SpO_2 (%)	97.0 ± 2.0
VO_2 (L·min^{-1})	0.1 ± 0.3
VO_2 (mL·kg^{-1}·min^{-1})	7.3 ± 2.9
Anaerobic threshold	
HR (beats·min^{-1})	152.0 ± 24.8
VO_2 (L·min^{-1})	1.2 ± 0.5
VO_2 (mL·kg^{-1}·min^{-1})	25.7 ± 7.4
VO_2 (%)	70.7 ± 15.4
V_E (L·min^{-1})	27.1 ± 10.5
V_E/VO_2	23.9 ± 4.3
V_E/VCO_2	23.4 ± 3.9
Peak exercise	
HR (beats·min^{-1})	180.0 ± 13.3
SpO_2 (%)	94.5 ± 4.0
VO_2 (L·min^{-1})	1.8 ± 0.8
VO_2 (mL·kg^{-1}·min^{-1})	36.6 ± 7.0
V_E (L·min^{-1})	45.8 ± 17.9
V_E/VO_2	27.4 ± 4.9
V_E/VCO_2	24.8 ± 3.9
RER	1.1 ± 0.1
Breathing reserve (%)	48.2 ± 13.6
Peripheral muscle strength (kgf·kg^{-1})[a]	
Biceps	0.29 (0.25-0.34)
Quadriceps	0.36 (0.31-0.43)
Hamstrings	0.15 (0.12-0.18)

Note: Values expressed as mean ± standard deviation.

Abbreviations: HR, heart rate; RER, respiratory exchange ratio; SpO_2, peripheral oxygen saturation; V_E, minute ventilation; V_E/VCO_2, ventilatory equivalent ratio for carbon dioxide production; V_E/VO_2, ventilatory equivalent ratio for oxygen uptake;VO_2, oxygen uptake.

[a]Values expressed as median (interquartile range).

performance variables, evaluated through CPET, both at AT and peak exercise, and with the use of ATB. Patients with reduced VO_2peak or needing to use ATB presented decreased peripheral muscle strength.

It is already known that patients with CF have lower peripheral muscle strength when compared with healthy individuals.[9,20] Although this muscle weakness has generally been attributed to factors such as reduced levels of physical activity, poor nutrition and chronic inflammation, it may also be related to the intrinsic defect in the skeletal muscle function caused by the lack of CFTR.[12] CFTR is expressed in the sarcoplasmic reticulum of human skeletal muscle and has intrinsic ATPase activity. Mitochondrial abnormalities have been reported in cells with impaired CFTR function,[33,34] which imply that the defective function or expression of the CFTR can disrupt the production and use of energy. Thus, changes in CFTR function and/or expression in the sarcoplasmic reticulum of skeletal muscle can lead to reduced muscle strength and endurance and increased fatigue, causing limitations in exercise capacity.[10] In addition, Meer et al[20] suggest the presence of intrinsic abnormalities in the skeletal

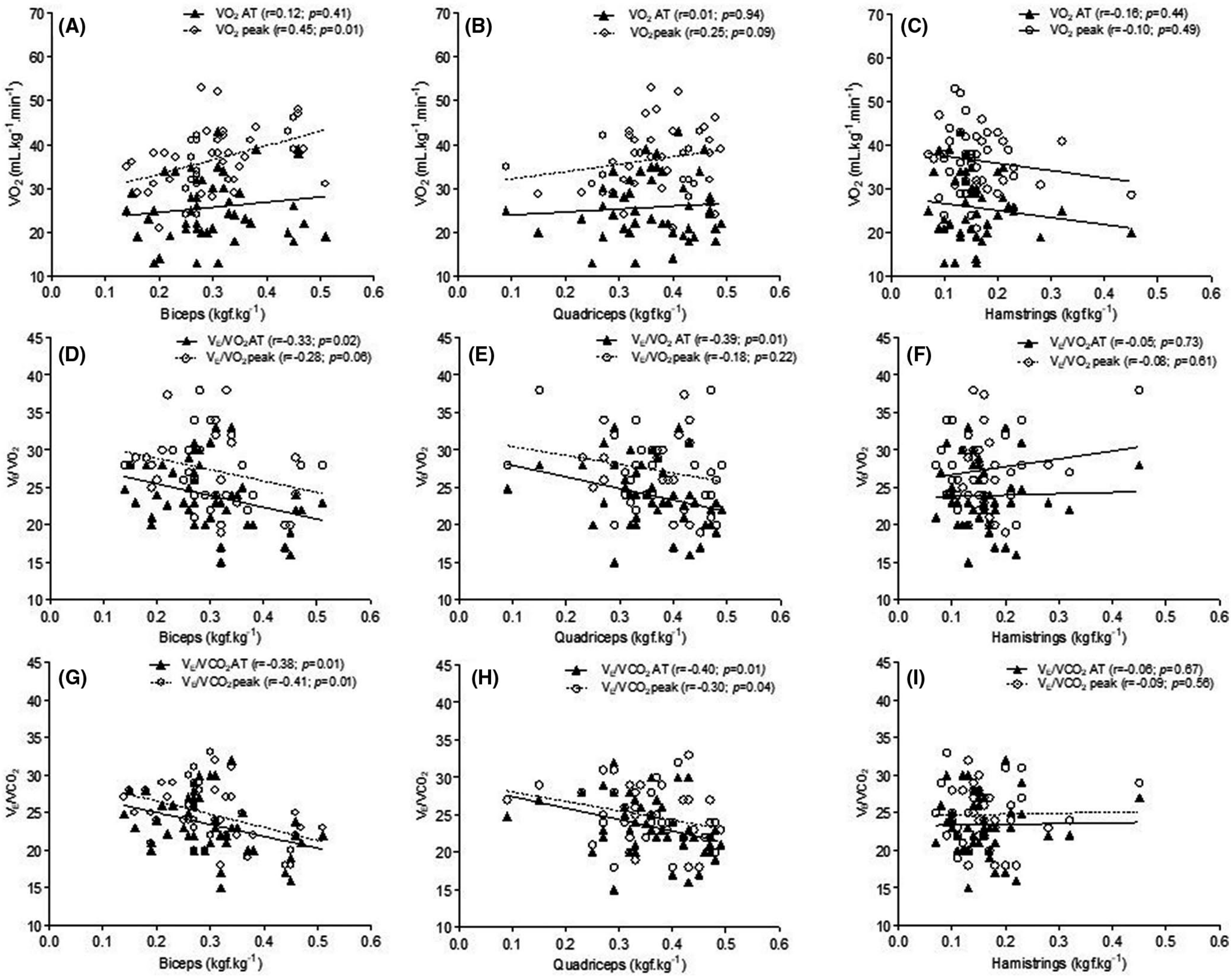

FIGURE 1 Correlation between biceps, quadriceps and hamstrings strength with oxygen consumption (VO_2) in (A), (B) and (C); with ventilatory equivalent for oxygen consumption (V_E/VO_2) in (D), (E) and (F); and with ventilatory equivalent for carbon dioxide production (V_E/VCO_2) in (G), (H) and (I). All correlations are shown both at the anaerobic threshold (AT) and peak exercise. *r*: coefficient of correlation. Level of significance set at $P \leq .05$

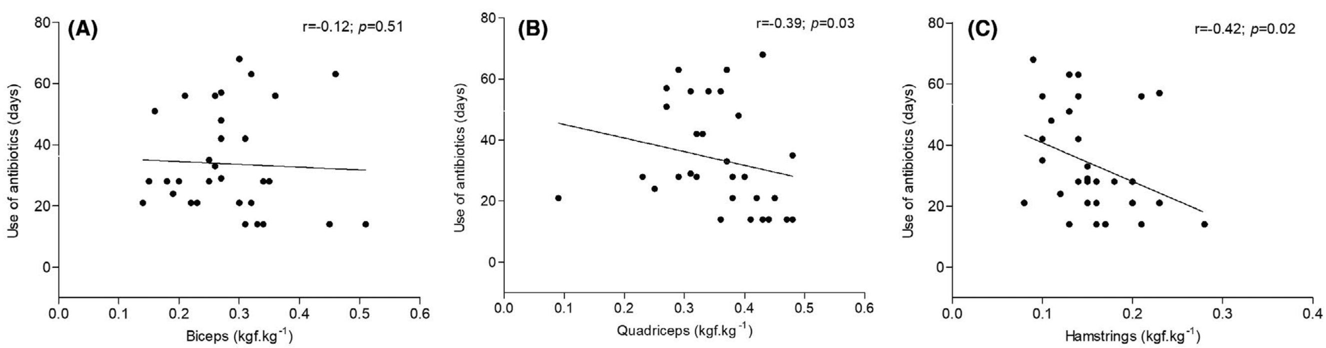

FIGURE 2 Correlation between biceps (A), quadriceps (B) and hamstrings (C) strength with the total days of antibiotics (ATB) use. Level of significance set at $P \leq .05$

muscle of patients with CF, consisting mainly of a decrease in the efficiency of the oxidative synthesis of ATP in the mitochondria, as well as abnormalities in the mechanics of myofibrils. On the other hand, the results by Gruet et al[16] did not indicate intrinsic changes in skeletal muscle in individuals with mild to moderate lung disease, demonstrating only changes in muscle mass.

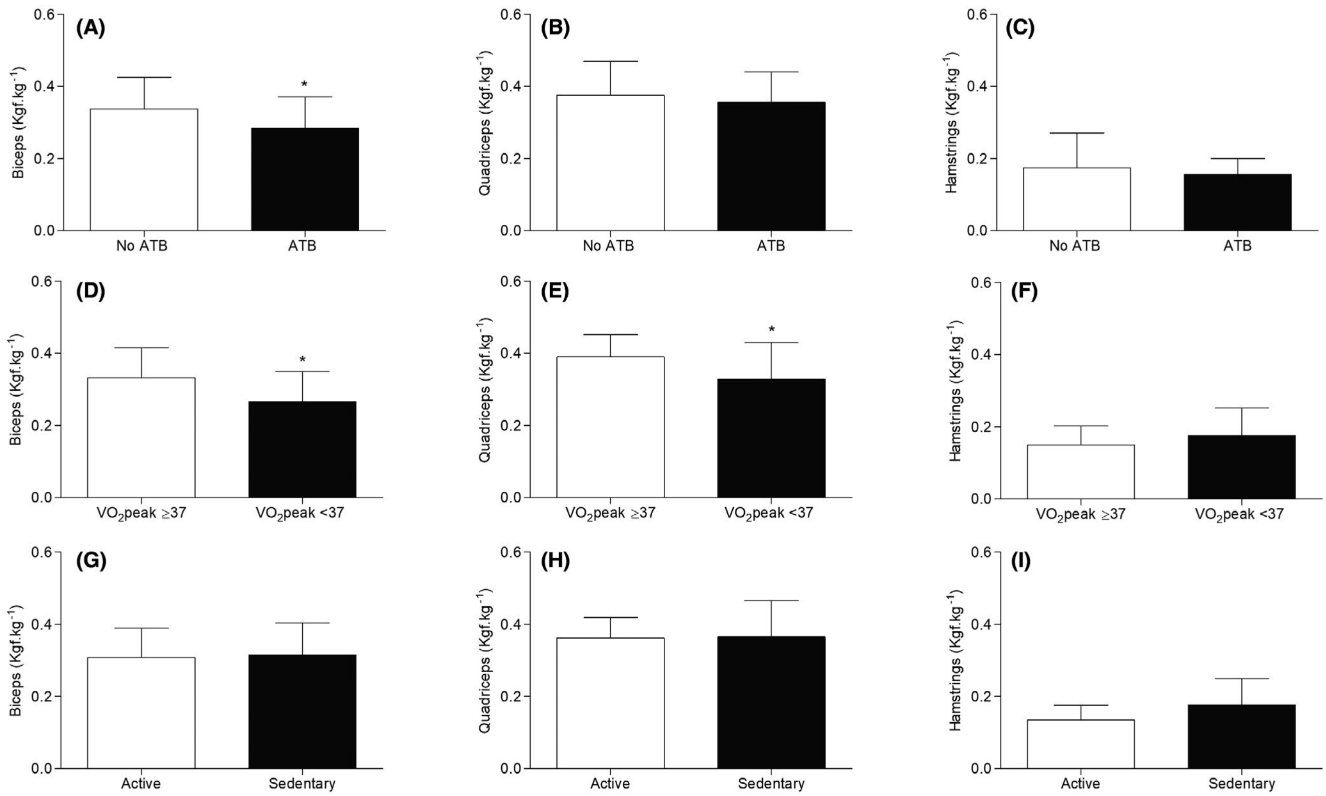

FIGURE 3 Comparison of biceps, quadriceps and hamstrings strength levels between patients who used or not used antibiotics (ATB) in (A), (B) and (C); patients with median peak oxygen consumption (VO_2peak) ≥37 or <37 mL·kg^{-1}·min^{-1} in (C), (D) and (E); and patients classified as active or sedentary in (F), (G) and (H). *Indicate significant difference at $P \le .05$

Previous studies[9,20,21] have demonstrated the relationship between peripheral muscle strength and exercise capacity, indicating that individuals with greater muscle strength in the lower limbs covered a greater distance in the 6MWT[9,21] or had a higher absolute maximum VO_2.[20] Troosters et al[9] assessed the correlation of quadriceps muscle strength with the distance covered on the 6MWT and VO_2peak, but found a significant correlation only with the 6MWT. Our results have shown a correlation between biceps strength and VO_2 at peak exercise. In addition, our data also showed correlations of biceps and quadriceps with the ventilatory equivalents (V_E/VO_2 and V_E/VCO_2), demonstrating an association of strength with variables of ventilatory efficiency. Moreover, when separating the sample by the aerobic fitness level, patients with lower VO_2peak presented decreased biceps and quadriceps strength. Our results highlight the importance of assessing peripheral muscle strength in individuals with CF, considering their influence on important physical performance variables, including the VO_2peak and the ventilatory equivalents, which are markers of dead space ventilation, as well as indexes of ventilatory efficiency.[35]

Our findings have also shown that there is a moderate correlation between quadriceps and hamstring strength with the total days of ATB use in the year following the assessments. In addition, patients who needed to use ATB presented a significant decrease in the biceps strength. To the best of our knowledge, this is the first study evaluating the association of peripheral muscle strength with one of the important markers of morbidity in patients with CF. It is well-known that subjects with CF present frequent pulmonary exacerbation episodes requiring oral or intravenous use of ATB and that these exacerbations can potentially worsen factors underlying muscle dysfunction, including physical inactivity, systemic inflammation and the anabolic status.[36,37] The study by Burtin et al[38] has shown that the quadriceps strength does not acutely decrease during a pulmonary exacerbation in adults with CF, although the long-term effects of multiple exacerbations are still poorly understood.

Studies that evaluated the association of peripheral muscle strength with lung function showed that both upper and lower limb strength correlated with FEV_1.[13,21] However, in our study, we found no differences in peripheral muscle strength between patients with FEV_1 < 80 or ≥80% of predicted. It is possible that this finding is related to the fact that present study includes a young sample with the majority of patients presenting only mild impairment of lung function.

The present study also presents limitations, including the fact that the subjects were evaluated at a single point in time, not allowing longitudinal monitoring, which could establish causal relationships between the studied outcomes. The absence of lung volume data (eg, RV/TLC values) may also be considered as a limitation, considering that its influence on exercise tolerance is well known.

5 | CONCLUSIONS

The results of the present study showed that peripheral muscle strength is associated with aerobic fitness and the use of antibiotics in patients with CF. The assessment of peripheral muscle strength should be part of the routine of monitoring of patients with CF and may help professionals on the routine clinical practice exercise recommendations.

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DISCLOSURES

The authors have no conflict of interests to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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