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ORIGINAL ARTICLE

Continuous positive airway pressure acutely increases exercise duration in children with severe therapy-resistant asthma: a randomized crossover trial

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Abstract

Background Lower exercise tolerance is an important component of asthma and the possible effects of non-invasive ventilation on exercise capacity in individuals with severe therapy-resistant asthma (STRA) are unknown. This study aimed to evaluate the immediate effect of continuous positive airway pressure (CPAP) on exercise tolerance in children with STRA.

Methods We performed a controlled, randomized, crossover clinical trial including subjects aged 6 to 18 years old diagnosed with STRA. Clinical, anthropometric and lung function data were collected. The participants in the intervention group (IG) used CPAP (PEEP 10cmH_2O and FiO_2 0.21) for a period of 40 min. Subjects in the control group (CG) used CPAP with minimum PEEP at 1 cmH_20 also for 40 min. Afterwards, subjects from both groups underwent cardiopulmonary exercise testing (CPET). After a 15-day washout period, on a subsequent visit, subjects participated in the opposite group to the initial one.

Results Thirteen subjects with a mean age of 12.30 ± 1.7 years were included. The variables of peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV_1) before using CPAP and after performing CPET did not show significant differences. Regarding CPET results, there was no significant difference ($P = 0.59$) between groups at peak exercise for oxygen consumption—VO_2 (CG: 33.4 ± 6.3 and IG: 34.5 ± 5.9, mL kg^{-1} min^{-1}). However, the IG (12.4 ± 2.1) presented a total test time (min) significantly ($P = 0.01$) longer than the CG (11.5 ± 1.3).

Conclusion The results suggest that the use of CPAP before physical exercise increases exercise duration in children and adolescents with STRA.

Keywords Asthma · Non-invasive ventilation · Oxygen consumption · Exercise test · Exercise tolerance · Exercise-induced bronchospasm

Introduction

Asthma is a chronic inflammatory disease of the lower airways characterized by limited airflow and bronchial hyperresponsiveness [1]. The condition has high prevalence and morbidity, involving significant personal, family, and social costs [2]. Children with severe asthma who do not respond adequately to treatment and who present poor symptom control even after optimization of clinical management are classified as having severe therapy-resistant asthma (STRA). This subgroup classically presents with frequent exacerbations, daytime and nighttime symptoms, and reduced pulmonary function, which lead to the limited quality of life, lower levels of physical activity, and increased hospitalizations [3, 4].

Lower exercise tolerance is an important component of asthma, and major determining factors may be associated with the degree of airway obstruction at rest, decreased ventilatory capacity, increased dyspnea, the occurrence of exercise-induced bronchospasm (EIB), psychological factors, physical fitness, and obesity [5, 6]. Subjects in asthmatic crisis exhibit a considerable reduction in exercise capacity,

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which is usually reversed when the crisis is under control. Conversely, a reduction in health-related quality of life due to asthma symptoms causes many subjects to adopt a more sedentary lifestyle [7, 8].

Because of a limited expiratory flow in asthma and EIB, dynamic pulmonary hyperinflation is a common factor. As a result, the ability of respiratory muscles to generate tension is reduced and, for any level of ventilation, work of breathing increases compared to individuals without asthma [9]. Such a mechanism may be responsible for increased fatigue, dyspnea, and early interruption of physical activity. Considering these, noninvasive ventilation (NIV) has been used to reduce the work of respiratory muscles, minimizing the effects of dynamic hyperinflation and improving the levels of exercise tolerance [10–13]. A recent study demonstrated positive effects of NIV on bronchial hyperresponsiveness as assessed in an exercise bronchial provocation test in children with asthma [14], although nocturnal use has shown no positive effects [15]. However, possible immediate effects of NIV on exercise capacity in individuals with STRA are unknown.

Thus, the present study aimed to evaluate the immediate effect of continuous positive airway pressure (CPAP) on exercise tolerance in children and adolescents with STRA. Peak oxygen uptake (VO_2peak), minute ventilation (V_E), ventilatory equivalents for oxygen uptake (V_E/VO_2) and for carbon dioxide production (V_E/VCO_2) at anaerobic threshold and at peak exercise were evaluated, as well as exercise duration. We hypothesized here that the use of NIV would contribute towards a better ventilatory efficiency leading to increased exercise tolerance.

Methods

A randomized, placebo-controlled, double-blinded, crossover trial was conducted. Male and female children and adolescents with confirmed STRA (asthma which requires treatment on GINA steps 4 and 5—high dose of inhaled corticosteroids and long-acting beta-agonists plus another controller therapy—in the previous year or systemic corticosteroids for 50% of the previous year to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy [16]), aged from 6 to 18 years, undergoing regular treatment and follow-up at an asthma outpatient clinic were included. Subjects with cognitive/motor impairments or other chronic diseases (neurological diseases, congenital heart abnormalities, or immunodeficiencies) that could compromise any study assessments were excluded. In addition, subjects who, on the day of the tests, presented with signs of pulmonary exacerbation, such as increased cough, sputum production, wheezing, or chest constriction, and those who could not undergo cardiopulmonary exercise testing (CPET), were excluded. Data were collected from July 2017 to December 2018. All guardians signed an informed consent form, and children and adolescents aged ≥ 8 years signed an assent form. The study was approved by the University research ethics committee with number 48678115.9.0000.5336 and registered at ClinicalTrials.gov with identifier NCT03215303.

Study design

On a first visit, subjects underwent routine medical consultation at the asthma outpatient clinic and completed a Global Initiative for Asthma (GINA) questionnaire to assess disease control and an international Physical Activity Questionnaire (PAQ) to assess level of daily physical activity. Then, anthropometric variables were measured and a pulmonary function test was performed. Subjects were then randomized using a sealed envelope to receive either the treatment (CPAP) or placebo (CON). On a second visit, subjects who initially used CPAP received placebo (CPAP with minimal positive end-expiratory pressure [PEEP]), while those who had previously used placebo were treated with CPAP. On both visits, CPET was performed and peak expiratory flow (PEF) was measured. Subjects had a 15-day washout period between the two visits. Patients were instructed not to use bronchodilators for at least 12 h before the tests. The sequential order of randomization was concealed by a single researcher, while other professionals involved in data collection were blinded throughout the study period. Similarly, subjects were blinded to the experimental group at each visit. The study flowchart is shown in Fig. 1.

CPAP intervention

CPAP was always administered by the same physical therapist at the Pediatric Physical Activity Laboratory. A facial mask was used for CPAP. Treatment was initiated with PEEP at 1 cmH_2O, which was then increased every 2 cmH_2O to a maximum of 10 cmH_2O, according to each subject's tolerance. Thus, the intervention consisted of NIV on CPAP mode with PEEP at 10 cmH_2O, fraction of inspired oxygen (FiO_2) at 0.21, for a single session of 40 min. Placebo, in turn, consisted of NIV (CPAP) with minimum PEEP at 1 cmH_20 and FiO_2 at 0.21, also for 40 min [17, 18]. On both visits, after NIV use, CPET was performed and PEF was measured.

Anthropometric assessment

Anthropometric assessment consisted of weight and height measurement in triplicate. Weight was obtained with participants in the upright standing position using a previously calibrated digital scale (G-Tech, Glass 1 FW, Rio de Janeiro, Brazil) accurate to 100 g. Height was obtained with

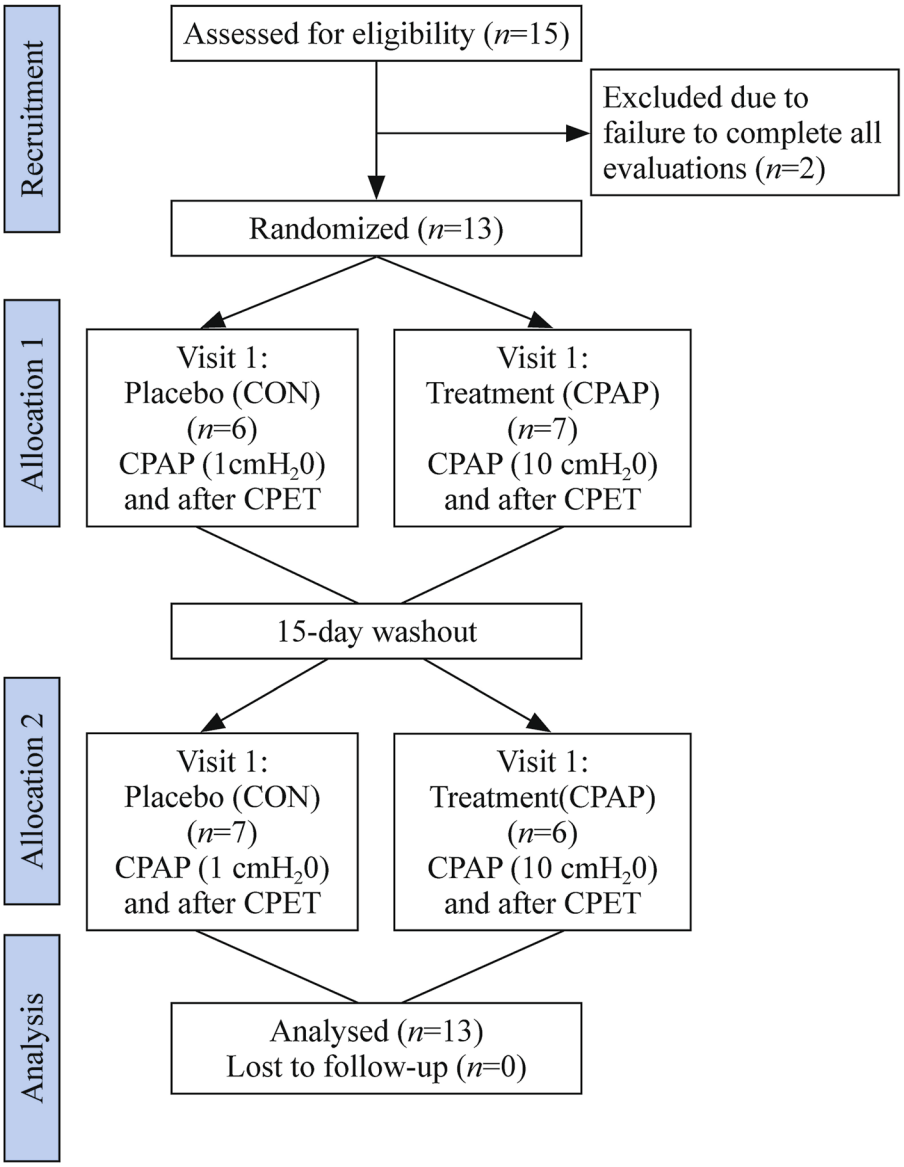

Fig. 1 Flow chart of study design

participants barefoot using a portable stadiometer (Altura Exata, TBW, São Paulo, Brazil) accurate to 1 mm. Then, body mass index (BMI = weight [kg]/height^2 [m]) was calculated and described as absolute value and *z*-score [16, 19].

Global initiative for asthma (GINA) questionnaire

The GINA questionnaire was used to assess the level of asthma control. It consists of 4 questions referring to daytime and nighttime symptoms, use of rescue medication, and limitation of activities in the past 4 weeks. The following responses were considered for classification purposes: all negative (controlled asthma); 1 or 2 positive (partially controlled asthma); and 3 or 4 positive (uncontrolled asthma) [1].

Physical activity assessment

The PAQ short form was used to assess the level of daily physical activity. This instrument refers to the past 7 days, comprising questions on frequency and time spent walking and doing moderate- and vigorous-intensity activities, as well as time spent sitting. Subjects aged ≥ 15 years completed PAQ-A (version for adolescents) and were classified as active if they practiced at

least 150 min of moderate-intensity physical activity. Subjects aged < 15 years completed PAQ-C (version for children) and were classified as active (score ≥ 3) or sedentary (score < 3) [20].

Pulmonary function

Spirometry was performed using KoKo spirometer (Louisville, USA). The parameters evaluated were forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, forced expiratory flow between 25 and 75% of vital capacity ($FEF_{25-75\%}$), and PEF. Three acceptable curves and two reproducible curves were obtained. All technical procedures followed the recommendations of the American Thoracic Society—European Respiratory Society ATS/ERS [21]. The Global Lung Function Initiative (GLI-2012) reference equation was used for data normalization [22].

Cardiopulmonary exercise testing (CPET)

Exercise capacity was assessed using an ergospirometry system with VO2000 gas analyzer (Medical Graphics Corporation, St. Paul, USA). To perform the test, a face mask connected to a previously calibrated electronic equipment was fitted to the child's face, allowing the passage of expired gases. A trained researcher conducted the test following the recommendations of the American College of Sports Medicine (ACMS) [23] and using a ramp protocol adapted from a previous study [24]. Heart rate (HR) was obtained through a heart rate sensor (Polar H10, Bethpage, NY, USA) directly connected to the gas analysis system, and peripheral oxygen saturation (SpO_2) was measured with a portable pulse oximeter (Nonin®, Minneapolis, USA). Data were collected at rest (after a 15-min resting period), every 60 s during the test, and immediately after the test completion. In short, participants were instructed to walk for 2 min to adapt to the treadmill, which was set to a speed of 3 km/h and no incline. Then, a fixed 3% incline was used, and speed gradually increased at a rate of 0.5 km/h every minute up to the end of the test [24]. All subjects were encouraged to keep pace until exhaustion or the appearance of limiting signs and/or symptoms (dyspnea, leg pain, and/or dizziness). For the test to be considered maximal, at least three of the following criteria should be observed: clear exhaustion, respiratory exchange ratio (RER) > 1.0, HR max > 85% of estimated HR (208 – age × 0.7), and presence of VO_2 plateau [25, 26]. Data were recorded, entered into a software (Aerograph), and then analyzed. The parameters evaluated were peak exercise oxygen uptake (VO_2peak) (mL kg^{-1} min^{-1}), V_E(L/min), V_E/VO_2, and V_E/VCO_2, VO_2 at anaerobic threshold, exercise duration (min), and HR max (bpm). At the beginning and at the end of the protocol, subjects were asked to rate the subjective degree of dyspnea using a modified Borg scale [27].

Statistical analysis

The Shapiro–Wilk test was used to assess the normality of data. Normally distributed variables were described as mean and standard deviation, and asymmetrically distributed variables as median and interquartile range. Categorical variables were described as absolute and relative frequency. Outcome comparisons between groups were performed using Student's *t*-test for paired samples. Standardized effect sizes were reported using Cohen's *d*. A generalized linear model was used to assess the interaction between treatment (CPAP and placebo) and time (before and after), followed by a least significant difference (LSD) test. All analyses were performed in SPSS, version 17.0, and differences were considered significant if $P < 0.05$.

Results

Fifteen children and adolescents with STRA were recruited, but two of them failed to complete all study steps. Thus, the total sample consisted of 13 subjects (7 females) with a mean age of 12.3 ± 1.7 years. Regarding disease control, 6 (46.2%) subjects were classified as uncontrolled asthma, 3 (23.1%) as partially controlled asthma, and 4 (30.8%) as controlled asthma. Eight subjects (61.5%) used omalizumab. Mean FEV_1 was 89.7 ± 17.9%, and 5 (38.5%) subjects had values < 80%. Regarding the level of physical activity, as assessed in PAQ-A and PAQ-C, median time was 60 min for moderate-intensity activity and 110 min for vigorous-intensity activity, suggestive of a sample of inactive children and adolescents with STRA. The clinical and demographic characteristics of the sample are shown in Table 1.

Table 2 shows PEF and FEV_1 results before CPAP use and after CPET administration. Although there was a decrease in PEF (L/min) and FEV_1 (L) after CPET, both in CON (ΔPEF − 0.88 ± 0.8; ΔFEV_1 − 0.39 ± 0.4) and CPAP (ΔPEF − 0.66 ± 0.8 e ΔFEV_1 − 0.34 ± 0.2) moments, these differences were not significant.

Variables at rest, at anaerobic threshold, and at peak exercise in CON and CPAP are shown in Table 3. According to CPET results, there was no significant difference between CON and CPAP at peak exercise; mean difference for VO_2 was 1.1 mL kg^{-1} min^{-1} between groups ($P = 0.59$; $d = 0.16$), and for V_E was 5.6 L min^{-1} ($P = 0.15$; $d = 0.42$). Values were within the normal range. Both HR max and RER in CON (190.9 ± 14.3 bpm; 1.09 ± 0.1, respectively) and in CPAP

Table 1 Characteristics of the study subjects

Variables	$n=13$
Demographics	
Age (y)	12.30 ± 1.7
Female [*n* (%)]	7 (53.8)
Anthropometry	
Weight (kg)	49.5 ± 9.5
Height (cm)	153.1 ± 10.9
BMI (kg/m^2)	20.6 ± 3.2
BMI (*z*-score)	0.6 ± 0.8
GINA questionnaire	
Controlled [*n* (%)]	4 (30.8)
Partially controlled [*n* (%)]	3 (23.1)
Not controlled [*n* (%)]	6 (46.2)
Lung function	
FEV_1 (L)	2.3 ± 0.8
FEV_1 (%)	89.7 ± 17.9
FVC (L)	2.9 ± 0.7
FVC (%)	97.8 ± 11.5
FEV_1/FVC (absolute)	0.8 ± 0.1
FEV_1/FVC (%)	91.5 ± 15.5
$FEF_{25–75\%}$ (L/min)	2.5 ± 1.6
$FEF_{25–75\%}$ (%)	80.66 ± 43.8
Physical activity level PAQ-A	
Sitting time (min)	345 (180–840)
Walking time (min)	37.5 (0–150)
Moderate activity time (min)	60 (90–300)
Vigorous activity time (min)	110 (0–150)
PAQ-C	2.17 ± 0.7

Data expressed as a percentage or mean ± standard deviation of the mean, except PAQ-A (median and interquartile range)

BMI body mass index, *GINA* global initiative for asthma, FEV_1 forced expiratory volume in one second, *FVC* forced vital capacity, $FEF_{25-75\%}$ forced expiratory flow between 25 and 75% of FVC

(188.7 ± 9 bpm; 1.1 ± 0.07, respectively) are suggestive of a maximal test. There was no decrease in SpO_2 in both moments. Mean differences between groups for V_E/VCO_2 and V_E/VO_2 were, respectively, − 0.3 ($P=0.65$; $d=-0.13$) and 0.3 ($P=0.76$; $d=0.09$). There was a significant difference ($P=0.01$) of 0.9 min in total exercise duration, with the highest effect size found ($d=0.45$), suggesting that subjects in the CPAP group remained exercising longer than those in CON.

Discussion

The results of the present study demonstrated that the use of CPAP before CPET in children and adolescents with STRA caused an increase in exercise duration. However, it did not improve major physiological variables that represent exercise capacity. To date, this seems to be the first study to evaluate the effect of NIV (CPAP) on exercise capacity in children and adolescents with STRA.

The use of CPAP in healthy participants during exercise at 80% of VO_2 max has previously been addressed, and data have shown a significant reduction in the subjective effort according to the Borg scale, as well as an increase in exercise time [28]. Results from the present study have also demonstrated that CPAP significantly increased total exercise time as assessed in CPET. Although a mean raw change of 0.9 min was found, we believe it is important to highlight that this increase in a maximum test would represent a larger gain in submaximal and/or functional daily activities. The factors leading to this increase remain unclear, but evidence from the literature suggests that the presence of EIB may play a role in this effect. David et al. evaluated the effect of NIV treatment (CPAP and combined bilevel pressure) associated with chest physical therapy on exercise-induced bronchial hyperresponsiveness in children and adolescents with asthma [14]. Results showed that CPAP treatment reduced the severity of EIB, with a significant increase in post-challenge FEV_1 [14], suggesting that the use of NIV may have positive effects on physical performance by reducing the occurrence and/or intensity of EIB.

Despite a positive effect on exercise duration, there were no changes in major performance variables in CPET in the present study. The lack of significant difference in VO_2peak was expected, as this variable depends on physical fitness

Table 2 Pulmonary function before the use of CPAP and after cardiopulmonary exercise testing

Variables	Control ($n=13$)			CPAP ($n=13$)			
	Before	After	P*	Before	After	P*	$P^{\dagger}$
PEF (L/min)	288.9 ± 89.6	235.7 ± 108.3	0.22	298.1 ± 107.9	262 ± 114.9	0.36	0.60
FEV_1 (L)	2.34 ± 0.2	1.94 ± 0.2	0.26	2.44 ± 0.2	2.09 ± 0.2	0.33	0.69

Data presented as mean and standard deviation

CPAP continuous positive airway pressure, *PEF* peak expiratory flow, FEV_1 forced expiratory volume in one second

*Significance level when comparing before and after values in each group

†Significance level when comparing final (after) values between groups

Table 3 Main variables evaluated in cardiopulmonary exercise testing (CPET)

Variables	Control	Intervention	Difference (95%CI)	*P*-value	*d*
At rest					
HR (bpm)	90.6 ± 15.4	92.7 ± 11.4	1.9 (– 6.1 to 9.8)	0.62	0.14
SpO_2 (%)	98.2 ± 0.9	97.6 ± 1.6	– 0.6 (– 1.9 to 0.7)	0.34	– 0.28
RER	0.8 ± 0.6	0.8 ± 0.4	– 0.02 (– 0.06 to 0.02)	0.29	– 0.30
VO_2 (L/min)	0.3 ± 0.1	0.3 ± 0.1	– 0.007 (– 0.1 to 0.09)	0.87	– 0.11
VO_2 (mL/kg/min)	6.6 ± 2.4	5.7 ± 2.7	– 0.8 (– 3.1 to 1.3)	0.41	– 0.23
V_E (L/min)	7.8 ± 2.8	6.9 ± 1.1	– 0.9 (– 2.6 to 0.8)	0.26	– 0.33
At anaerobic threshold					
HR (bpm)	161.5 ± 24.6	159.5 ± 18.2	– 2.0 (– 14.2 to 10.6)	0.73	– 0.10
VO_2 (L/min)	1.2 ± 0.3	1.1 ± 0.2	– 0.09 (– 0.02 to 0.07)	0.24	– 0.34
VO_2 (mL/kg/min)	25.3 ± 5.7	23.5 ± 4.7	– 1.7 (– 5.3 to 1.8)	0.30	– 0.30
VO_2%max	76.4 ± 12.6	69.4 ± 14.3	– 7.0 (– 14.6 to 0.6)	0.06	– 0.56
V_E (L/min)	26.6 ± 6.7	25.3 ± 5.3	– 1.3 (– 5.5 to 3.1)	0.53	– 0.18
V_E/VO_2	21.5 ± 1.5	22.1 ± 1.6	0.6 (– 0.4 to 1.6)	0.26	0.32
V_E/VCO_2	21.1 ± 1.5	21.4 ± 1.5	0.3 (– 0.6 to 1.0)	0.54	0.17
At peak exercise					
HR (bpm)	190.9 ± 14.3	188.7 ± 9.2	– 2.1 (– 8.8 to 4.5)	0.49	– 0.19
SpO_2 (%)	97.2 ± 1.0	96.7 ± 1.7	– 0.5 (– 2.0 to 0.9)	0.44	– 0.22
RER	1.1 ± 0.1	1.1 ± 0.1	0.02 (– 0.02 to 0.07)	0.25	0.33
VO_2 (L/min)	1.6 ± 0.4	2.1 ± 1.3	0.5 (– 0.5 to 1.4)	0.29	0.30
VO_2 (mL/kg/min)	33.4 ± 6.3	34.5 ± 5.9	1.1 (– 2.8 to 4.9)	0.59	0.16
V_E (L/min)	38.6 ± 12.3	44.2 ± 14.8	5.6 (– 2.4 to 13.6)	0.15	0.42
V_E/VO_2	25.4 ± 3.4	25.7 ± 3.2	0.3 (– 1.7 to 2.3)	0.76	0.09
V_E/VCO_2	23.1 ± 1.9	22.8 ± 2.0	– 0.3 (– 1.6 to 1.1)	0.65	– 0.13
Total test duration (min)	11.5 ± 1.3	12.4 ± 2.1	0.9 (0.1 to 1.5)	0.01*	0.45

Data presented as mean and standard deviation

BPM beats per minute, the heart rate unit; *CI* confidence interval, *HR* heart rate, SpO_2 oxygen saturation, *RER* respiratory exchange ratio, VO_2 oxygen uptake, V_E minute ventilation, V_E/VO_2 ventilatory equivalent for oxygen uptake, V_E/VCO_2 ventilatory equivalent for carbon dioxide production

*Indicates significant difference ($P < 0.05$) between groups. Standardized effect sizes were reported using Cohen's *d*

and involves interactions of the respiratory, cardiac, and musculoskeletal systems. However, changes in variables such as V_E, V_E/VO_2, and V_E/VCO_2 would be more likely because these parameters depend, at least in part, on airway resistance. The use of positive pressure could increase lung volume, producing a mechanical effect and optimizing bronchodilation [14]. Evidence from an experimental model demonstrated that the use of CPAP reduced methacholine-induced airway responsiveness, even in the presence of atopic inflammation [12]. Similarly, in adults with stable asthma, results showed that nighttime CPAP use for 7 days reduced airway reactivity [13]. Conversely, the use of nighttime CPAP (8–10 cmH_2O) for 4 weeks in children and adolescents with moderate-to-severe asthma did not reduce airway reactivity in a methacholine-induced bronchoconstriction test [29]. Factors such as disease severity, age, time, and period of CPAP use may have been decisive for a lack of consensus on the effects of CPAP on physical performance.

Although STRA affects a small proportion of children with asthma, quality of life in this subgroup of subjects is significantly impaired, contributing to a sedentary lifestyle. In the present study, almost half (46.2%) of subjects with STRA had the disease uncontrolled, and results from the physical activity questionnaire showed that subjects were classified as inactive or sedentary. David et al. in their study of asthmatic children and adolescents did not evaluate the level of physical activity [14]. However, disease control was assessed using the Asthma Control Questionnaire (ACQ) after NIV treatment and chest physical therapy, and results revealed improved asthma control after NIV use, as status changed from partially controlled to controlled asthma. Taken together, these data demonstrate the importance of new non-pharmacological therapeutic strategies as a complement to drug therapy.

This study has some important limitations. First, the small sample size makes it difficult to generalize the results of this

study, and it is important to interpret the findings with caution. Second, it is important to note that subjects had optimized treatment, as they were regularly followed up at a specialized center, which may reduce the magnitude of the changes usually found in subjects with STRA. In addition, some subjects used omalizumab (nonspecific anti-IgE immunotherapy), which may have contributed to a better performance, as the medication has known benefits for subjects with STRA and may have influenced exercise capacity and lung function results [30, 31]. However, discontinuing the use of medication to conduct a study is not possible from an ethical viewpoint.

In conclusion, the results of the present study suggest that the use of CPAP before physical exercise increases exercise duration in children and adolescents with STRA. The use of complementary non-pharmacological therapeutic strategies may help patients with limited exercise tolerance. The effects of CPAP in medium to long term should still be addressed in future studies.

Author contributions MD had substantial contributions to the study including Conceptualization, Data curation, Formal analysis, Project administration, Resources, Supervision, Writing—review & editing. CS had substantial contributions to the study including Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft. DS, NC, JHF, and PP had substantial contributions to the study including Data curation, Investigation, Methodology, Writing—review & editing.

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Declarations

Ethical approval The study was approved by the University research ethics committee (CEP-PUCRS) with number 48678115.9.0000.5336. All guardians signed an informed consent form, and children and adolescents aged ≥ 8 years signed an assent form.

Conflict of interest No financial or nonfinancial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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