Original Article

Sleep disorders are distinctively associated with exercise intolerance and sedentary behavior in children with cystic fibrosis

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ABSTRACT

Objective: To evaluate the presence of sleep disorders and its associations with exercise capacity and daily physical activity levels among children and adolescents with CF.
Methods: Children age 6–18 years with a diagnosis of CF were recruited. Information regarding socio-demographic profile, pulmonary function and nutritional status were collected. Sleep disorders (polysomnography), exercise capacity (modified shuttle test - MST) and daily physical activity levels (questionnaire and five days accelerometer use) were evaluated.
Results: Thirty-one patients, median age of 9.6 years and forced expiratory volume in 1 s (FEV_1) of 68.1 ± 24.4%, were included. Obstructive sleep apnea syndrome (OSAS) was present in 32.3% and nocturnal hypoxemia in 29%. The MST distance correlated with the mean peripheral oxyhemoglobin saturation (SpO_2) during sleep (r = 0.40) and the percent of total sleep time with $SpO_2<90\%$ (r = −0.49). The final MST SpO_2 correlated with the occurrence of OSAS (r = −0.48) and mean nocturnal SpO_2 (r = 0.45). Sedentary activities, as measured by accelerometry, correlated with sleep architecture, including the percent of stage II (r = 0.60) and rapid eye movement (REM) stage sleep (r = −0.37). Patients with OSAS and nocturnal hypoxemia presented lower values ($p < 0.05$) of distance and final SpO_2 in the MST. Nocturnal hypoxemia was the main variable to influence exercise capacity ($r^2 = 0.521$).
Conclusion: Sleep disorders are distinctively related with exercise capacity and daily physical activity levels, as nocturnal hypoxemia is associated with exercise intolerance and sleep architecture disorders are associated with sedentary physical activity levels.

1. Introduction

Cystic fibrosis (CF) is a multisystemic genetic disease with significant morbidity and mortality [1]. Although the principal cause of mortality is respiratory, deterioration of pulmonary function does not in isolation explain development of the diverse changes that have an impact on quality of life, since other systemic manifestations such as compromised peripheral muscle function, low body mass index, low skeletal muscle mass, and low bone mineral density also contribute to reduced exercise capacity and worse prognosis [2,3]. Many studies have demonstrated that exercise capacity is predictive of hospital admissions and mortality among patients with CF [4–6], so monitoring exercise capacity is recommended [7,8].

Moreover, daily physical activity levels also appear to be affected, since regardless of pulmonary function, children with CF have less vigorous daily physical activity levels than their healthy peers [9–12]. Studies in healthy participants have shown that high

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levels of moderate and vigorous intensity physical activity are associated with a lower probability of sleep disorders, whereas inactivity has been identified as a risk factor [13,14]. However, little is known about the relationship between exercise capacity, daily physical activity levels, and sleep disorders in people with CF. Studies have found high prevalence rates of sleep disorders in children and adolescents with CF, including abnormalities of sleep architecture, increased number of arousals, presence of obstructive sleep apnea syndrome (OSAS) [15], and presence of nocturnal hypoxemia [16]. There is evidence that nocturnal hypoxemia precedes daytime hypoxemia and that the magnitude of oxyhemoglobin desaturation during sleep is superior to desaturation during exercise in participants with CF, which could contribute to worse prognosis, irrespective of pulmonary function [17,18].

No prior studies have evaluated if sleep disorders distinctively impact exercise capacity and daily physical activity levels in children with CF. Thus, the objective of this study was to evaluate the presence of sleep disorders and its associations with exercise capacity and daily physical activity levels among children and adolescents with CF. We hypothesized that different aspects of sleep disorders would distinctively impact exercise tolerance and daily physical activity levels.

2. Materials and methods

A cross-sectional study was conducted, enrolling children and adolescents with a CF diagnosis aged from 6 to 18 years. Patients were excluded if they had been admitted to hospital or had a pulmonary exacerbation during the previous 30 days, were on oxygen therapy, or had motor or cognitive difficulties that would interfere with completion of the tests involved in the study. Sample size was calculated taking the apnea and hypopnea rate as reference variable [19]. Considering a standard deviation of 2.0, 95% power, significance of 5%, and a minimum correlation between variables of 0.5, the sample size was estimated at 30 participants. The study complies with ethical criteria for research with human beings and was approved by the Research Ethics Committee under protocol number 2.459.354. All parents or guardians who gave consent to participation in the study signed a free and informed consent form and all children and adolescents signed an assent form.

2.1. Study design

Initially, data were recorded on age, sex, type of genetic mutation, colonization of airways by *Pseudomonas aeruginosa* and Shwachman-Kulczycki score. Chronic colonization by *P. aeruginosa* was defined as persistent presence of this bacteria in samples collected by oropharynx swab or in sputum samples over the preceding 6 months or in three consecutive samples [20]. Participants underwent spirometry, bioimpedance, and the modified shuttle test (MST). The short form, for children and adolescents, of the Physical Activity Questionnaire (PAQ) was also administered.

In the evening, participants were referred to a specialist sleep study clinic for preparation for overnight polysomnography, according to the American Academy of Sleep Medicine criteria [21]. After preparation, participants were discharged to sleep at home and returned the following morning for removal of the equipment and data download. At this visit, participants were given an accelerometer and instructed to wear it for 5 consecutive days in order to record 3 days of daily physical activity on weekdays and 2 days at the weekend.

2.2. Procedures

2.2.1. Bioimpedance

Bioelectrical impedance analysis was conducted with an Inbody 720 system (InBody Co., Los Angeles, United States), which uses a direct segmental multi-frequency measurement method, with an 8-point tactile electrode system measuring frequencies from 1 KHz to 1000 KHz.

2.2.2. Pulmonary function

A KoKo spirometer was used to assess pulmonary function (nSpire Health, Inc., Circle Longmont, United States). Participants were instructed to perform a maximum forced expiration, in accordance with American Thoracic Society reccomendations [22]. At least three maneuvers were performed and the curves and their respective values considered acceptable when differences were less than 5% or 150 mL. All exams were performed by an experienced and trained lung function respiratory therapist. The Global Lung Initiative 2012 international reference equation was used to calculated predicted values [23].

2.2.3. Polysomnography

For sleep analysis, all participants underwent type II baseline nocturnal polysomnography, conducted at home, using an Alice PDx portable sleep diagnostic system (Philips Respironics, Murrysville, United States). Sleep stages and arousals were evaluated using the electroencephalogram, electrooculogram and electromyogram. Respiratory analysis was based on nasal airflow recorded using a nasal cannula pressure transducer, respiratory effort was measured with chest and abdominal effort belts, snoring was monitored using a piezoelectric sensor, and peripheral oxyhemoglobin saturation (SpO_2) was continuously monitored with a digital pulse oximeter.

The polysomnography traces were read manually by a specialist professional trained in pediatric sleep medicine, using the criteria set out in the Manual for Scoring of Sleep and Associated Events [21]. Obstructive apnea was defined as when there was a greater than 90% reduction in the flow detected by the oronasal flow sensor for at least 2 respiratory cycles, with ongoing respiratory effort. Hypopneas were defined as a greater than 30% drop in flow for more than 2 respiratory cycles, with a fall of $\geq3\%$ in SpO_2 and/or arousal, and were defined as obstructive when combined with snoring, paradoxical thoracoabdominal movement, or flattening of the flow curve [21]. The apnea and hypopnea index was defined as the number of apneas and hypopneas per hour of sleep. The obstructive sleep apnea and hypopnea syndrome (OSAS) was defined as an obstructive AHI ≥ 2 per hour [24]. Nocturnal hypoxemia was defined as present when $SpO_2 <90\%$ was $\geq5\%$ or more of total time asleep [15].

2.2.4. Modified shuttle test (MST)

The 15-stage MST was used to assess exercise capacity [25]. A 10-m track marked with two cones was used and the participant was instructed to walk from one cone to the other, according to the audible signals, until exhaustion or a limiting symptom. The test was stopped if the participant was unable to maintain the displacement velocity, i.e, if the participant failed to reach the next cone in the time established by the audible signals twice in a row. Before and after taking the test, the participant's blood pressure, heart rate, SpO_2, and respiratory rate were measured and the Borg scale of perceived exertion was administered to gauge perceived dyspnea. Heart rate was recorded at the end of each stage. A predicted value was calculated for distance covered [26] and estimated peak oxygen uptake was also calculated [8].

2.2.5. Daily physical activity

Participants' daily physical activity levels were recorded using the Actigraph wGT3X-BT triaxial accelerometer (Actigraph LLC, Pensacola, FL, USA) for 5 consecutive days (2 day at the weekend and three days during the week), worn on the left side of the waist, which was removed only for aquatic activities or for sleeping. Data were downloaded using the ActiLife software (v6.10.4; ActiGraph LLC, Pensacola, FL, USA) and processed into 60-s epochs. For each participant, a minimum of 4 consecutive days, at least one day on the weekend, and at least 9 h of complete accelerometry data per calendar day were required for data to be included in the analysis. Periods over 20 consecutive minutes with a sequence of zero counts were considered as "non-use" and excluded from the analysis [12]. As an indicator of average intensity of physical activity, time spent in activities was classified according to intensity as sedentary (<100 counts), light (from 100 to 2295 counts), or moderate to vigorous (>2296 counts) [27]. The outcome variables were expressed in time (min.day^{-1}) spent for the different physical activity intensity categories. Percent of physical activity intensity in each category was calculated based on the mean value of the total number of valid hours of use per day.

Physical activity level was also assessed subjectively using a physical activity questionnaire. The PAQ for children was used for participants aged up to 12 years, on which each question has a response scale from 1 (very sedentary) to 5 points (very active). The mean score was used to classify participants as active (≥3 points) or sedentary (<3 points). The PAQ for adolescents was used for participants over the age of 12 years. This scale assessed time spent walking and moderate or vigorous activity performed for at least 10 continuous minutes during the previous week. Participants were classified as active when they summed at least 150 min per week of moderate physical activity at least 3 times/week or at least 3 sessions of 20 min per week of vigorous physical activities [28].

2.3. Statistical analysis

The normality of data was assessed with the Kolmogorov–Smirnov test. Continuous data with symmetrical distribution were expressed as mean and standard deviation, while asymmetrical data were expressed as median and interquartile range. Categorical variables were expressed as absolute and relative frequencies. Spearman coefficients were calculated to test for correlations and comparisons were analyzed using Student's t test and the Mann–Whitney test. The coefficient of correlation (r) was used to classify correlations as weak (between 0 and 0.39), moderate (≥0.4 and < 0.7) and strong (≥0.7). A forward stepwise multivariate linear regression model was used to test the influence of sleep variables and clinical variables on reduced exercise capacity (<80% of the MST predicted distance). All analyses and data processing were performed using SPSS 25.0. The significance level was set at 5% ($p < 0.05$).

3. Results

A total of 57 patients were invited to participate, 20 of whom did not agree to take part because of transport difficulties, while four had signs of exacerbation on the assessment day, one was dependent on oxygen therapy, and one did not complete the polysomnography test. Therefore, the final sample comprised 31 patients with a median of age of 9.6 years, the majority female (64.5%) and heterozygous for the F508del mutation (45.2%) (Table 1). Table 2 lists the results for pulmonary function and polysomnography variables. Mean forced expiratory volume in 1 s (FEV$_1$) (%) was 68.1 ± 24.0. A total of 13 patients (41.9%) exhibited values greater than 80% and six (19.4%) had values lower than 40%

Table 1
Characteristics of the study sample.

Variables	n = 31
Demographics	
Age (years)[a]	9.6 (7.9–15.1)
Female, n (%)	20 (64.5)
Genotyping	
F508del homozygous, n (%)	7 (22.6)
F508del heterozygote, n (%)	14 (45.2)
Other mutations, n (%)	10 (32.3)
Airway chronic Colonization	
Pseudomonas aeruginosa, n (%)	10 (32.3)
Shwachman-Kulczycki score[a]	90.0 (75.0–95.0)
Anthropometrics	
Height (cm)	139.2 ± 16.6
Weight (kg)	33.3 ± 12.2
BMI (kg/m^2)	16.6 ± 2.6
BMI (z-score)[a]	−0.4 (−1.7–0.1)
Skeletal muscle mass (kg)[a]	11.9 (8.8–19.4)
Fat Mass (kg)[a]	5.3 (3.3–10.3)
Body fat percentage[a]	20.1 (12.1–27.2)

[a] Median and 25–75 interquartile range; BMI: body mass index; cm: centimeters; m: meters; kg: kilogram.

Table 2
Pulmonary function and polysomnographic variables.

Variables	n = 31
Pulmonary function	
FEV$_1$ (%)	68.1 ± 24.4
FVC (%)	77.8 ± 21.4
FEF$_{25-75\%}$ (%)	53.8 ± 29.4
FEV$_1$/FVC	0.8 ± 0.1
Polysomnographic	
TST, min	449.5 ± 68.1
Sleep efficiency, %	67.0 ± 12.1
NREM stages, %TST	
Stage 1[a]	4.2 (2.8–6.0)
Stage 2	45.5 ± 10.7
Stage 3	27.7 ± 7.9
REM, %TST	20.9 ± 6.3
Arousal (n)[a]	69.0 (49.0–89.0)
Arousal index, n/h[a]	8.8 (6.7–11.2)
Obstructive apnea, n[a]	0.0 (0.0–1.0)
Obstructive hypopnea, n[a]	9.0 (6.0–17.0)
Respiratory events index, n/h[a]	2.6 (1.9–4.4)
AHI, n/h[a]	2.1 (1.3–3.9)
OAHI, n/h[a]	1.3 (1.0–2.2)
Mean sleep SpO$_2$, %[a]	95.0 (94.0–97.0)
Minimum sleep SpO$_2$, %[a]	88.5 (83.0–91.0)
SpO$_2$<90%, %TST[a]	0.3 (0.1–5.6)

[a] Median and 25–75 interquartile range; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; FEF$_{25-75\%}$: forced expiratory flow between 25 and 75% of FVC; L: liters; SpO$_2$: peripheral oxyhemoglobin saturation; TST: total sleep time; Min: minutes; REM: rapid eye moviment; NREM: non-rapid eye movement; AHI: apnea hypopnea index; OAHI: obstructive apnea hypopnea index; n: number; h: hour.

of predicted. We found a median obstructive apnea and hypopnea index of 1.3 per hour and OSAS was present in 10 participants (32.3%). Nocturnal hypoxemia was identified in 9 participants (29%).

Mean distance covered in the MST was 792 ± 260 m (79.5% of predicted), and 18 patients (58.1%) covered less than 80% of the predicted distance. According to the daily physical activity level assessment (PAQ), 20 participants (66.7%) were classified as sedentary. The accelerometer data showed that the majority spent a median time of 354.2 min (42.9%) in sedentary activities and only 14.9 min (2.4%) in moderate to vigorous activities (Table 3).

Fig. 1 illustrates the correlations between sleep parameters and exercise capacity (MST). The distance covered correlated

Table 3
Exercise capacity and daily physical activity levels.

Variables	
Modified shuttle test (n = 31)	
Resting	
Heart rate (bpm)	100.0 ± 14.0
SpO$_2$ (%)	96.9 ± 2.3
Respiratory rate (rpm)	24.4 ± 8.3
Borg scale for dyspnea[a]	0.0 (0.0—0.5)
Peak exercise	
Heart rate (bpm)	190.0 ± 16.0
SpO$_2$ (%)	96.0 ± 4.9
Respiratory rate (rpm)	41.7 ± 10.6
Borg scale for dyspnea[a]	7.0 (4.0—10.0)
Test level	11.0 (9.0—12.0)
Distance (m)	792.0 ± 260.0
Distance (% of predicted)	79.5 ± 27.7
VO$_2$ estimated (mL.kg^{-1}.min^{-1})	35.3 ± 4.9
Physical activity questionnaire (n = 30)	
Active, n (%)	10 (33.3)
Sedentary, n (%)	20 (66.7)
Accelerometer (n = 30)	
Sedentary (min.day^{-1})[a]	354.2 (246.2—488.5)
Sedentary (%)	42.9 ± 15
Light (min.day^{-1})[a]	479.7 (371.2—561.3)
Light (%)	54.7 ± 13.5
Moderate-to-vigorous (min.day^{-1})[a]	14.9 (2.1—36.9)
Moderate-to-vigorous (%)	2.4 ± 2.4

[a] Median and 25—75 interquartile range; bpm: beats per minute; rpm: respirations per minute; SpO$_2$: peripheral oxyhemoglobin saturation; m: meters; VO$_2$: oxygen uptake; min: minutes; kg: kilograms.

moderately with mean SpO$_2$ during sleep (r = 0.40; p = 0.026) and percentage of total time asleep at SpO$_2$<90% (r = −0.49; p = 0.005). Additionally, SpO$_2$ at the end of the MST correlated moderately with number of apneas (r = 0.48; p = 0.007) and mean nocturnal SpO$_2$ (r = 0.45; p = 0.01). Daily physical activity levels (accelerometer) were not correlated with sleep-disordered breathing, but with sleep architecture (Fig. 2). The longer the time spent in sedentary activities per day, the greater the percentage of time spent in stage II sleep (r = 0.60; p < 0.001) and the smaller the amount of time that the participant spent in rapid eye movement (REM) sleep (r = −0.37; p = 0.04).

Comparison of participants with and without sleep-disordered breathing revealed that both the subset with OSAS and the subset with hypoxemia exhibited significantly lower (p < 0.05) values for distance covered and SpO$_2$ at the end of the MST than the subset without respiratory sleep disorders (Table 4). No associations were observed between OSAS or nocturnal hypoxemia and daily physical activity levels.

A multivariate linear regression model for those patients who had reduced exercise capacity (distance on MST <80%) including sleep variables (mean SpO$_2$, presence of OSAS, and presence of hypoxemia) and clinical variables (age, sex, chronic colonization by *P. aeruginosa*, body mass index, FEV$_1$ [%] and forced vital capacity [%]) showed that nocturnal hypoxemia was the variable with the greatest association (r^2 = 0.521) with exercise capacity (Table 5).

4. Discussion

Our results demonstrate an association between presence of sleep-disordered breathing and exercise intolerance in children and adolescents with CF, showing that nocturnal hypoxemia appears to be one of the predominant factors involved in this effect. Exercise capacity is an important prognostic factor in patients with
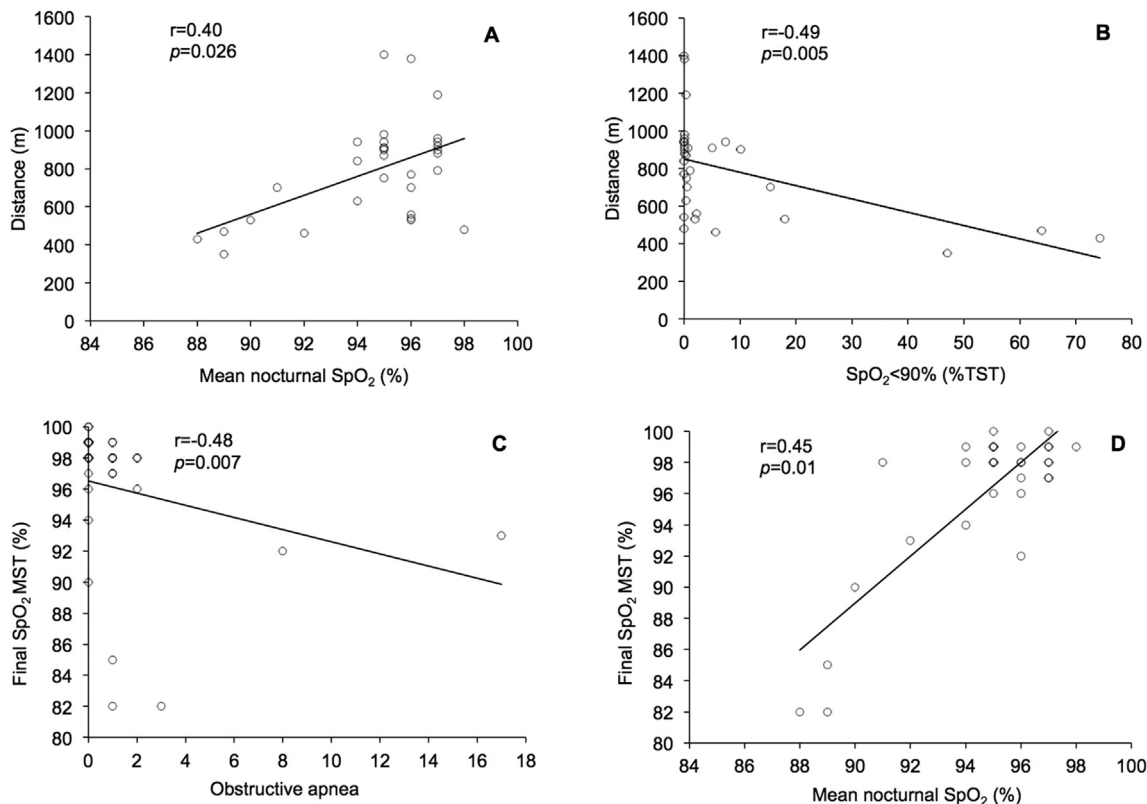

Fig. 1. Correlations between sleep variables and exercise capacity. (A) Mean (%) peripheral oxyhemoglobin saturation (SpO$_2$) at night and distance (m) covered in the modified shuttle test (MST); (B) Percentage of total sleep time (TST) with SpO$_2$ less than 90% and distance (m) covered in the MST; (C) Number of obstructive sleep apneas and SpO$_2$ at the end of the MST; (D) Mean (%) SpO$_2$ at night and SpO$_2$ at the end of the MST.
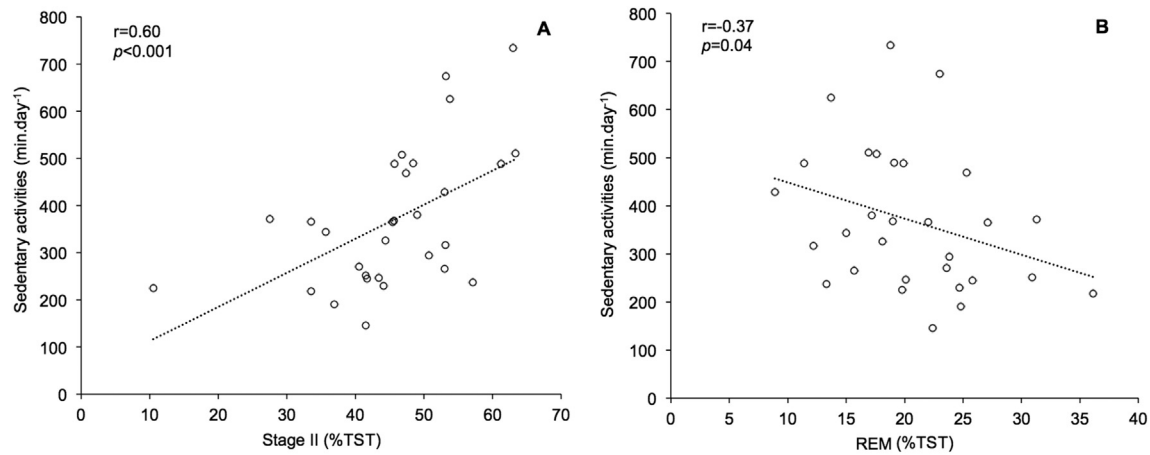
Fig. 2. Correlations between sleep variables and time in sedentary activities. Minutes of daily sedentary activity with (A) Percentage of total sleep time (%TST) in stage 2 sleep and (B) Percentage of total sleep time (%TST) in REM sleep stage.

Table 4
Effects of obstructive sleep apnea syndrome (OSAS) and nocturnal hypoxemia on exercise capacity and levels of daily physical activity.

Variables	OSAS		p	Nocturnal Hypoxemia		p
	Yes (n = 10)	No (n = 21)		Yes (n = 9)	No (n = 22)	
Modified shuttle test (n = 31)						
Distance (m)	722.7 ± 333.7	825.2 ± 217.9	0.309	632.2 ± 233.2	857.3 ± 245.5	**0.026**
Distance (%)*	65.4 (38.3–78.5)	84.0 (64.5–110.3)	**0.027**	51.4 (38.3–89.7)	78.9 (65.4–111.1)	**0.046**
VO_2 estimated	34.2 ± 6.1	36.0 ± 4.3	0.309	32.3 ± 4.4	36.9 ± 5.2	**0.026**
SpO_2 peak	92.4 ± 7.1	97.6 ± 1.9	**0.046**	91.6 ± 7.2	97.7 ± 1.8	**0.037**
RR peak (rpm)	46.8 ± 9.4	39.2 ± 10.4	0.061	43.7 ± 11.7	40.8 ± 10.2	0.512
HR peak (bpm)	181.0 ± 18.0	194.0 ± 13.0	**0.026**	177.3 ± 19.0	192.7 ± 12.2	**0.003**
Dyspnea peak	6.8 ± 2.9	6.7 ± 2.9	0.939	6.4 ± 2.8	6.9 ± 2.9	0.716
PAQ (n = 30)						
Active, n (%)	2 (6.7)	8 (26.7)	0.273	2 (6.7)	8 (26.7)	0.398
Sedentary, n (%)	8 (26.7)	12 (40.0)		7 (23.3)	13 (43.3)	
Accelerometer (n = 30)						
Sedentary (min.day^{-1})*	366.4 (256.3–508.4)	334.5 (245.0–458.5)	0.567	325.6 (233–428.2)	365.8 (249.0–488.8)	0.483
Sedentary (%)	45.9 ± 15.2	41.4 ± 15	0.451	41.8 ± 15.2	43.4 ± 15.2	0.794
Light (min.day^{-1})*	432.0 (343.4–511.8)	524 (386.5–575.5)	0.159	504.2 (332.2–556)	448.8 (378.6–569.9)	0.946
Light (%)	52.6 ± 14.2	55.7 ± 13.3	0.556	56.4 ± 13.8	53.9 ± 13.6	0.651
Moderate-to-vigorous (min.day^{-1})*	7.1 (1.1–20.2)	18.9 (3.6–42.8)	0.146	2.2 (0.9–34.1)	18.6 (4.3–43.3)	0.197
Moderate-to-vigorous (%)	1.5 ± 1.9	2.8 ± 2.5	0.152	1.7 ± 2	2.7 ± 2.5	0.335

Data expressed as mean ± standard deviation and differences analyzed using the Student's t test, except for variables marked with an asterisk* that were expressed as median (interquartile range) and compared using the Mann–Whitney test. m: meters; VO_2: oxygen uptake; SpO_2: peripheral oxyhemoglobin saturation; RR: respiratory rate; HR: heart rate; bpm: beats per minute; rpm: respirations per minute; PAQ: physical activity questionnaire; min: minutes. p-values considered as significant when <0.05 (indicated in bold).

Table 5
Multiple linear regression model to explain the reduced exercise capacity (distance covered in the modified shuttle test less than 80% of predicted values).

	β	SE	95%CI		p	R^2 adjusted
			Minimum	Maximum		
Exercise capacity - distance (%)						
Constant	20.915	9.09	1.646	40.184	0.035	0.521
Nocturnal hypoxemia[a]	23.168	5.248	12.043	34.293	0.0001	

[a] Presence of nocturnal hypoxemia defined as peripheral oxyhemoglobin saturation <90% for more than 5% of total sleep time. β: beta standardized coefficient; SE: standard error; CI: confidence interval; R^2: coefficient of determination.

CF, since aerobic fitness is related to quality of life and is a predictor of hospital admissions and mortality [5,6,29].

While exercise intolerance in CF is multifactorial, studies indicate that reduced pulmonary function is the principal factor [17,30], although others have attributed just 30% of variability in exercise performance to airway obstruction [31]. In our study, the linear regression model demonstrated that pulmonary function variables did not exhibit associations with exercise capacity. Other factors described in the literature to influence exercise

capacity are age, nutritional status, and respiratory and peripheral muscle strength [30]. In adults with CF, chronic colonization and distances shorter than 475 m, SpO_2 < 90%, and level of dyspnea during a 6-min walk test (6MWT) were predictive of mortality and lung transplant, while higher values of FEV_1 (%) were associated with increased survival [32]. Additionally, the evaluation of functional capacity (6MWT) is associated with days in hospital, although it does not follow the decline in pulmonary function [6].

Hypoxemia in situations such as exercise and sleep is more frequent in adults with CF than in healthy subjects [17]. Presence of hypoxia accelerates disease progression, as it increases pulmonary inflammation and stimulates growth of *P. aeruginosa* in the lungs, aggravating pulmonary damage and accelerating dysfunction of the skeletal muscle system [33]. Deterioration of pulmonary function, combined with reduced muscle mass, limits exercise capacity and can initiate a vicious cycle through which reduced exercise capacity reduces sputum clearance, leading once more to hypoxia, thereby perpetuating inflammation and stimulating bacterial growth in the lungs [34]. There is evidence that nocturnal hypoxemia precedes daytime hypoxemia and that the magnitude of oxyhemoglobin desaturation during sleep is superior to desaturation during exercise in people with CF, which can contribute to development of pulmonary hypertension and *cor pulmonale*, reduction of exercise capacity, and worse prognosis, irrespective of pulmonary function [18].

While the effects of hypoxemia and reduced exercise capacity in CF have already been well described, to date, only one study has investigated the association between both factors. Using data on nocturnal SpO$_2$, measured through oximetry, it demonstrated that desaturation during the 6MWT was not predictive of nocturnal desaturation in adults with CF [16]. The results of the present study demonstrate that nocturnal desaturation was moderately correlated with performance and final desaturation in the MST and that children and adolescents with nocturnal hypoxemia had significantly reduced exercise capacity. Furthermore, this appears to be the first study to demonstrate an association between nocturnal hypoxemia and exercise, explaining around 52% of the reduction in exercise capacity in patients with exercise intolerance.

Another sleep disorder observed in patients with CF is abnormal sleep architecture, demonstrated in terms of increased number of arousals and reductions in sleep efficiency and percentage of time in REM sleep when compared with healthy subjects [35]. The hypothesis for this finding in CF is that frequent nocturnal coughing during the early stages of sleep leads to increased arousals and delayed progression to the deeper stage and REM sleep, reducing the duration of REM [36]. Studies in healthy people demonstrate that quality of sleep is commonly associated with daily physical activity levels [13,37,38]. In addition, a recent study by Cox and collaborators [39] has demonstrated, in adult patients with CF, that fragmented sleep was associated with less time in moderate-to-vigorous physical activity and reduced exercise capacity. However, to date, no studies that have assessed sleep, using polysomnography, and correlated it with daily physical activity levels, measured using an accelerometer, in children and adolescents with CF. The results of the present study indicate a relationship between sleep architecture and daily physical activity levels, since a greater percentage of time in stage II sleep and a smaller percentage of time in REM sleep was observed among participants who spent a larger proportion of the day in sedentary activities. The increased percentage of time in stage II sleep leads to a reduction in the time in the deeper sleep stage, which is of fundamental importance for physical recovery, and also reduces the time in REM sleep, responsible for cerebral development, essential for learning, memory, and emotions, particularly in children and adolescents [40]. Therefore, we believe that the changes to sleep architecture identified in our study may have daytime consequences and could be related to the sedentary behavior observed in these patients, although a bidirectional relationship between sleep and physical activity has also been described [38].

Notwithstanding, we also confirmed the results of other studies using nocturnal oximetry [41,42], finding no association between daily physical activity levels, measured with the accelerometer, and presence of OSAS or of nocturnal hypoxemia. However, since presence of hypoxemia was a determinant factor in explaining exercise capacity, the use of nocturnal oximetry for monitoring these patients should be considered. The possibility of early identification and correction of hypoxemia could contribute to limiting advance or worsening of the inflammatory vicious cycle, enabling improvement of skeletal muscle strength and increased exercise capacity. Moreover, a complete sleep study using nocturnal polysomnography can contribute to identification of possible sleep disorders that could be interfering with the daily activity levels of people with CF, especially those with sedentary behavior.

This study is subject to limitations, including the cross-sectional design, which does not allow cause—effect relationships to be assessed. Additionally, it was not possible to perform cardiopulmonary exercise testing, considered the gold standard for assessment of exercise capacity. Nevertheless, we believe that MST, which has been validated for use with CF patients and has a strong correlation with oxygen consumption [8], was an adequate method for assessing exercise intolerance. Finally, the sample size of the present study may also be considered as a possible limitation, especially for subgroup comparisons, although significance was reached in several analyses.

5. Conclusion

The results indicate that sleep disorders are distinctively related with exercise capacity and daily physical activity levels. Nocturnal hypoxemia is associated with exercise intolerance and sleep architecture disorders are associated with sedentary physical activity levels. Therefore, sleep disorders may have negative daytime impacts, with repercussions for the physical condition of children and adolescents with CF. Further research is needed to investigate the effects of sleep disorder treatment on exercise tolerance and daily physical activity levels in children with CF.

CRediT authorship contribution statement

Roberta Ribeiro Batista Barbosa: Conceptualization, Data curation, Investigation, Formal analysis, Writing - original draft. **Pitiguara de Freitas Coelho:** Conceptualization, Investigation, Writing - review & editing. **Fernanda Mayrink Gonçalves Liberato:** Investigation, Writing - review & editing. **Pâmela dos Reis Vidal:** Data curation, Investigation, Writing - review & editing. **Roberta Barcellos Couto Olimpio de Carvalho:** Supervision, Writing - review & editing. **Roberta de Cássia Nunes Cruz Melotti:** Supervision, Writing - review & editing. **Márcio Vinícius Fagundes Donadio:** Conceptualization, Supervision, Project administration, Formal analysis, Writing - review & editing.

Conflict of interest

All authors declare that they have no conflict of interests to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.07.004

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2020.07.004.

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