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

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Abstract

Introduction. Exercise intolerance is common in chronic respiratory diseases (CRD), 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_{2}peak), forced expiratory volume in 1 second (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_{2}peak 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 ventilatory limitation to maximum exercise testing in children and adolescents with CRD.

INTRODUCTION

Chronic respiratory diseases (CRD) are associated with abnormalities in the airways and other structures of the lung, with asthma being the most common CRD in the pediatric age range, and cystic fibrosis (CF) being the most frequent genetic disease in Caucasians [1]. Asthma is a chronic inflammatory disease characterized by variable airway obstruction, leading to hyperresponsiveness, inflammation, and respiratory symptoms, representing a major cause of pediatric hospitalization worldwide [2]. On the other hand, CF is a hereditary, autosomal recessive disease, caused by the mutation of a gene that encodes the transmembrane conductance regulator protein (CFTR). The absence or dysfunction of the protein leads to a multisystem disease, inducing obstruction in secretory glands and a pro-inflammatory state, especially in the lungs [3].

In patients with CRD, 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[4]. 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 [5]. Despite this, there is no clear consensus on their exercise capacity. Some studies reported no differences between healthy and asthmatic patients [6,7], while others showed lower respiratory capacity in those with a diagnosis of asthma [8–10]. For children and adolescents with CF, evidence reports a reduction in exercise capacity compared to healthy controls [11].

The forced expiratory volume in the first second (FEV_1) is one of the most used clinical parameters for monitoring CRD, including asthma [2] and CF [3]. 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 CRD 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 [5]. 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 (VE) must increase through a combination of a rapid increase in tidal volume to a maximum of approximately 50% of forced vital capacity (FVC) and a progressive but steady increase in respiratory rate [16]. The most typical feature of CRD is progressive expiratory airflow obstruction and the development of expiratory flow 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 CRD can be reflected in different parameters during 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 due to abnormal ventilatory control in CRD 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[7,19]. 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 CRD the BRI is elevated, suggesting reduced BR at peak exercise[11,22]. 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 CRD 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.

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 was used as a reference to draft the manuscript.

Participants

Participants with a diagnosis of mild-to-moderate asthma and CF, as well as healthy children and adolescents were selected. General inclusion criteria was children and adolescents aged 7–18 years. General exclusion criteria were: (i) respiratory exacerbations 4 weeks prior to 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). 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)[25], or score 2–3 in question 7 of the asthma control in children (CAN) [26]. Specific exclusion criteria were: (i) need for increased use of basal medication, inhaled corticosteroid dose, 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. Participants with CF were also recruited at Hospital Niño Jesus in Madrid. Specific inclusion criteria was 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 [27]. Specific exclusion criteria were the diagnosis of cardiac, neurological, or chronic respiratory diseases that would impair cardiorespiratory fitness.

Outcomes

The primary outcomes of the study were VO_2peak, FEV_1, breathing reserve (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).

Assessments

Cardiopulmonary exercise testing (CPET)

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. 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(r)) and SpO_2 was monitored with a pulse oximeter (TrueSat^{TM}, GE Healthcare, Finland). 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) respiratory exchange ratio above 1.0, and (iii) clear exhaustion according to the perceived exertion (RPE).

Lung function

Spirometry was performed using a Spirostik spirometer (Jaeger, Germany) with a Blue Cherry diagnostic software platform, following the American Thoracic Society-European Respiratory Society (ATS/ERS) guidelines[28]. The main variables collected were FEV_1, forced vital capacity (FVC), and the ratio between FEV_1 and FVC. Data were interpreted according to the unified approach of the Global Lung Initiative (GLI), establishing as a limit of normality (LIN) a z-score value for FEV_1between - 1.64 and + 1.64.

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: [?]-2SD; severely thin: [?]-3SD.

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 (IQ), following their distribution. Categorical variables are shown in absolute and relative frequencies. Comparisons between groups were performed using the one-way analysis of variance (ANOVA), 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., USA) and the significance level adopted was *P* [?]0.05.

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. Asthma and CF groups presented lower $FEV_1$when compared to healthy controls, although there was no difference between asthmatics and CF patients in lung function.

As for cardiorespiratory fitness, significant differences were found for both VO_2peak ($F_{(2,144)}=16.992, p < 0.0001$) and BR ($F_{(2,144)}=12.067, p < 0.0001$) (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).

The main cardiopulmonary exercise testing variables at VT_1 and peak exercise are presented in Table 2. Significant differences between groups were observed for both V_E/VO_2 ($F_{(2,143)}=15.384, p < 0.0001$) and V_E/VCO_2($F_{(2,143)}=15.194$, $p < 0.0001$) at VT_1 (Figure 2A and 2B). 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 ($F_{(2,139)}=7.895, p = 0.001$) and V_E/VCO_2($F_{(2,144)}=6.802$, $p = 0.002$) at peak exercise, indicating that CF patients presented higher values for both variables when compared to healthy individuals (Figures 2C and 2D).

DISCUSSION

The present study further explored physiological responses of aerobic fitness in children and adolescents with CRD. The main findings have shown that 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 CRD.

The effects of asthma on the exercise capacity of children and adolescents are still controversial. Patients in the asthma group reported BR and ventilatory efficiency at peak exercise comparable to the healthy controls but failed to achieve good exercise capacity. The results presented here agree with previous studies showing a decrease in VO_2peak [8–10], although there is also evidence reporting no differences [6,7]. For children and adolescents with CF, we have described maintenance of exercise capacity, contrary to evidence reporting reduced levels compared to healthy controls [11]. Interestingly, this effect was seen even though CF patients presented lower BR and poor ventilatory efficiency both at VT_1 and peak exercise. Although the reasons for these differences are not fully comprehended, we hypothesize that physical conditioning may play a 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 [29]. European Cystic Fibrosis Society states that physical activity and exercise must be integral to the overall physiotherapy management suggested for every individual with CF, irrespective of age and disease severity [30]. 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 [31]. On the other hand, although physical activity and exercise should be encouraged in children and adolescents with asthma [32], a lower active lifestyle compared to their peers has been reported[33]. The decrease in physical activity reduces the stimuli to improve muscular and cardiorespiratory fitness, producing a progressive and sustained deconditioning [13]. 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[34]. Taken together, we believe that the most likely hypothesis for the reduced exercise capacity in asthmatics compared to patients with CF is physical deconditioning.

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%[35].

In our study, comparisons between asthmatic and healthy controls revealed no differences in BR, which seems to be in accordance with previous evidence [6,7]. Santuz et al. reported that BR was comparable among asthmatic and healthy individuals[6], as well as Moraes et al. described no significant differences between children and adolescents with both mild-to-moderate and mild-persistent asthma as compared to healthy peers[7]. 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, confirming evidence that reported reduced BR at peak exercise[11,22]. Ronen Bar-Yoseph et al. observed low BR in 49% of patients with CF[11], while Borel et al. found a reduced BR for patients with CF when compared to healthy children [22]. It is also important to highlight that MVV was estimated using the FEV_1 [36]. 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 [37].

Ventilatory efficiency has also been considered an important component of aerobic fitness in CRD [7,38]. Our results have shown that, 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, which was previously described [38]. Moorcroft et al. have also described differences in the

V_E/VO_2 between patients with CF who survived or not [39]. 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. These results are consistent with those reported by a previous study [7]. There is scarce evidence on possible factors explaining lower ventilatory efficiency at $VT_1$for asthmatics, although an obstructive origin may be the most likely. 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 [40].

The present study presents limitations, including the lack of measures of the degree of airway inflammation, such as exhaled nitric oxide fraction, sputum analysis, or exhaled breath condensate, 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 [36], 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 CRD. 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 CRD. These results may contribute to a better understanding of the influence of CRD 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.

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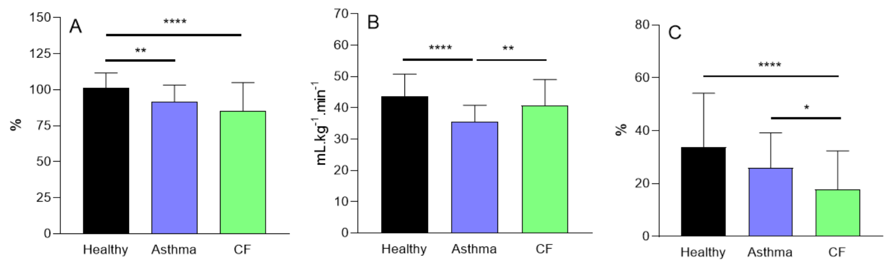
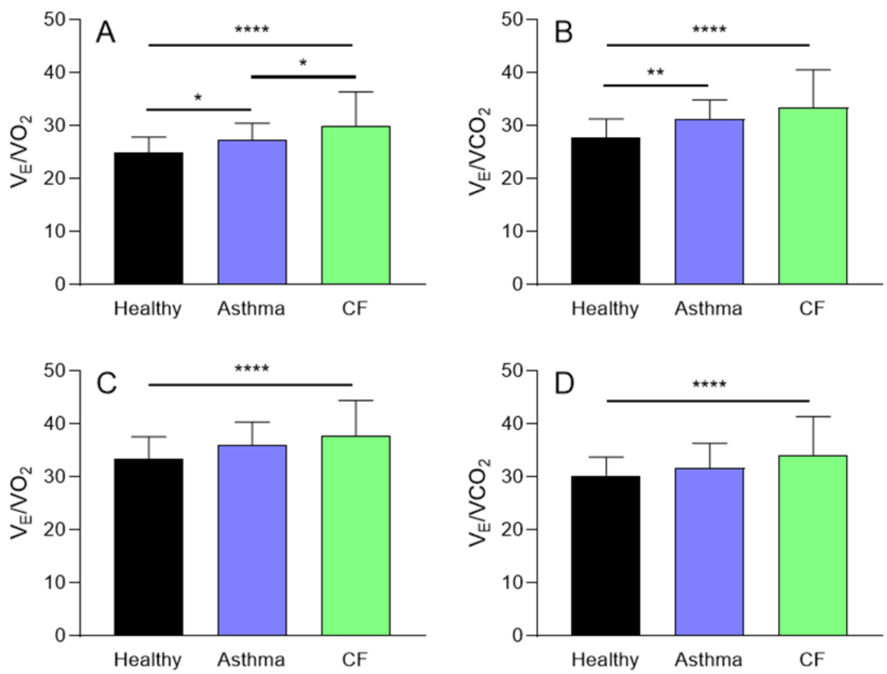
Figure Legends

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$p$ <0.05, **indicates significant differences at$p$ <0.001, and ****indicates significant differences at$p$ <0.0001.

Figure 2. Comparison of ventilatory equivalent for oxygen consumption (V_EVO_2) and ventilatory equivalent for carbon dioxide production (V_EVCO_2) at the ventilatory threshold (VT_1) (A) and (B), and peak exercise (C) and (D), respectively, 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 <0.05, **indicates significant differences at p <0.001, and ****indicates significant differences at p <0.0001.





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