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Mechanisms of ventilatory limitation to maximum exercise in children and adolescents with chronic airway diseases

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Abstract

Introduction: Exercise intolerance is common in chronic airway diseases (CAD), but its mechanisms are still poorly understood. The aim of this study was to evaluate exercise capacity and its association with lung function, ventilatory limitation, and ventilatory efficiency in children and adolescents with cystic fibrosis (CF) and asthma when compared to healthy controls.

Methods: Cross-sectional study including patients with mild-to-moderate asthma, CF and healthy children and adolescents. Anthropometric data, lung function (spirometry) and exercise capacity (cardiopulmonary exercise testing) were evaluated. Primary outcomes were peak oxygen consumption (VO_2peak), forced expiratory volume in 1 s (FEV_1), breathing reserve (BR), ventilatory equivalent for oxygen consumption (V_E/VO_2) and for carbon dioxide production (V_E/VCO_2), both at the ventilatory threshold (VT_1) and peak exercise.

Results: Mean age of 147 patients included was 11.8 ± 3.0 years. There were differences between asthmatics and CF children when compared to their healthy peers for anthropometric and lung function measurements. Asthmatics showed lower VO_2peak when compared to both healthy and CF subjects, although no differences were found between healthy and CF patients. A lower BR was found when CF patients were compared to both healthy and asthmatic. Both CF and asthmatic patients presented higher values for V_E/VO_2 and V_E/VCO_2 at VT_1 when compared to healthy individuals. For both V_E/VO_2 and V_E/VCO_2 at peak exercise CF patients presented higher values when compared to their healthy peers.

Conclusion: Patients with CF achieved good exercise capacity despite low ventilatory efficiency, low BR, and reduced lung function. However, asthmatics reported reduced cardiorespiratory capacity and normal ventilatory efficiency at peak exercise. These results demonstrate differences in the mechanisms of

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ventilatory limitation to maximum exercise testing in children and adolescents with CAD.

KEYWORDS
asthma, breathing reserve, carbon dioxide production, cystic fibrosis, equivalent for oxygen consumption

1 | INTRODUCTION

Chronic airway diseases (CAD) are associated with abnormalities in the airways and other structures of the lung, with asthma being the most common CAD in the pediatric age range, and cystic fibrosis (CF) being the most frequent genetic disease in Caucasians.[1] In patients with CAD and even in healthy children, exercise intolerance is common and is usually considered as the inability of individuals to perform exercise at the same levels that would be expected for an age-matched control.[2] Patients with asthma use to report exercise-associated symptoms which are related to multiple factors, including the degree of airway obstruction, decreased ventilatory capacity, a greater sensation of dyspnea, exercise-induced bronchoconstriction (EIB), or low exercise capacity.[3] Despite this, there is no clear consensus on their exercise capacity. Some studies reported no differences between healthy and asthmatic patients,[4,5] while others showed lower respiratory capacity in those with a diagnosis of asthma.[6–8] For children and adolescents with CF, evidence reports a reduction in exercise capacity compared to healthy controls.[9]

Lung function measurements including forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio are the most used clinical parameters for monitoring CAD, including asthma[10] and CF.[11] Evidence indicates that FEV_1 correlates with clinical worsening and EIB in children and adolescents with asthma,[12] but implications of lung function on reduced exercise capacity are still unclear.[13,14] In patients with CF, evidence suggests that only a part of the variability in exercise capacity can be explained by FEV_1.[15] In general, the mechanisms responsible for exercise limitation in CAD are still poorly understood. In individuals with asthma, exercise intolerance may result from a combination of complex interactions between mechanical, physiological, and psychological mechanisms, including bronchial smooth muscle contraction due to increased breathing, loss of heat, and moisture in the respiratory tract.[3] On the other hand, there are controversial data on mechanisms underlying low exercise capacity in CF, which may be related to poor nutritional status, peripheral muscle dysfunction, dysfunctional gas exchange, and exercise-induced ventilatory dysfunction.[15]

During progressive exercise, minute ventilation (V_E) must increase through a combination of a rapid increase in tidal volume to a maximum of approximately 50% of FVC and a progressive but steady increase in respiratory rate.[16] The most typical feature of CAD is the progressive airway obstruction causing airflow limitation. As exercise ventilatory demands increase, the combination of high respiratory rates and decreased expiratory flows may result in an insufficient expiratory time to completely exhale the inspired breath.[17] Ventilatory limitation in CAD can be reflected in different parameters during cardiopulmonary exercise testing (CPET), such as ventilatory efficiency or breathing reserve (BR). Ventilatory efficiency is represented by ventilatory equivalents for oxygen consumption (V_E/VO_2), and for carbon dioxide production (V_E/VCO_2).[18] The increase in ventilatory demand in CAD can lead to poor ventilatory efficiency, with a need for greater minute ventilation (V_E) to eliminate the same amount of carbon dioxide as compared to healthy children.[5,19] On the other hand, BR compares how closely V_E achieved in peak exercise approaches the maximal voluntary ventilation (MVV).[20] The ratio of peak exercise minute ventilation to MVV (BRI), ranges from 0.40 to 0.75 in untrained healthy individuals.[21] In patients with CAD the BRI is elevated, suggesting reduced BR at peak exercise.[9,22] BR has been considered a powerful predictor of mortality in CF patients awaiting lung transplantation,[23] although it has not been reported in patients with asthma.[24]

A better understanding of how CAD may affect aerobic fitness and the identification of the main mechanisms leading to exercise intolerance may help researchers and health professionals to better monitor and treat those patients. Thus, the aim of this study was to evaluate exercise capacity and its association with lung function, ventilatory limitation, and ventilatory efficiency in children and adolescents with mild-to-moderate CF and asthma when compared to healthy controls.

2 | METHODS

A cross-sectional study was carried out in a tertiary children's Hospital following all principles described in the Declaration of Helsinki. The study was approved by the Hospital Research Ethics Committee (R-0031/14). All legal guardians and patients over 12 years signed informed consent to participate in the study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[25] was used as a reference to draft the manuscript.

2.1 | Participants

Participants with a diagnosis of mild-to-moderate asthma[26] and CF, as well as healthy children and adolescents[26] were selected. General inclusion criteria were children and adolescents aged 7–18 years. General exclusion criteria were: (i) respiratory exacerbations 4 weeks before the evaluation, and (ii) presence of musculoskeletal condition or any other

disorder that influences exercise capacity. Patients with mild-to-moderate asthma were selected consecutively in the outpatient clinics of the Pediatric Pulmonology department (Hospital Universitario Infantil Niño Jesús), as previously described.[26] Specific inclusion criteria were: (i) asthma diagnosis with at least 6 months of evolution, (ii) exercise-associated symptoms (score 0–1 in question 2 of the asthma control test (c-ACT),[27] or score 2–3 in question 7 of the asthma control in children.[28] Specific exclusion criteria were: (i) therapeutic step increase in usual asthma control medication in the previous month (inhaled corticosteroids, long-acting β2 agonist, leukotriene receptor antagonists, oral corticosteroids or omalizumab), (ii) respiratory exacerbation requiring systemic corticosteroids in the last 3 months or presence of mild exacerbations in the last month (need for a higher-than-usual dose of short-acting beta-agonist), (iii) irregular use of the medication prescribed by the physician, and (iv) presence of another chronic respiratory or cardiac disease. No medications were withdrawn during the test days and patients kept their usual treatment regimen. Results from a previous EIB test were also collected and patients were considered as having a positive test when a fall of 10% or more was seen in the FEV_1. Participants with CF were also recruited at Hospital Niño Jesus in Madrid. Specific inclusion criteria were a genetic diagnosis of CF. Specific exclusion criteria were: (i) having severe lung deterioration, as defined by an FEV_1 lower than 50% of the predicted, and (ii) presenting unstable clinical condition (i.e., hospitalization within the previous 3 months or exacerbation in the previous 4 weeks). None of the patients included received CF modulator therapy at the moment of evaluation.

Healthy children were recruited from schools in the same district as the hospital to avoid significant differences in environmental conditions (levels of air contamination, presence of environmental allergens, and pollen). Children were selected by convenience sampling, using a covariate adaptive randomization to reduce selection bias. Specific eligibility criteria were: (ii) attending schools in the same district as the hospital, and (ii) having no positive answers in the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[29] Specific exclusion criteria were the diagnosis of cardiac, neurological, or chronic respiratory diseases that would impair cardiorespiratory fitness.

2.2 | Outcomes

The primary outcomes of the study were VO_2peak, FEV_1, BR, ventilatory equivalent for oxygen consumption (V_E/VO_2), and ventilatory equivalent for carbon dioxide production (V_E/VCO_2).

Other variables of interest comprised demographic (age and sex) and anthropometric (height, weight, and body mass index [BMI]).

2.3 | Assessments

2.3.1 | Cardiopulmonary exercise testing

To evaluate exercise capacity, a treadmill (Technogym Run Race 1400HC) maximum test was performed. The protocol started with an initial speed and slope of 2.5 km h^{-1} and 0.5%, respectively. Increases in both variables of 0.1 km h^{-1} and 0.5%, respectively, were used every 15 s.[30] Gas exchange data were measured breath-by-breath using open-circuit spirometry (Vmax 29C; Sensor Medics). The variables collected included VO_2peak, maximum minute ventilation (V_E), respiratory exchange ratio (RER), V_E/VO_2, V_E/VCO_2, BR, peripheral oxygen saturation (SpO_2), and maximum heart rate (HRmax). HRmax was measured using a heart rate monitor (Polar®) and SpO_2 was monitored with a pulse oximeter (TrueSat™, GE Healthcare). VO_2peak was recorded as the highest value obtained for any continuous 20 s period. The ventilatory threshold (VT_1) was determined using the criteria of an increase in both the V_E/VO_2 and end-tidal pressure of oxygen, with no increase in the V_E/VCO_2. BR was calculated as the difference between MVV and the maximum ventilation at peak exercise. An indirect estimate was used to predict MVV by multiplying FEV_1 by 35. The test was considered as maximum if the following criteria were met: (i) heart rate greater than 180 beats per minute, (ii) RER above 1.0, and (iii) clear exhaustion according to the perceived exertion (RPE).

2.3.2 | Lung function

Spirometry was performed using a Spirostik spirometer (Jaeger) with a Blue Cherry diagnostic software platform, following the American Thoracic Society-European Respiratory Society (ATS/ERS) guidelines. The main variables collected were FEV_1, FVC, and the ratio between FEV_1 and FVC. Data were interpreted according to the unified approach of the Global Lung Initiative, establishing as a limit of normality a z-score value for FEV_1 between −1.64 and +1.64.

2.3.3 | Anthropometric data and body composition

Height and weight were measured using a mechanical balance (ASIMED model BARYS PLUS C) equipped with a telescopic height measuring meter to calculate BMI. Cut-offs to describe nutritional status were those proposed for subjects aged 5–19 years, according to the World Health Organization, converted into z-scores. Nutritional status classification was: obese: ≥+2 SD; overweight: >+1 SD; normal weight: −1 to +1 SD; thin: ≤−2 SD; severely thin: ≤−3 SD.

2.4 | Statistical analysis

For statistics, data normality was evaluated through the Kolmogorov–Smirnov test. Variables are presented as mean ± standard deviation or median and interquartile range, following their distribution. Categorical variables are shown in absolute and relative frequencies. Comparisons between groups were performed using the one-way analysis of variance, followed by the Bonferroni post hoc test. Associations were evaluated using the Pearson Chi-square test. All analyses and data

processing were performed using SPSS version 18.0 (SPSS Inc.) and the significance level adopted was $p \leq .05$.

3 | RESULTS

A total of 147 children and adolescents were recruited (healthy $n = 48$, asthmatic $n = 48$, and CF = 51). Table 1 presents the baseline characteristics of the study sample. Participants were homogeneous in age (11.8 ± 3.0 years) and sex distribution. As expected, there were significant differences between asthmatics and CF children when compared to their healthy peers for anthropometric and lung function measurements. In addition, asthma and CF groups presented lower FEV_1 when compared to healthy controls ($F_{(2,144)} = 14.628$, $p < .001$), although there was no difference between asthmatics and CF patients in lung function, except for the $FEF_{25\%-75\%}$ (%), which was significantly lower in CF individuals ($F_{(2,134)} = 52.680$, $p < .001$).

As for cardiorespiratory fitness, significant differences were found for both VO_2peak ($F_{(2,144)} = 16.992$, $p < .001$) and BR ($F_{(2,144)} = 12.067$, $p < .001$) (Figure 1). Asthmatics showed lower VO_2peak when compared to both healthy and CF subjects. On the other hand, no differences in VO_2peak between healthy and CF patients were described. Although patients with CF had no decrease in VO_2peak, a lower BR was found when compared to both healthy and asthmatic groups. Comparison between asthmatic and healthy children revealed no differences in the BR (Figure 1). Although 54.2% of asthmatics presented EIB, no significant differences between those with or without EIB were seen for both VO_2peak (34.6 ± 4.4 vs. 36.7 ± 6.1; $p = .20$) and BR (23.2 ± 14.0 vs. 29.3 ± 11.8; $p = .11$).

The main CPET variables at VT_1 and peak exercise are presented in Table 2. As for the workload achieved in the test, speed ($F_{(2,135)} = 21.722$, $p < .001$), incline ($F_{(2,135)} = 23.810$, $p < .001$) and time ($F_{(2,135)} = 23.528$, $p < .001$) at VT1 were higher in healthy and CF patients as compared to asthmatics. On the other hand, at peak exercise, no differences were found for speed and incline, but healthy

TABLE 1 Demographic, anthropometric, and lung function characteristics.

Variables evaluated	Healthy ($n = 48$)	Asthma ($n = 48$)	CF ($n = 51$)	p value
Demographics				
Age (years)	11.3 ± 2.7	12.0 ± 2.7	12.1 ± 3.6	.33
Male, n (%)	18 (37.5)	17 (35.4)	29 (56.9)	.06
Anthropometrics				
Weight (kg)	42.2 ± 10.8	46.6 ± 14.2	40.4 ± 12.8	.05
Height (cm)	148.1 ± 14.2	149.9 ± 16.1	147.0 ± 17.1	.67
BMI (kg/m^2)	18.9 ± 2.4	20.3 ± 3.7	18.1 ± 2.9	**.002°**
BMI (z-score)	0.54 ± 0.94	0.70 ± 1.36	−0.26 ± 1.05	**.001#°**
Lean mass (%)	71.1 ± 7.4	73.9 ± 7.6	77.8 ± 11.3	**.003#**
Lung function				
FEV_1 (L)	2.4 ± 0.7	2.3 ± 0.6	2.1 ± 0.8	**.04#**
FEV_1 (% predicted)	101.1 ± 10.5	91.6 ± 11.7	85.2 ± 19.8	**.001*#**
FEV_1 (z-score)	0.11 ± 0.91	−0.70 ± 0.99	−1.35 ± 1.62	**.001*#°**
FVC (L)	2.6 ± 0.8	2.9 ± 1.6	2.6 ± 1.0	.28
FVC (% predicted)	95.0 ± 9.3	94.5 ± 14.4	91.2 ± 17.8	.36
FVC (z-score)	−0.43 ± 0.79	−0.47 ± 1.22	−0.84 ± 1.50	.18
FEV_1/FVC (absolute)	0.93 ± 0.05	0.86 ± 0.08	0.81 ± 0.09	**.001*#°**
$FEF_{25\%-75\%}$ (L/s)	3.6 ± 1.2	2.5 ± 0.9	2.0 ± 1.0	**<.001*#**
$FEF_{25\%-75\%}$ (% predicted)	121.1 ± 27.5	81.3 ± 22.7	64.1 ± 29.6	**<.001*#°**
$FEF_{25\%-75\%}$ (z-score)	0.9 ± 1.1	−0.9 ± 1.1	−2.0 ± 1.6	**<.001*#°**

Note: Values are expressed as mean ± standard deviation or absolute (relative) frequency. Significant p values are highlighted in bold, following the one-way analysis of variance, except for sex (male) which was evaluated using a Pearson Chi-square test. Significant differences between groups are identified as follows: healthy versus asthma (*), healthy versus cystic fibrosis (#), asthma versus cystic fibrosis (o).

Abbreviations: BMI, body mass index; cm: centimeter; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75% of vital capacity; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; kg, kilogram; L, liters; m, meter; S: seconds.

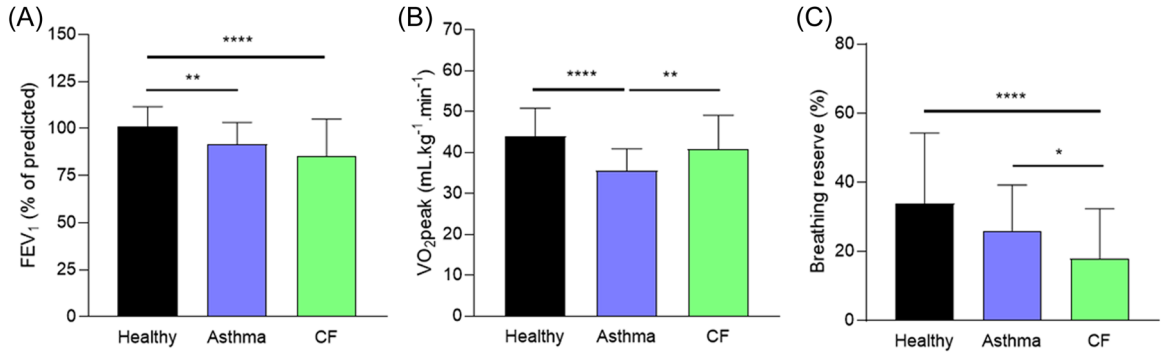

FIGURE 1 Comparison of (A) forced expiratory volume in the first second (FEV_1), (B) peak oxygen uptake (VO_2peak), and (C) breathing reserve (BR) between healthy individuals and patients with asthma and cystic fibrosis (CF). Comparisons were performed using the one-way ANOVA followed by the Bonferroni post hoc test. *Indicates significant differences at $p < .05$, **indicates significant differences at $p < .001$, and ****indicates significant differences at $p < .0001$. ANOVA, analysis of variance. [Color figure can be viewed at wileyonlinelibrary.com]

individuals presented a significantly ($F_{(2,136)} = 21.066$, $p = .001$) higher test time as compared to both CF and asthmatics. Respiratory rate at peak exercise was significantly higher in the healthy group ($F_{(2,141)} = 3.592$, $p = .03$) and no differences were identified for the tidal volume (Table 2). In addition, significant differences between groups were observed for both V_E/VO_2 ($F_{(2,143)} = 15.384$, $p < .001$) and V_E/VCO_2 ($F_{(2,143)} = 15.194$, $p < .001$) at VT_1 (Figure 2A,B). For the V_E/VO_2 at VT_1, patients with CF reported the highest values when compared to both asthma and healthy individuals. In addition, asthmatic patients also presented higher V_E/VO_2 at VT_1 when compared to healthy subjects (Figure 2A). As for V_E/VCO_2 at VT_1 both asthmatic and CF patients showed higher values when compared to healthy participants, while no differences between asthma and CF groups were revealed (Figure 2B). There were also differences for both V_E/VO_2 ($F_{(2,139)} = 7.895$, $p = .001$) and V_E/VCO_2 ($F_{(2,144)} = 6.802$, $p = .002$) at peak exercise, indicating that CF patients presented higher values for both variables when compared to healthy individuals (Figure 2C,D).

4 | DISCUSSION

The present study further explored physiological responses of aerobic fitness in children and adolescents with CAD. The main findings have shown that children and adolescents with CF perform better than patients with asthma. CF patients presented lower ventilatory efficiency, lower BR and reduced lung function. In spite of that, a good exercise capacity was achieved, meaning no difference in VO_2peak when compared with healthy controls. On the other hand, the asthma group was not able to reach a cardiorespiratory capacity comparable to the healthy group. These data may contribute to a better understanding of different factors influencing aerobic fitness, helping to develop more efficient strategies for monitoring and treatment of patients with CAD.

The effects of asthma on the exercise capacity of children and adolescents are still controversial. We have previously demonstrated a reduction in VO_2peak, muscle strength, lifestyle, and functionality in a group of asthmatic children with exercise symptoms.[26] In addition, there are previous data showing a decrease in VO_2peak,[6–8] although there is also evidence reporting no differences.[4,5] For children and adolescents with CF, we have described maintenance of exercise capacity, contrary to evidence reporting reduced levels compared to healthy controls.[9] As for the workload achieved in the test, time was longer for the healthy group at VT_1 and peak exercise, while speed and incline only presented significant differences at VT_1. These data indicate that participants in the healthy group, despite presenting no differences in VO_2peak with respect to CF patients, maintain the exercise workload for a longer time. In addition to the VO_2, patients with asthma also reached VT_1 in a shorter time, speed, and incline when compared to both CF and healthy individuals. On the other hand, the impact of BR on exercise limitation has not been studied so far. Participants in the asthma group reported BR and ventilatory efficiency at peak exercise comparable to the healthy controls but failed to achieve good exercise capacity. Interestingly, patients with CF achieved good exercise capacity even though they presented lower BR and poor ventilatory efficiency both at VT_1 and peak exercise. Our study highlights the importance of analyzing BR as part of the interpretation of functional assessment in children and adolescents with CAD.

Although the reasons for these differences are not fully comprehended, one of the most discussed causes of exercise limitation in asthmatic patients is EIB.[31] Individuals who develop EIB would have reduced exercise capacity compared to those without EIB due to a drop in FEV_1. However, present data has demonstrated no differences in both VO_2peak and BR values between those with and without EIB, indicating that EIB may not be an isolated cause of exercise limitation that would explain the differences found between asthma and CF groups. We hypothesize that physical conditioning may play a principal role to explain the maintenance of VO_2peak in patients with CF. A recent systematic review and meta-analysis concluded that CF children and adolescents have similar moderate-to-vigorous physical activity and sedentary time as healthy controls.[32] European Cystic Fibrosis Society states that physical activity and exercise must be integral to the overall

TABLE 2 Indices of cardiopulmonary exercise testing.

CPET variables	Healthy ($n = 48$)	Asthma ($n = 48$)	CF ($n = 51$)	p value
Baseline				
RR (rpm)	23.4 ± 3.9	18 ± 3.7	23.9 ± 5.9	**<.001*°**
Tidal volume (L)	0.56 ± 0.16	0.55 ± 0.18	0.52 ± 0.16	.46
Ventilatory threshold				
Speed (km h^{-1})	4.2 ± 0.6	3.4 ± 0.5	3.8 ± 0.7	**<.001*#°**
Incline (%)	9.3 ± 3.1	5.4 ± 2.4	7.5 ± 2.7	**<.001*#°**
Time (min)	6.1 ± 1.6	4.1 ± 1.2	5.2 ± 1.4	**<.001*#°**
HR (beats min^{-1})	148.6 ± 12.6	137.5 ± 12.2	136.3 ± 13.7	**<.001*#**
RR (rpm)	34.3 ± 7.0	30.1 ± 6.9	32.2 ± 8.3	**.02***
Tidal volume (L)	0.93 ± 0.33	0.86 ± 0.30	0.88 ± 0.32	.44
VO_2 (mL kg^{-1} min^{-1})	27.4 ± 4.8	19.8 ± 3.2	23.9 ± 6.3	**<.001*#°**
V_E (L min^{-1})	28.1 ± 7.4	24.8 ± 8.0	26.2 ± 9.0	.13
V_E/VO_2	24.9 ± 3.0	27.3 ± 3.2	30.0 ± 6.4	**<.001*#°**
V_E/VCO_2	27.8 ± 3.6	31.2 ± 3.7	32.8 ± 8.3	**<.001*#**
RER	0.90 ± 0.06	0.88 ± 0.07	0.91 ± 0.13	.29
Peak exercise				
Speed (km h^{-1})	6.0 ± 0.8	5.7 ± 0.6	5.7 ± 0.9	.06
Incline (%)	17.6 ± 5.1	16.8 ± 2.4	16.8 ± 4.1	.06
Time (min)	11.0 ± 1.5	9.9 ± 1.2	9.8 ± 2.0	**.001*#**
HR (beats min^{-1})	192.4 ± 6.9	191.9 ± 8.3	185.8 ± 6.1	**<.001#°**
O_2 pulse (mL $beats^{-1}$)	9.6 ± 3.3	8.7 ± 3.1	9.5 ± 3.6	.32
RR (rpm)	51.4 ± 9.8	46.8 ± 9.0	46.3 ± 11.4	**.03#**
Tidal volume (L)	1.23 ± 0.40	1.24 ± 0.42	1.40 ± 0.65	.18
VO_2 (L min^{-1})	1.85 ± 0.63	1.66 ± 0.58	1.66 ± 0.66	.20
VO_2 (mL kg^{-1} min^{-1})	43.8 ± 7.0	35.5 ± 5.3	40.7 ± 8.4	**<.001*°**
V_E (L min^{-1})	60.6 ± 19.2	59.0 ± 17.5	60.8 ± 1.8	.88
V_E/VO_2	38.4 ± 18.8	36.0 ± 4.3	37.7 ± 6.7	**.001#**
V_E/VCO_2	30.3 ± 3.5	31.8 ± 4.5	34.2 ± 7.2	**.002#**
RER	1.12 ± 0.09	1.16 ± 0.12	1.15 ± 0.15	.31
BR (%)	33.9 ± 20.3	26.0 ± 13.3	17.8 ± 14.6	**<.001#°**

Note: Values are expressed as mean ± standard deviation. Significant p values are highlighted in bold, following the one-way analysis of variance. Significant differences between groups are identified as follows: healthy versus asthma (*), healthy versus cystic fibrosis (#), asthma versus cystic fibrosis (o).

Abbreviations: BR, breathing reserve; CPET, cardiopulmonary exercise testing; h, hour; HR, heart rate; kg, kilogram; km, kilometers; L, liter; min, minute; mL, milliliter; RER, respiratory exchange ratio; RR, respiratory rate; rpm, respirations per minute; VE, minute ventilation; VE/VCO_2, ventilatory equivalent ratio for carbon dioxide production; VE/VO_2, ventilatory equivalent ratio for oxygen consumption; VO_2, oxygen uptake.

physiotherapy management suggested for every individual with CF, irrespective of age and disease severity.[33] As an active lifestyle is considered part of standard care, CF patients participate in a wide range of physical activities and sports. One study demonstrates that 22.7% of school children with CF reported participating in three or more (un)structured physical activities or sports compared to 4.4% of healthy children.[34] These results suggest that physical deconditioning could also be one of the factors related to exercise intolerance even in healthy children. On the other hand, although physical activity and exercise are encouraged in children and adolescents with asthma,[35] a

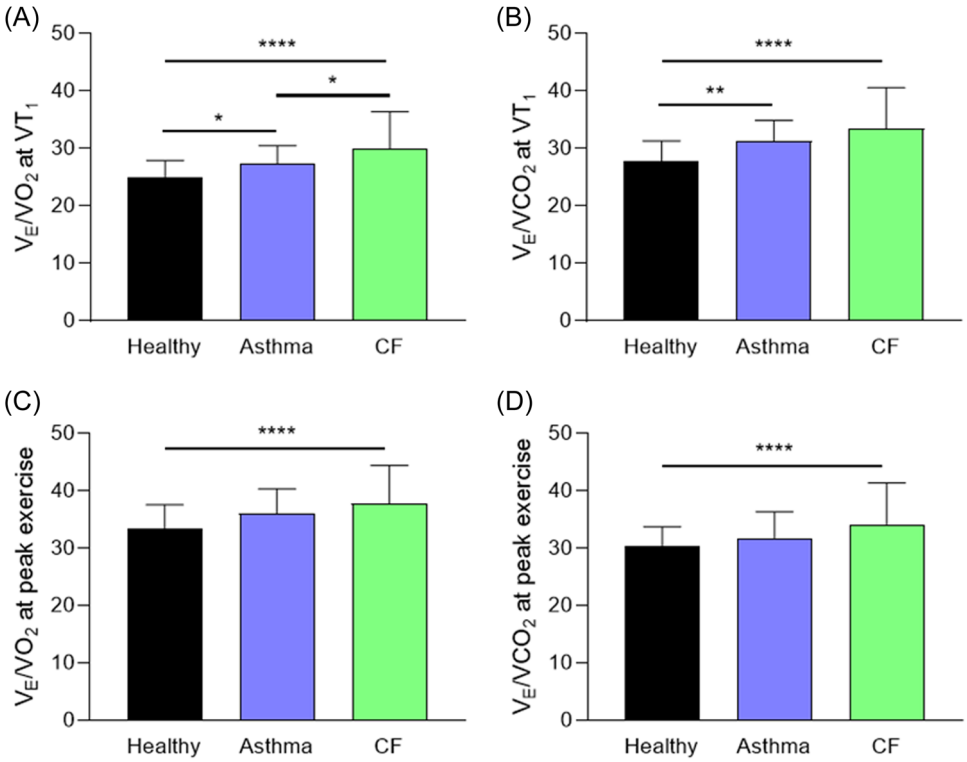

FIGURE 2 Comparison of ventilatory equivalent for oxygen consumption (V_E/VO_2) and ventilatory equivalent for carbon dioxide production (V_E/VCO_2) at the ventilatory threshold (VT_1) (A and B) and at peak exercise (C and D). Comparisons were performed using the one-way ANOVA followed by the Bonferroni post-hoc test. *Indicates significant differences at $p < .05$, **indicates significant differences at $p < .001$, and ****indicates significant differences at $p < .0001$. ANOVA, analysis of variance. [Color figure can be viewed at wileyonlinelibrary.com]

lower active lifestyle has been reported. While most CF patients are aware of the importance of physical activity and exercise, possibly due to the severity of the disease, it has been observed that many asthma patients do not follow these recommendations.[36] The decrease in physical activity reduces the stimuli to improve muscular and cardiorespiratory fitness, producing progressive and sustained deconditioning.[13] Our data demonstrated that the asthmatic patients presented the shorter time to achieve VT_1. A recent study reported that physical deconditioning is the only significant determinant of reduced exercise capacity in asthma, irrespective of asthma diagnosis, BMI, ventilatory limitation or presence of EIB in children and adolescents with controlled mild-to-moderate asthma.[37] Taken together, we believe that the most likely hypothesis for the reduced exercise capacity in asthmatics compared to patients with CF would be physical deconditioning. In addition, body composition is also influenced by physical activity and may play a role to explain these results. Our data shows that in spite of the reduced BMI when compared to asthmatics, patients with CF demonstrated a higher percentage of lean mass. Finally, we cannot rule out the possibility that asthmatics may develop acutely significant ventilation and perfusion mismatch. In children with CF, it has been described that ventilation and perfusion are normal in early disease, but it may become abnormal as the disease progresses.[38]

The influence of lung function on exercise capacity in children and adolescents with asthma and CF is also still a matter of debate. Although FEV_1 is an important clinical parameter, according to our results, it does not influence the VO_2peak achieved, at least for patients with mild-to-moderate impairments. In asthmatic children and adolescents, previous studies reported no significant correlations between FEV_1 and exercise capacity,[13] while others found a positive correlation.[14] For children and adolescents with CF, some studies found a positive correlation between FEV_1 and exercise capacity, while others reported that VO_2peak could be preserved until FEV_1 falls below the predicted 60%.[39] Although a significant reduction in $FEF_{25\%-75\%}$ was seen in CF patients as compared to asthmatics, it did not seem to affect oxygen consumption. The use of $FEF_{25\%-75\%}$ as a marker of small airways disease may also present its imitations, as previously demonstrated.[40]

In our study, comparisons between asthmatic and healthy controls revealed no differences in BR, which seems to be in accordance with previous evidence.[4,5] Santuz et al.[4] reported that BR was comparable among asthmatic and healthy individuals, as well as Moraes et al.[5] described no significant differences between children and adolescents with both mild-to-moderate and mild-persistent asthma as compared to healthy peers. On the other hand, our results have shown the patients with CF presented lower BR than the healthy and asthmatic groups. The reduced BR found for the CF group indicates that these patients require higher ventilatory demands during exertion, but does not necessarily mean that there is exercise limitation.[9,22] Ronen Bar-Yoseph et al.[9] observed low BR

in 49% of patients with CF, while Borel et al.[22] found a reduced BR for patients with CF when compared to healthy children. It is also important to highlight that MVV was estimated using the FEV_1.[41] Although this is a widely used method, it is also subjected to underestimation of true ventilatory capacity in obstructive diseases with low FEV_1, which may have influenced the present results.[42]

Ventilatory efficiency, evaluated through V_E/VO_2 and V_E/VCO_2, has also been recognized as one of the factors that may contribute to the limitation of exercise in patients with CAD.[5,43] The V_E is the product of tidal volume and respiratory rate, which may be affected by disease or deconditioning.[16,31] The present results have shown no differences between groups on V_E and tidal volume at peak exercise, indicating that individuals were able to achieve the same "levels." However, both at VT_1 and peak exercise, an increase in V_E/VO_2 and V_E/VCO_2 was found for the CF group, as previously described,[43] indicating that the increase in V_E was not sufficient to guarantee the necessary O_2 consumption and CO_2 elimination. Moorcroft et al.[44] has also described differences in the V_E/VO_2 between patients with CF who survived or not. Several factors may explain lower ventilatory efficiency in patients with CF. As exercise ventilatory demand increases, progressive expiratory airflow obstruction and increasing flow resistance occur, leading to dynamic hyperinflation. In addition, ventilatory efficiency is also reduced by increased dead space ventilation, even in mildly affected CF patients.[16] Regarding the asthma group, patients have shown an increase in V_E/VO_2 and V_E/VCO_2 at VT_1, but not at peak exercise. Although the results on V_E/VO_2 at peak exercise are consistent with those reported by a previous study,[5] there is scarce evidence on possible factors explaining lower ventilatory efficiency at VT_1 for asthmatics. Future studies should investigate possible individual effects of transitory airway obstruction and deconditioning on submaximal ventilatory efficiency in children with asthma. In addition, the role of inflammatory mediators could also be important, as there is evidence correlating exercise-induced sputum histamine levels with low arterial oxygen partial pressure.[45]

The present study presents limitations, including the lack of measures of the degree of airway inflammation, exhaled breath condensate or ventilation and perfusion scanning, as these measures could correlate with the outcome measures and help us to understand the main mechanisms involved in exercise intolerance. In addition, our study did not evaluate participants' daily levels of physical activity, which prevented us from further discussion on the topic. On the other hand, although indirect estimation of MVV is likely the optimal test in pediatric patients,[41] it may underestimate the true ventilatory capacity in obstructive diseases where a low FEV_1 is present.

In conclusion, the findings of the present study provide evidence on aerobic fitness and its related determinants in children and adolescents with CAD. Patients with CF achieved good exercise capacity despite low ventilatory efficiency, low BR, and reduced lung function. However, asthmatics presented reduced cardiorespiratory capacity and normal ventilatory efficiency at peak exercise, although there were differences in the ventilatory threshold, when compared to healthy peers, highlighting the different mechanisms implicated in determining aerobic fitness in CAD. These results may contribute to a better understanding of the influence of CAD on exercise capacity, providing data to support exercise practice aiming to improve physical conditioning, and emphasizing the importance of routine evaluation of BR and ventilatory efficiency as part of CPET outcomes.

AUTHOR CONTRIBUTIONS

Márcio Vinícius Fagundes Donadio: conceptualization; formal analysis; writing—original draft; Writing—review & editing. **Marta Amor Barbosa**: writing—original draft; writing—review & editing; formal analysis; conceptualization. **Fernanda Maria Vendrusculo**: writing—review & editing; investigation; conceptualization; formal analysis. **Tamara Iturriaga Ramirez**: investigation; methodology; writing—review & editing; data curation. **Elena Santana-Sosa**: investigation; writing—review & editing; data curation. **Veronica Sanz-Santiago**: investigation; writing—review & editing; data curation; formal analysis; supervision. **Margarita Perez-Ruiz**: conceptualization; writing—review & editing; supervision; investigation; writing—original draft; methodology; formal analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data is available upon request to the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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