Hong Kong Physiotherapy Journal
https://www.worldscientific.com/worldscinet/hkpj

Heart rate variability, exercise capacity and levels of daily physical activity in children and adolescents with mild-to-moderate cystic fibrosis

Pitiguara de Freitas Coelho[1], Roberta Ribeiro Batista Barbosa[1],
Rodrigo dos Santos Lugao[1], Fernanda Mayrink Gonçalves Liberato[2],
Pâmela Reis Vidal[1], Roberta de Cássia Nunes Cruz Melotti[2] and
Márcio Vinícius Fagundes Donadio[3,*]

[1]*Escola Superior de Ciências da Santa Casa de Misericórdia de
Vitória – EMESCAM,
Vitória, Espírito Santo, Brazil*

[2]*Cystic Fibrosis Reference Center
Hospital Infantil Nossa Senhora da Glória
Vitória, Espírito Santo, Brazil*

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

*mdonadio@pucrs.br

Background: Autonomic nervous system balance is altered in cystic fibrosis (CF), although its influence on physical fitness has been poorly explored.
Objective: This study aimed to evaluate the association of heart rate variability (HRV) with exercise capacity and levels of daily physical activity in children and adolescents with mild-to-moderate CF.

**Corresponding author.

Methods: A cross-sectional study including individuals with CF aged 6–18 years, not under CFTR modulator therapy, was performed. Sociodemographic (age, sex) and clinical information (airway colonization, pancreatic insufficiency, and genotyping) were collected. In addition, exercise capacity (modified shuttle test — MST), lung function (spirometry), body composition (bioimpedance), levels of daily physical activity (5-day accelerometer), and HRV (both at rest and during the MST) were evaluated.
Results: 30 individuals (20 females) aged 11.2 ± 3.7 years, mean FEV_1 $62.8 \pm 27.6\%$, were included. A sympathovagal balance (LF/HF) increase ($p < 0.001$) during the MST was shown, indicating a predominance of sympathetic modulation. The standard deviation of all RR intervals (SDNN) and the high frequency (HF) index during exercise correlated significantly with FEV_1 ($r = 0.45$, $p = 0.01$ and $r = 0.46$, $p = 0.01$; respectively). MST distance also correlated positively and significantly with SDNN ($r = 0.43$, $p = 0.01$), square root of the mean of the sums of squares of frequencies between RR intervals greater than 50 ms — RMSSD ($r = 0.53$, $p < 0.01$), low frequency — LF ($r = 0.48$, $p < 0.01$), HF ($r = 0.64$, $p < 0.01$), dispersion of points perpendicular to the short-term identity line — SD1 ($r = 0.40$, $p = 0.02$) and negatively with LF/HF ($r = -0.57$, $p < 0.01$). Regarding daily physical activity, SDNN at rest ($r = 0.37$, $p = 0.04$) and exercise ($r = 0.41$, $p = 0.02$) showed positive correlations with time in moderate-to-vigorous activities. When normalizing the SDNN and classifying individuals as normal or altered, those presenting altered SDNN showed poorest FEV_1 ($p = 0.001$) and lower exercise capacity ($p = 0.027$).
Conclusion: HRV correlates with lung function, exercise capacity and levels of daily physical activity in children and adolescents with CF. The study highlights the influence of CF on autonomic function and suggests HRV measurement as an easy tool to be used in clinical settings as an alternative marker to monitor CF individuals.

Keywords: Cystic fibrosis; heart rate variability; exercise capacity; modified shuttle test; pediatrics.

Introduction

Cystic fibrosis (CF) is a genetic, autosomal recessive disease, which primarily affects epithelia of several organs, with significant morbidity and mortality. These changes result from a gene mutation that encodes the CF transmembrane conductance regulator (CFTR) protein, located on the long arm of chromosome 7.[1] Although the lungs are usually the most compromised organ, it also affects the liver, pancreas and intestine.[2]

In individuals with CF, peripheral muscle strength and exercise capacity[3] may be affected compared to healthy individuals in an effect of multifactorial origin,[4] including limitations of pulmonary function and muscle deconditioning, which contributes to shortness of breath. Patients with CF do not express the CFTR protein in the muscles, which results in metabolic and contractile impairment,[5] compromising peripheral muscle strength and leading to plain myopathy.[6] In addition, individuals with CF may have impaired cardiac and vascular function.[7] Evidence is growing to support the existence of CFTR dysfunction directly affecting cardiac function, leading to myocardial impairment, including diminished right and left ventricular function.[8] Nevertheless, a greater exercise capacity is associated with a better quality of life, reduced risk of hospitalization due to respiratory infections and survival rate.[9] Furthermore, in addition to aerobic fitness, daily physical activity levels are also considered as an important health-related measure, as people with CF spend less time performing moderate to vigorous intensity activities than their healthy peers[10] and daily physical activity levels are independently related to aerobic capacity.[11]

There is a growing interest in the involvement of the autonomic nervous system (ANS) and its role on clinical manifestations in CF, as these have been demonstrated for several chronic diseases and syndromes.[12–15] Therefore, studies have used the heart rate variability (HRV) as a method of evaluating the ANS, as it is a non-invasive form of assessment and considered as a cardiac mortality risk indicator.[13] However, the study of HRV in both children and adults with CF has been poorly explored to date. The limited evidence available has shown increased dysautonomia, although these abnormalities are still contradictory, with results that point to both an increase[14] and a reduction[15] in the sympathetic tone. In individuals with chronic diseases, the increase in sympathetic tone is associated with worse clinical status and mortality, including less tolerance to exercise.[16,17] When submitted to cardiorespiratory tests, these

patients demonstrate altered HRV behavior with increasing loads.[17] Although autonomic dysfunction has been suggested to be associated with the pathologic response to exercise and changes in HRV with increasing exercise effort have been previously documented,[16] there is no data on autonomic modulation to physical stress from exercise in children with CF. In addition, the association of HRV with exercise capacity and daily physical activity levels of children and adolescents with CF has also not been explored yet.

Therefore, considering that the ANS is directly influenced by the physical conditioning levels in both healthy individuals and in chronic diseases, we hypothesized that HRV would be associated to exercise capacity and/or daily physical activity levels in patients with CF. Thus, the present study aimed to assess the association of HRV with exercise capacity and the levels of daily physical activity in children and adolescents with mild-to-moderate CF.

Methods

This is a cross-sectional study in individuals with CF aged between 6 and 18 years, who were being followed in a specialized CF center and were not under CFTR modulator therapy. The study included children and adolescents with a diagnosis of CF confirmed by genetic test, in stable clinical conditions (no signs of pulmonary exacerbation in the previous 3 months), without heart disease, and who were able to fully comprehend all evaluations performed. Individuals who failed to complete all tests were excluded. The present study followed the Ethics Criteria in Research with Human Beings and was approved by the University Research Ethics Committee (No. 2,459,354). Parents and/or legal guardians signed and informed consent form and patients signed an assent form before inclusion.

The experimental protocol was carried out over a period of seven consecutive days, following a routine consultation at the CF center. During the consultation, a spirometry test was performed to assess lung function and bioimpedance to assess body composition. To assess the sociodemographic and clinical profile, data including age, sex, type of mutation, type of airway colonization, pancreatic insufficiency, in addition to the Shwachman–Kulczycki score, were collected. Then, participants were referred to perform the HRV assessment using a cardiofrequency meter. The evaluation was performed during 25 min at rest and during the Modified Shuttle Test (MST), which evaluates the exercise capacity. Levels of daily physical activity were assessed by accelerometry for five consecutive days, using a triaxial accelerometer.

Lung function

The pulmonary function assessment was performed using a KoKo spirometer (nSpire Health, USA). The individuals were instructed to perform an exhalation, followed by a slow and deep inhalation, and then verbally encouraged to perform a maximum and forced exhalation. At least three maneuvers were conducted and accepted when the curves and their respective values were reproducible, with differences of less than 5% or 150 mL between them, according to the criteria of the American Thoracic Society.[18] The variables studied were forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), forced expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$) and the FEV_1/FVC ratio. In order to obtain predicted values, an international equation was used.[19]

Nutritional status

The assessment of nutritional status and body composition was performed using bioimpedance (Inbody 720, InBody Co., Los Angeles, USA). Data were obtained on weight, skeletal muscle mass, fat mass and body mass index (BMI). The BMI z-score was calculated and values ≤ 2 were defined as indicative of malnutrition.[20]

Heart rate variability

HRV was measured for 25 min at rest and during the MST using the Polar RS800CX cardio-frequency meter (Polar Electro Oy Inc., Finland). For data analysis, the first 5 min were eliminated for the purpose of stabilizing the parameters and an automated low filter was used in the Kubios HRV Standard version 3.1.0 software (HRV analysis, University of Eastern Finland), with adjustment of up to 5%, and ectopic beats eliminated in manual filtration. Data were analyzed for time domain (SDNN: standard deviation of all RR intervals, expressed in ms; RMSSD: square root of the mean of the sums of squares of frequencies between RR intervals greater than 50 ms, expressed

in ms; pNN50: percentage of successive cycles with differences in duration above 50 ms, expressed as a percentage) and to frequency domain (LF: low frequency; HF: high frequency; LF/HF: low frequency/ high frequency ratio), in addition to geometric indices (SD1: dispersion of points perpendicular to the short-term identity line and SD2: dispersion of points along the identity line). The SDNN index at rest was used to classify participants as normal and abnormal. The classification was performed using the reference values published by Gasior *et al.*[21]

Exercise capacity

Exercise capacity was assessed using the MST, which has been validated for use in CF[22] and strongly correlates with oxygen consumption.[23,24] A 10-meter 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 interrupted when the participants failed to reach the subsequent cone twice, arriving after the beep time. Before and after the test, blood pressure, heart rate (HR), peripheral oxygen saturation (SpO_2), respiratory rate (RR) and subjective sensation of dyspnea and fatigue in the lower limbs (modified BORG scale) were measured. A predicted value was calculated for the distance covered.[25]

Levels of daily physical activity

The levels of physical activity were assessed using a triaxial accelerometer (wGT3X-BT), for five consecutive days, worn on the left side of the waist, which was removed only for aquatic activities or for sleeping.[10] The results for physical activity variables were expressed in mean counts per minute, as an indicator of average intensity of physical activity, and time spent in activities was classified according to intensity as sedentary (<100 counts), light physical activity (from 100 to 2295 counts), or moderate to vigorous (>2296 counts).[26]

Statistical analysis

For sample size calculation purposes, we used the McNarry & Mackintosh[13] study, which evaluated HRV in individuals with CF. Using HRV RR intervals (SDNN) as a reference variable, a power of 95%, a significance index of 5% and a correlation between variables of 0.5, a sample size of 30 individuals was estimated.

The Kolmogorov–Smirnov test was used to assess the normality of the data and the results presented according to the distribution (mean±standard deviation or median plus interquartile range). Qualitative variables were presented as absolute frequency and relative frequency. To compare the HRV variables between rest and exercise, the Wilcoxon test was used. Student's *t*-test was used to compare lung function and exercise capacity between individuals with normal and altered SDNN. The Spearman's correlation test was used to assess correlations. The level of significance adopted was 5% in all cases and the Stata version 12.0 statistical program was used.

Results

The sample consisted of 30 individuals, with a mean age of 11.2 ± 3.7 years, most of them female (66.6%). The majority had a heterozygous F508del genotype (43.3%) and were colonized by *Staphylococcus aureus* (63.3%). Pancreatic insufficiency was present in 86.4% of the patients. As for lung function, the mean FEV_1 (% of predicted) was $62.8 \pm 27.6\%$ and the mean FVC was $78.6 \pm 21.3\%$. Regarding daily physical activity levels, the data shows that participants spent most time in light and sedentary activities. The Shwachman–Kulczycki score was 86.2 ± 13.4, representing individuals in good clinical status. The characterization data are shown in Table 1.

The distance covered in the MST showed a mean of $80.9 \pm 27.0\%$ of the predicted, with an estimated oxygen consumption (VO_2) of $35.5 \pm 4.8 \, \text{mL.kg}^{-1}.\text{min}^{-1}$. The main physiological variables such as HR, RR, blood pressure, borg for dyspnea and borg for fatigue in lower limbs showed the expected increase at peak of exercise, as shown in Table 2.

The HRV indices are described in Table 3. A decrease in the linear indices of the time-domain (representing vagal modulation) when comparing rest and exercise moments was observed for SDNN ($p < 0.001$), RMSSD ($p < 0.001$) and pNN50 ($p < 0.001$). In addition, as for the linear indices of the frequency-domain, the LF (nu), indicating sympathetic modulation, was higher in exercise compared to rest ($p < 0.001$), while the HF (nu), indicating vagal modulation, decreased at exercise ($p < 0.001$). The sympathovagal balance (LF/HF) increased at exercise ($p < 0.001$), which indicates a

Table 1. Characteristics of the studied sample.

Variables evaluated	$n = 30$
Demographics	
Age (years)	11.2 ± 3.7
Female, n (%)	20 (66.6)
Anthropometrics	
Height (cm)	139.2 ± 16.9
Weight (kg)	33.4 ± 12.4
BMI (absolute)	16.6 ± 2.6
BMI (z-score)	-0.66 ± 1.1
Skeletal muscle mass	13.4 ± 5.7
Fat Mass	7.0 ± 4.8
Malnutrition, n (%)	6 (20)
Genotyping	
F508del Homozygous. n (%)	7 (23.3)
F508del Heterozygote. n (%)	13 (43.3)
Other mutations, n (%)	10 (33.3)
Chronic airway colonization	
Staphilococus aureus, n (%)	20 (63.3)
Pseudomonas aeruginosa, n (%)	10 (33.3)
Pancreatic insufficiency	
Yes, n (%)	19 (86.4)
Lung function	
FEV_1 (L)	1.48 ± 0.74
FEV_1 (% predicted)	62.8 ± 27.6
FVC (L)	1.92 ± 0.89
FVC (% predicted)	78.6 ± 21.3
Levels of daily physical activity	
Sedentary (%)	42.3 ± 14.7
Light (%)	55.3 ± 13.3
Moderate-to-vigorous (%)	2.5 ± 2.4
Days of use	4.7 ± 0.5
Shwachmam-Kulczycki score	86.2 ± 13.4

Notes: Values expressed as mean ± standard deviation or absolute (relative) frequencies. BMI: body mass index; cm: centimeters; Kg: kilograms; L: liters; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity.

Table 2. Evaluation of the exercise capacity using the MST.

Variables evaluated	$n = 30$
Rest	
HR (bpm)	99.2 ± 14.1
SpO_2 (%)	97.0 ± 2.3
RR (rpm)	24.4 ± 8.5
SBP (mmHg)	112.2 ± 6.8
DBP (mmHg)	68.5 ± 8.6
Borg for dyspnea	0.3 ± 0.5
Borg for leg discomfort	0.2 ± 0.4
Peak exercise	
HR (bpm)	190.6 ± 15.2
SpO_2 (%)	96.0 ± 4.9
RR (rpm)	42.0 ± 10.6
SBP (mmHg)	120.6 ± 13.1
DBP (mmHg)	73.1 ± 12.7
Borg for dyspnea	6.8 ± 2.8
Borg for leg discomfort	5.0 ± 3.6
MST level	10.8 ± 2.0
MST distance (m)	803.0 ± 256.6
MST (% of predicted)	80.9 ± 27.0
VO_2 estimated (mL.kg^{-1}.min^{-1})	35.5 ± 4.8

Notes: Data expressed as mean and standard deviation. HR: heart rate; bpm: beats per minute; SpO_2: peripheral oxygen saturation; RR: respiratory rate; rpm: respirations per minute; SBP: systolic blood pressure; mmHg: millimeters of mercury; DBP: diastolic blood pressure; MST: modified shuttle test; VO_2: oxygen consumption; m: meters; mL: milliliters. Kg: kilogram.

Table 3. Comparison of HRV variables at rest and during exercise.

Variables evaluated	Rest	Exercise	p
SDNN (ms)	60.8 ± 45.9	29.6 ± 19.6	$< 0.001^*$
RMSSD (ms)	59.9 ± 61.3	13.3 ± 10.9	$< 0.001^*$
pNN50 (%)	22.4 ± 20.6	2.1 ± 5.0	$< 0.001^*$
LF (nu)	60.4 ± 17.2	74.1 ± 15.5	$< 0.001^*$
HF (nu)	38.9 ± 17.2	25.8 ± 15.3	$< 0.001^*$
LF/HF	2.0 ± 1.9	4.7 ± 4.3	$< 0.001^*$
SD1	43.8 ± 42.7	10.9 ± 10.2	$< 0.001^*$
SD2	66.9 ± 53.3	20.8 ± 15.3	$< 0.001^*$

Notes: Variables expressed as mean ± standard deviation. Comparisons performed with the Wilcoxon test. SDNN: standard deviation of all normal RR intervals recorded in a time interval; RMSSD: square root of the mean of the square of the differences between adjacent normal RR intervals in a time interval; PNN50: percentage of adjacent RR intervals with a difference in duration greater than 50 ms; LF: low frequency; HF: high frequency; nu: normalized units; LF/HF: low frequency/high frequency ratio; SD1: scattering of points perpendicular to the identity line; SD2: scattering of points along the identity line.

predominance of sympathetic modulation. In the geometric indices of HRV (SD1 and SD2), a decrease during exercise compared to rest ($p < 0.001$) was observed in SD1, which is predominantly vagal, and in SD2 index ($p < 0.001$), which represents the global modulation.

During rest and exercise, SDNN showed a positive correlation with the percentage of time in moderate to vigorous daily physical activity measured by the accelerometer. Regarding exercise capacity, the MST level and distance correlated with the SDNN, RMSSD, LF, HF, LF/HF and SD1 indexes during exercise. SDNN and HF correlated positively with FEV_1 and FVC, while LF/HF correlated negatively with FVC. The correlations between HRV, lung function, exercise

Table 4.   Correlation of HRV variables with lung function, exercise capacity and levels of daily physical activity.

| Variables evaluated | Lung function | | | | MST | | | | Accelerometer | | | | | |
| | FVC% | | FEV$_1$% | | Level | | Distance | | Sedentary/ day (%) | | Light/ day (%) | | Moderate-to-vigorous/day (%) | |
	Rho	p*	rho	p*	rho	p*	rho	p*	rho	p*	rho	p*	rho	p*
Rest														
SDNN	0.07	0.69	0.13	0.46	0.29	0.11	0.26	0.15	−0.22	0.23	0.20	0.29	0.37	0.04*
RMSSD	0.05	0.75	0.13	0.47	0.28	0.12	0.28	0.12	−0.12	0.51	0.12	0.53	0.22	0.25
LF	0.11	0.56	0.17	0.36	0.37	0.04*	0.34	0.06	−0.15	0.42	0.12	0.50	0.30	0.10
HF	0.16	0.39	0.23	0.21	0.31	0.09	0.31	0.08	−0.15	0.43	0.14	0.45	0.27	0.14
LF/HF	−0.31	0.09	−0.34	0.06	−0.24	0.19	−0.29	0.12	0.10	0.50	−0.17	0.37	−0.09	0.63
SD1	−0.00	0.97	0.08	0.64	0.13	0.46	0.16	0.37	−0.10	0.59	0.10	0.57	0.16	0.39
SD2	0.02	0.87	0.11	0.53	0.22	0.22	0.24	0.19	−0.05	0.76	0.03	0.85	0.22	0.23
Exercise														
SDNN	0.48	< 0.01*	0.45	0.01*	0.45	0.01*	0.43	0.01*	−0.25	0.18	0.26	0.16	0.41	0.02*
RMSSD	0.27	0.14	0.34	0.06	0.51	< 0.01*	0.53	< 0.01*	−0.15	0.41	0.09	0.63	0.30	0.11
LF	0.28	0.13	0.35	0.05	−0.50	< 0.01*	0.48	< 0.01*	−0.08	0.67	0.04	0.83	0.19	0.30
HF	0.41	0.02*	0.46	0.01*	0.50	< 0.01*	0.64	< 0.01*	0.07	0.99	−0.05	0.78	0.22	0.24
LF/HF	−0.39	0.03*	−0.35	0.05	−0.58	< 0.01*	−0.57	< 0.01 *	−0.05	0.75	0.09	0.64	−0.20	0.28
SD1	0.21	0.25	0.19	0.30	0.39	0.03*	0.40	0.02*	−0.24	0.19	0.24	0.20	0.29	0.12
SD2	0.25	0.17	0.21	0.26	0.34	0.06	0.35	0.05	−0.10	0.58	0.09	0.62	0.23	0.23

Notes: *Spearman's correlation test; SDNN: standard deviation of all normal RR intervals recorded in a time interval, expressed in ms; RMSSD: square root of the mean of the square of the differences between adjacent normal RR intervals, in a time interval, expressed in ms; PNN50: percentage of adjacent RR intervals with a difference in duration greater than 50 ms; LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio; SD1: scattering of points perpendicular to the identity line; SD2: scattering of points along the identity line; FEV$_1$: forced expiratory volume in the first second; FVC: forced vital capacity; MST: modified shuttle test.

capacity and daily physical activity are shown in Table 4.

When SDNN was normalized and then classified as normal ($n = 22$; 73.3%) or altered ($n = 8$; 26.7%) based on available reference values,[21] individuals with altered SDNN presented worse lung function [Figs. 1(a) and 1(b)], both for FEV$_1$ ($p = 0.001$) and FVC ($p = 0.002$), and lower exercise capacity [Figs. 1(c) and 1(d)], both for the distance covered ($p = 0.027$) and for the percentage of the predicted distance ($p = 0.030$).

Discussion

The present study shows that HRV indices presented a sympathetic predominance and a normal physiological exercise response in children and adolescents with mild-to-moderate CF. When assessing the exercise capacity through the MST level, a positive correlation with the indices that represent parasympathetic modulation (SDNN, RMSSD, HF, SD1) and a negative correlation with the global low-frequency indices (LF and LF/HF) were observed. The distance covered in the MST showed similar results, differing only in the LF index, which increased while reaching a greater distance. Although the MST is not considered as the gold standard for exercise capacity evaluation,[27] its use has been validated for children with CF and results have shown a good correlation between the distance achieved in the test and oxygen consumption.[22,23] Nevertheless, it is known that there is an important increase in sympathetic modulation before and after submaximal exercise tests.[14] However, no studies were found to measure HRV specifically in children with CF during exercise or exercise capacity testing, such as the MST. Gomes *et al.*[28] in an analysis performed with asthmatic patients during a submaximal test, showed a similar result, demonstrating that there was no vagal withdrawal, while Poehling and Llewellyn[29] showed a divergent result, as in healthy adults a submaximal test was associated to lower vagal and higher sympathetic indexes, in addition to the fact that participants with greater sympathetic predominance at rest obtained better performance during the test.
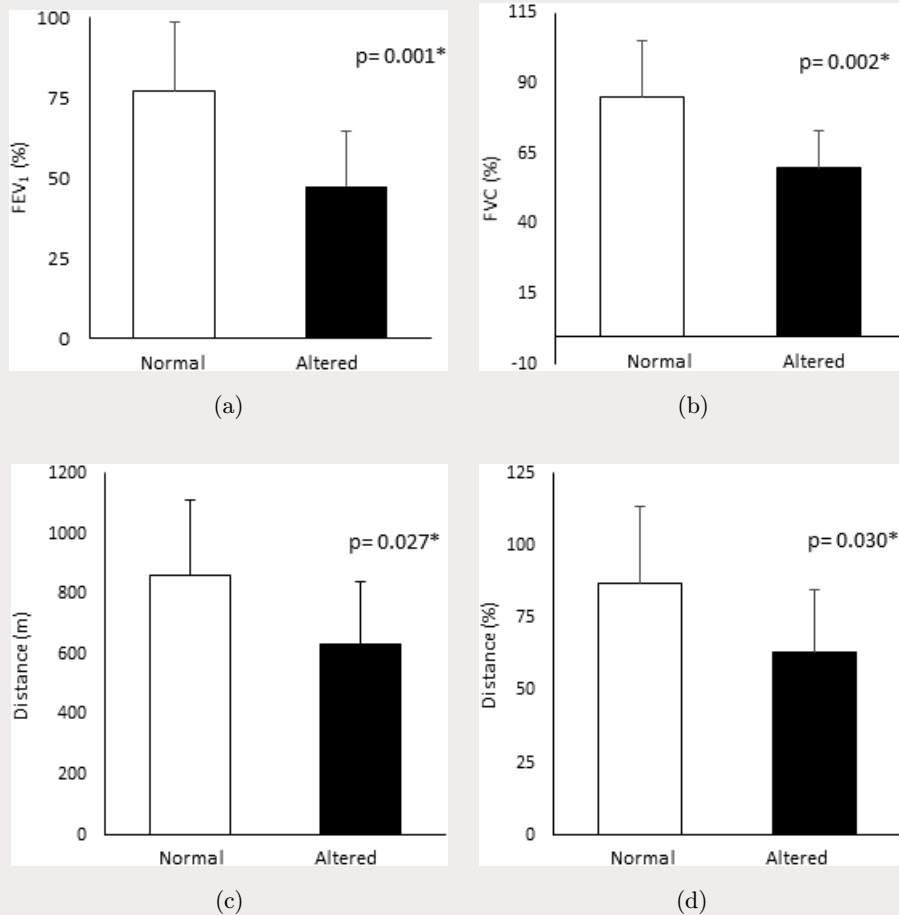
Fig. 1. Comparison of lung function and exercise capacity between individuals with the SDNN within normal reference values (normal: $n = 22$; 73.3%) or outside normal reference values (altered: $n = 8$; 26.7%). (a) Forced expiratory volume of the first second (FEV_1), expressed as a percentage of the predicted; (b) Forced vital capacity (FVC), expressed as a percentage of the predicted; (c) Distance covered in the modified shuttle test (MST), in meters; (d) Distance covered in the MST, expressed as a percentage of the predicted. The Student's t-test was used for comparisons. Significance set at $p < 0.05$.

Regarding the levels of daily physical activity (accelerometer), individuals with moderate to vigorous physical activity levels showed a positive correlation with SDNN, demonstrating that the individual's global modulation tends to improve as physical activity increases. Although individuals with other chronic diseases tend to present a predominantly sedentary level of physical activity,[26,30,31] there is still no consensus for children with CF. Kilbride *et al.*[32] have shown that both children with CF and healthy presented comparable (light) levels of physical activity. In the present study, most patients presented more time in light and sedentary activities.

When the HRV was compared between rest and exercise, the linear time-domain indices that represent vagal modulation decreased. The SDNN index of the sample was similar to values of children who underwent heart transplantation.[33]

The SDNN and RMSSD indices during rest are equivalent to those found for obese children, based on the study by Paschoal *et al.*,[34] representing a low vagal predominance. At exercise, the frequency-domain indices showed important changes compared to rest, where LF (nu) and LF/HF increased and HF (nu) decreased, showing low vagal predominance. A similar result was also observed in the study by Florêncio *et al.*[14] evaluating HRV before and after the 6-minute walk test in children with CF. Geometric indices showed a decrease between rest and exercise, with SD1 of vagal predominance and SD2 of global modulation, presenting good adaptation to physical stimulus. These indices were, respectively, higher than those of obese children and equivalent to eutrophic children.[35] Few studies have performed HRV measurements during exercise. The study by Winsley *et al.*[36] carried out in healthy children shows that

there is a significant vagal withdrawal from the moment of rest to exercise and an increase in the sympathetic and global modulation, corroborating the results of the present study. It is also important to highlight that individuals with CF may have impaired cardiac function[7] as a result of CFTR-induced myocardial dysfunction,[8] although Szollosi *et al.*[15] demonstrated that individuals with CF have normal cardiac autonomic modulation when compared to healthy individuals, even though parasympathetic modulation is expected to decrease as lung disease progresses. Recent evidence has shown that a short-term exercise resistance training program was effective in modulating HRV in children and adolescents with CF.[37]

Regarding lung function, FVC showed a positive correlation with HRV indices during exercise (SDNN and HF), and a negative correlation with LF/HF. FEV_1 correlated with SDNN and HF. In children and adolescents with CF presenting mild-to-moderate lung function impairment and a good physical state, 57.9% of individuals presented at least one altered HRV variable.[37] Based on the study by Gasior *et al.*,[21] which defines the normalization of HRV indices for school-aged children, we have used the SDNN vagal modulation index of the sample at rest to show that individuals with altered SDNN had worse lung function (FEV_1 and FVC) and less exercise capacity (distance covered in absolute and percentual values). Nevertheless, we believe current knowledge on the influence of respiratory diseases on cardiac autonomic modulation is still incipient and may be addressed in future studies. HRV clinical measurement may help healthcare providers to monitor autonomic balance changes and evolution in individuals with CF.

The present study has some limitations, including the cross-sectional design and the characteristics of the sample, comprised of children and adolescents aged 8–15 years, which may have influenced comparisons between HRV indices, considering a possible influence of puberty. In addition, it was not possible to use the gold standard for exercise testing (CPET — cardiopulmonary exercise testing) to assess exercise capacity. However, we believe that the use of the MST, which has already been validated for use in CF patients,[22,23] was adequate to assess exercise intolerance in the studied sample.

In conclusion, HRV correlates with lung function, exercise capacity and levels of daily physical activity in children and adolescents with mild-to-moderate CF. When normalized using reference values, patients with abnormal HRV presented reduced lung function and exercise tolerance. The study highlights the influence of CF on autonomic function and, considering the practicality of measuring HRV in a clinical setting, we believe it could also be used as an alternative marker to monitor CF individuals.

Conflict of Interest

The authors have no conflict of interests to declare.

Funding/Support

Author Contributions

PFC, RRBB and MVFD participated in the conception of the work, analysis and interpretation of data, and critical review. PFC drafted the manuscript. PFC, RRBB, RSL, FMGL, PRV and RCNCM participated in data collection. All authors read, revised and approved the final version.

References

1. Ramos RTT, Salles C, Gregorio PB, Barros AT, Santana A, Araújo-Filho JB, Gregório PB. Evaluation of the upper airway in children and adolescents with cystic fibrosis and obstructive sleep apnea syndrome. Int J Pediatr Otorhinolaryngol 2009;73(12):1780–85.

2. Al-Abadi B, Al-Hiary M, Khasawneh R, Al-Momani A, Bani-Salameh A, Al-Saeidat S, et al. Cystic fibrosis gene mutation frequency among a group of suspected children in King Hussein Medical Center. Med Arch 2019;73(2):118–20.

3. Arikan H, Yatar İ, Calik-Kutukcu E, Aribas Z, Saglam M, Vardar-Yagli N et al. A comparison of respiratory and peripheral muscle strength, functional exercise capacity, activities of daily living and physical fitness in patients with cystic fibrosis and healthy subjects. Res Dev Disabil 2015;45–46:147–56.

4. Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical

implications and response to therapeutic interventions. J Cyst Fibros 2017;16(5):538–52.

5. Divangahi M, Balghi H, Danialou G, Comtois AS, Demoule A, Ernest S et al. Lack of CFTR in skeletal muscle predisposes to muscle wasting and diaphragm muscle pump failure in cystic fibrosis mice. PLoS Genet 2009;5(7):e1000586.

6. Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions. J Cyst Fibros 2017;16(5):538–52.

7. Rodriguez-Miguelez P, Thomas J, Seigler N, Crandall N, McKie KT, Forseen C, Harris RA. Evidence of microvascular dysfunction in patients with cystic fibrosis. Am J Physiol Heart Circ Physiol 2016;310(11):H1479–1485.

8. Saynor ZL, Gruet M, Rodriguez-Miguelez P, Harris RA. Oxygen transport and utilisation during exercise in cystic fibrosis: Contributors to exercise intolerance. Exp Physiol 2020;105(12):1979–83.

9. Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database of Syst Rev 2017;1(11):CD002768.

10. Bradley J, O'Neill B, Kent L, Hulzebos EHJ, Arets B, Hebestreit H. Physical activity assessment in cystic fibrosis: A position statement. J Cyst Fibros 2015;14(6):e25–32.

11. Hebestreit H, Kieser S, Rüdiger S, Schenk T, Junge S, Hebestreit A. Physical activity is independently related to aerobic capacity in cystic fibrosis. Eur Respir J 2006;28(4):734–39.

12. Rawenwaaij-Arts CM, Kallee LA, Hopman JC. Heart rate variability. Standards of measurement, physiologic interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043–65.

13. McNarry MA, Mackintosh KA. Reproducibility of heart rate variability indices in children with cystic fibrosis. PLoS One 2016;11(3):e0151464.

14. Florêncio R, Fregonezi G, Brilhante S, Borghi-Silva A, Dias F, Resqueti V. Heart Rate Variability at rest and after the 6-minute walk test (6MWT) in children with cystic fibrosis. Brazilian J Phys Ther 2013;17(5):419–26.

15. Szollosi I, King SJ, Wilson JW, Naughton MT. Tachycardia in adults with cystic fibrosis is associated with normal autonomic function. Intern Med J 2009;41(6):455–61.

16. McNarry MA, Lewis MJ, Wade N, Davies GA, Winn C, Eddolls WTB et al. Effect of asthma and six-months high-intensity interval training on heart rate variability during exercise in adolescents. J Sports Sci 2019;37:2228–35.

17. Fu Q, Levine BD. Exercise and the autonomic nervous system. Handb Clin Neurol 2013;117:147–60.

18. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK et al. American Thoracic Society Recommendations for a Standardized Pulmonary Function Report An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med 2017;196:14.

19. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: The global lung function 2012 equations. Eur Respir 2012; J40:1324–43.

20. De Onis M. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85(09):660–67.

21. Gasior JS, Sacha J, Pawlowski M, Zieliński J, Jeleń PJ, Tomik A et al. Normative values for heart rate variability parameters in school-aged children: Simple approach considering differences in average heart rate. Front Physiol 2018;9:1495.

22. Selvadurai HC, Cooper PJ, Meyers N, Blimkie CJ, Smith L, Mellis CM, Van Asperen PP. Validation of shuttle tests in children with cystic fibrosis. Pediatr Pulmonol 2003;35(2):133–38.

23. Vendrusculo FM, Heinzmann-Filho JP, Campos NE, Gheller MF, de Almeida IS, Donadio MVF. Prediction of peak oxygen uptake using the modified shuttle test in children and adolescents with cystic fibrosis. Pediatr Pulmonol 2019;54(4):386–92.

24. Lang RL, Stockton K, Wilson C, Russell TG, Johnston LM. Exercise testing for children with cystic fibrosis: A systematic review. Pediatr Pulmonol 2020;55(8):1996–2010.

25. Lanza F de C, Zagatto E do P, Silva JC, Selman JPR, Imperatori TBG, Zanatta DJM et al. Reference equation for the incremental shuttle walk test in children and adolescents. J Pediatr 2015;167:1057–61.

26. Stephens S, Takken T, Esliger DW, Pullenayegum E, Beyene J, Tremblay M et al. Validation of accelerometer prediction equations in children with chronic disease. Pediatr Exerc Sci 2016;28:117–32.

27. Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH et al. Statement on exercise testing in cystic fibrosis. Respiration. 2015;90(4):332–51.

28. Gomes FD, Sampaio LM, Costa IP, Dias FD, Ferneda VS, Silva GA, Costa D. Analysis of autonomic modulation during maximal and submaximal work rate and functional capacity in asthmatic children. J Asthma 2013;50:613–18.

29. Poehling CP, Llewellyn TL. The effects of submaximal and maximal exercise on heart rate variability. Int J Exerc Sci 2019;12:9–14.

30. Stephens SL, Tremblay MS, Faulkner G, Beyene J, Nguyen TH, Koohsari S et al. Validity of the stage of exercise scale in children with rheumatologic conditions. J Rheumatol 2016;43:2189–98.

31. Walker RG, Obeid J, Nguyen T, Ploeger H, Proudfoot NA, Bos C et al. Sedentary time and screen-based sedentary behaviors of children with a chronic disease. Pediatr Exerc Sci 2015;27: 219–25.

32. Kilbride E, Widger J, Hussey J, El Nazir B, Greally P. Exercise capacity in prepubertal children with cystic fibrosis. Int Scholar Res Notice 2012;2012: 578240.

33. Williams T, Tang X, Gilmore G, Gossett J, Knecht KR. Measures of and changes in heart rate variability in pediatric heart transplant recipients. Pediatr Transplant 2017;21:4.

34. Paschoal MA, Trevizan PF, Scodeler NF. Variabilidade da frequência cardíaca, lípides e capacidade física de crianças obesas e não-obesas. Arq Bras Cardiol 2009;93:239–46.

35. Jeon S, Oh S, Cho SJ, Lee YJ, Kim SJ. Association between snoring and heart rate variability in adolescents: Effects of gender and insufficient sleep. Sleep Breath 2020;24(2):561–70.

36. Winsley RJ, Armstrong N, Bywater K, Fawkner SG. Reliability of heart rate variability measures at rest and during light exercise in children. Br J Sports Med 2003;37(6):550–52.

37. Estévez-González AJ, Donadio MVF, Cobo-Vicente F, Fernández-Luna Œ, Sanz-Santiago V, Villa Asensi JR et al. Effects of a short-term resistance-training program on heart rate variability in children with cystic fibrosis-a randomized controlled trial. Front Physiol. 2021;12:652029.