Effects of constant-load exercise and high-intensity interval training on reliever medication consumption and peak expiratory flow in individuals with asthma: a randomised controlled trial

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Shareable abstract (@ERSpublications)
HIIT and CLE reduce SABA consumption and improve aerobic fitness but only HIIT improves PEF and induces better asthma control. Our results reinforce the importance of exercising in moderate-to-severe asthma and suggest greater improvements induced by HIIT. https://bit.ly/3u0aQyc

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Abstract

Introduction The effect of aerobic training on reliever medication consumption (short-acting β_2-agonist (SABA)) and peak expiratory flow (PEF) in participants with asthma is poorly known. The comparison between constant-load exercise (CLE) and high-intensity interval training (HIIT) in these outcomes has never been tested. The purpose of the present study was to compare the effects of CLE or HIIT in SABA consumption and PEF improvement during an exercise programme in subjects with asthma.

Methods Clinically stable participants were randomised into CLE (n=27; 70–85% of the maximal load (W_{max})) or HIIT (n=28; 80–140% W_{max}). The programme lasted 12 weeks (two sessions per week, 40 min per session), and the intensity was based on cardiopulmonary exercise testing (CPET). PEF was assessed before and after each exercise session. SABA was used if PEF was <70%. Clinical control (Asthma Control Questionnaire (ACQ)-6), CPET and aerobic fitness were also assessed before and after the intervention.

Results Both groups were similar at baseline. CLE and HIIT reduced SABA consumption throughout the intervention ($p<0.05$). Before training, 14 patients required SABA before exercising, but only one needed it after the intervention. Changes in post-exercise PEF were lower in the CLE group than in the HIIT group (1.6±25.3 *versus* 10.3±13.7%). Both groups improved aerobic fitness (10.1±12.8% *versus* 5.7±15.6%) and clinical asthma control; however, only the HIIT group achieved a minimal clinically important difference in the ACQ-6 post-intervention (−0.23±1.06 *versus* −0.52±0.73 Δ score).

Conclusion CLE and HIIT reduced SABA consumption; however, only HIIT increased PEF and asthma clinical control after the intervention. These results reinforce the importance of exercise training in moderate-to-severe asthma.

Introduction

The Global Initiative for Asthma (GINA) defines asthma as a heterogeneous lung disease usually characterised by chronic airway inflammation [1]. The clinical history includes respiratory symptoms such as wheezing, shortness of breath, chest tightness, variable expiratory airflow limitation, and cough, that vary over time and in intensity [1]. Asthma treatment is based on pharmacological and nonpharmacological treatments [1].

Pharmacological treatment for moderate-to-severe asthma is based on the use of controllers, *e.g.* inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA), and relievers, *e.g.* short-acting bronchodilators (SABA) or SABA+ICS, as needed [1]. SABA are mainly used as a pharmacological strategy to reduce dyspnoea symptoms during daily life activities and exercise or to prevent exercise-induced bronchoconstriction [1]. However, the excessive use of SABA has been associated with a

higher risk of exacerbation and increased mortality [2, 3]. Additionally, not all individuals with asthma take their anti-asthma reliever medication for several reasons, including the side-effects such as nervousness, trembling, heart palpitations, muscle cramps and headaches [4, 5].

Nonpharmacological treatments include physical training, and constant-load exercise (CLE) is the most commonly used exercise modality in adults with asthma [5]. In addition, high-intensity interval training (HIIT) also induces benefits [6–8]. Previous findings showed that CLE reduces asthma symptoms [9], inflammation and airway hyperresponsiveness [10] and increases clinical control [9, 11], quality of life [11, 12] and aerobic fitness [11, 13]. Similarly, HIIT reduces dyspnoea, fatigue [6, 8] and anxiety symptoms [7] and increases physical activity levels [6].

Regardless of the benefits of CLE and HIIT, their effects on medication consumption and peak expiratory flow (PEF) remain poorly understood [5]. Neder *et al*. [14] and Fanelli *et al*. [15] demonstrated that CLE reduces ICS consumption in children with asthma, and Pitzner-Fabricius *et al*. [16] showed a reduction of ICS after a HIIT programme; however, reliever medication consumption as SABA before and after exercise intervention was not standardised at that time. Furthermore, in the past decade, studies aiming to insulate the effect of exercise on people with asthma have been performed between two medical appointments to avoid changes in medication during the intervention [10, 11, 17]. Consequently, the focus on the benefits of exercise training on medication consumption has been reduced.

A recent study demonstrated that HIIT and CLE induced similar benefits in individuals with moderate to severe asthma [6]; however, changes in medication consumption and airway response after exercise were not measured. Hence, we tested the hypothesis that CLE and HIIT could improve asthma participants' aerobic fitness and reduce symptoms during exercise and SABA requirements. In addition, we assessed changes in PEF during the intervention.

Objective

To compare the effects of CLE and HIIT programmes on SABA consumption and PEF in individuals with moderate-to-severe asthma.

Methods

Participants treated at a university hospital with clinically stable (without exacerbations or changes in medication for ⩾30 days) moderate or severe persistent asthma, aged between 20 and 59 years, with a body mass index (BMI) ⩽35 $kg \cdot m^{-2}$ were included. Asthma was diagnosed, and disease severity was determined by combining the current level of symptoms, pulmonary function and maintenance treatment(s) [18]. Participants who were under optimal medical treatment and monitored by pulmonologists for ⩾6 months were included. The ethics review board approved the study (number 534 507). The study was registered at ClinicalTrials.gov (NCT02489383). Participation was voluntary, and all provided informed consent before participation. The exclusion criteria were as follows: cardiovascular and musculoskeletal diseases or other chronic lung diseases; current participation in an exercise programme; and current smokers or ex-smokers (>10 pack-years) [16].

Experimental design

The medication was prescribed according to the GINA guidelines [18] based on the use of LABA and ICS and SABA as needed [18]. Before the intervention, all subjects participated in a 4-h educational programme and were randomised into either the CLE or HIIT group. Before and after the intervention, participants were evaluated for the following: Asthma Control Questionnaire (ACQ)-6, PEF and lung function. Asthma symptom-free status before and after exercise sessions was also quantified. Participants from both groups completed all 24 intervention sessions of either CLE or HIIT (figure 1).

Allocation

Eligible subjects were randomly allocated to their respective intervention groups using a computer-generated randomisation schedule completed by an investigator blinded to the participants' recruitment, evaluation and treatment [6, 9].

Interventions

Educational programme

All participants attended an educational programme consisting of four sessions held twice a week before the interventions, each lasting 90 min. During the final two sessions, participants received information and educational materials regarding current international physical activity recommendations, the use of medicine and PEF, as described previously [13].

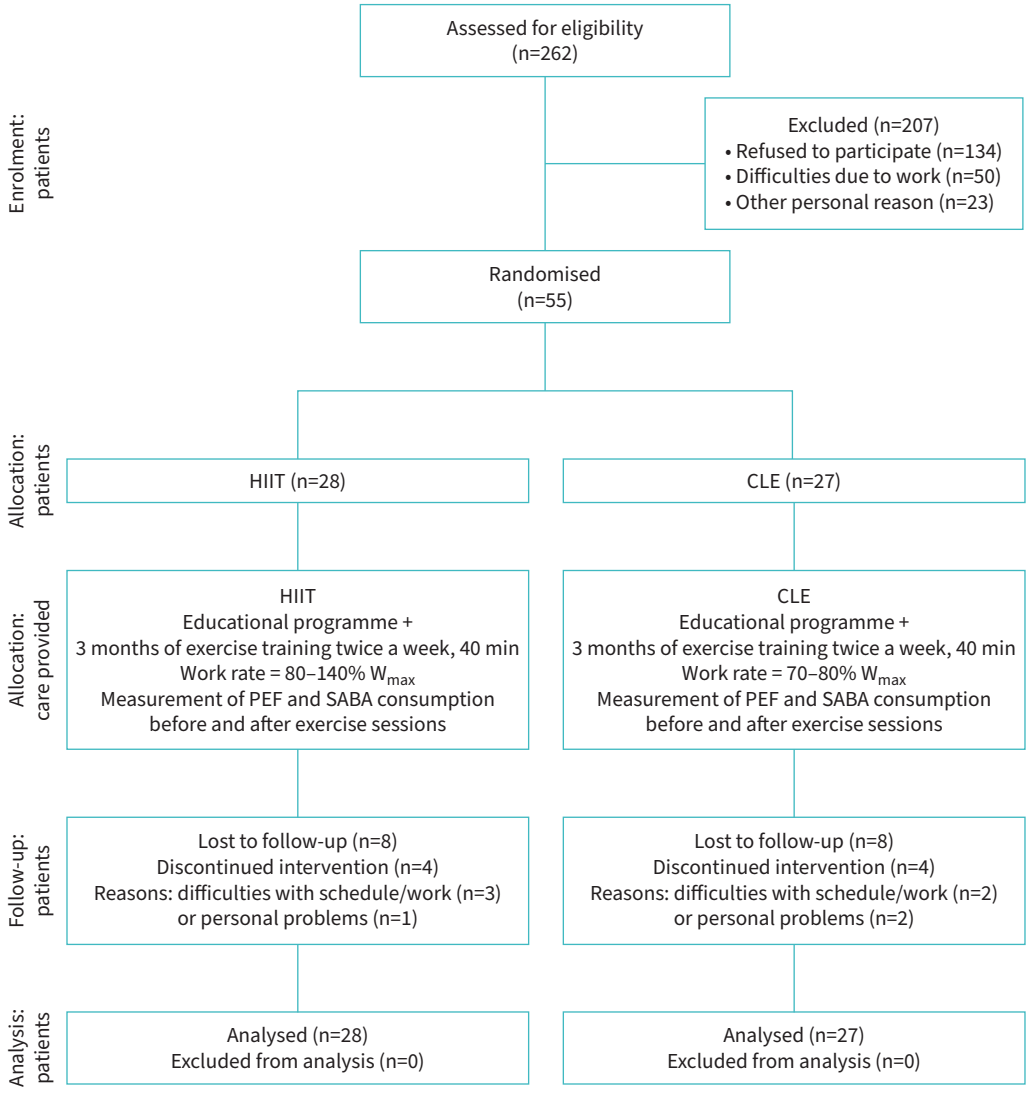

FIGURE 1 Study design. Consolidated Standards of Reporting Trials flowchart of the participants throughout the study. HIIT: high-intensity interval training; CLE: constant-load exercise; W_{max}: maximal Watts obtained in the cardiopulmonary exercise testing; PEF: peak expiratory flow; SABA: short-acting β_2-agonist.

HIIT

Each session lasted 40 min (5 min warm-up, 30 min exercise, 5 min cool-down) and was performed on a cycle ergometer (Bike 700; Technogym, Italy). HIIT was performed in bouts, with workload (W_{max}) based on the CPET, as described previously [6], and adapted for participants with asthma. The HIIT regimen lasted 12 weeks, with two sessions per week. In the first 2 weeks, participants performed HIIT at 80% W_{max}; in weeks 3 and 4, 90–100% W_{max}; in weeks 5 and 6, 110–120% W_{max}; in weeks 7 and 8, 120% W_{max}; in weeks 9 and 10, 130% W_{max}; and in weeks 11–12, 140% W_{max}. Each session comprised rounds of 30 s of HIIT and 30 s of recovery (active exercise at 40% W_{max}). For better physiological adaptation, the first four sessions lasted 20 min (supplementary figure E1) [6].

CLE

Participants performed exercise training twice weekly for 12 weeks for 24 sessions. Each session lasted 40 min (5 min warm-up, 30 min exercise, 5 min cool-down) and was performed on a cycle ergometer (Bike 700). Exercise intensity for the CLE group was performed at 60–80% of the CPET-derived W_{max}, with an increase of 5% every 2 weeks if the individual participant could maintain the effort and if their symptoms and perceived exertion were appropriate, as reported previously [6].

Outcome assessments

PEF and SABA consumption

Every participant received a PEF device free of charge (Medicate, Brazil), was taught how to use it, and was instructed to use it for daily control and before and after physical training sessions. Briefly, in the week before the exercise intervention, participants performed three measures of PEF for seven consecutive days after waking up and before using a SABA [9, 13]. PEF average value obtained during the 7 days (best daily PEF values) was considered the best reference PEF for each participant (100%). In addition, before each exercise session, the participants were asked to obtain their PEF value. If the measurement was <70% of the predicted value, the participant was advised to use a SABA (two 100 µg doses, totalling 200 µg salbutamol). Furthermore, PEF was assessed before and after CLE and HIIT exercise sessions, and if the value was reduced by <70% from their best reference value (100%) before exercising, participants were advised to use a SABA [9, 11, 17].

CPET

The CPET was performed using a cycle ergometer following European Respiratory Society guidelines [19].

Asthma clinical control

The ACQ-6 was used to measure clinical control, as described previously [9, 13, 20].

Statistical analysis

This is a secondary analysis from a previous study [6], and the sample size calculation on SABA or PEF was difficult, because no previous study had assessed those outcomes after exercise training. The normality of continuous outcomes was assessed using the Shapiro–Wilk test. The initial and final data were compared *via* a two-way repeated-measures ANOVA, and the categorical outcomes were assessed *via* the Chi-squared test. The level of significance was set at 5% ($p<0.05$) for all tests. The statistical analysis was blinded to the treatment regimen and was performed using statistical software (Sigmaplot 12.0; Systat Software Inc. USA). An intention-to-treat analysis was used to preserve the effects of group allocation and assess the treatment's practical impact. The effect size was used as a quantitative measure of the magnitude of the experimental effect. The effect size was expressed using Cohen's d index, which is determined by calculating the mean difference between the two groups and dividing the result by the pooled standard deviation [6, 9].

Results

262 adults were trialled: 134 did not meet the inclusion criteria; 50 were unavailable due to work schedules; and 23 were excluded because they had other pulmonary diseases. A total of 55 participants were randomised into CLE (n=27) or HIIT (n=28) (figure 1). The participants of both groups were similar when comparing sex, age, BMI, pulmonary function, clinical control, aerobic fitness and medication consumption ($p>0.05$) (table 1).

Effects of SABA consumption between CLE and HIIT

Figure 2a shows that 30% (n=8) of the CLE and 21% (n=6) of the HIIT participants required SABA consumption based on the PEF measurement in the first week of the intervention. However, in the last week of intervention, 3.7% (n=1) of the participants in the CLE group and none of the HIIT group required SABA ($p<0.05$), and there were no differences between CLE and HIIT ($p>0.05$). Our results also show that 60% of the participants in the CLE and HIIT groups who had uncontrolled asthma (ACQ-6 >1.5) consumed 80% of the SABA used in the first week of intervention, and no between-group difference was observed ($p>0.05$). In addition to the total amount of SABA consumed before the exercise sessions, participants also required a post-exercise SABA, but in a smaller amount (figure 2b) ($p<0.05$) and without a between-group difference ($p>0.05$). Finally, figure 2c shows a near-linear reduction in SABA consumption for CLE *versus* HIIT in both groups.

Comparison of the PEF between CLE and HIIT

Participants in the CLE presented a small but persistent post-exercise reduction in PEF during the intervention. In contrast, the HIIT group presented PEF values above baseline (figure 3a) ($p<0.05$). In addition, the total area under the curve in the HIIT group was 2.8 times greater than that in the CLE group. Finally, the change in the PEF during all interventions was compared, and it was observed that participants who performed CLE presented with a PEF reduction when considering all exercise sessions combined (figure 3b) ($p<0.05$).

TABLE 1 Baseline characteristics of participants with moderate and severe asthma

	CLE	HIIT
Participants	27	28
Anthropometric data		
Female	23 (86)	23 (83)
Age years	48.0 (34.2–52.7)	42.5 (33.5–49.0)
BMI kg·m^{-2}	30.4 (25.5–31.6)	27.2 (24.8–31.8)
Lung function after bronchodilation		
FEV_1 %	72.0 (62.5–85.7)	79.0 (67.0–84.6)
FVC %	92.0 (82.2–100.0)	99.5 (83.0–95.5)
FEV_1/FVC %	86.3 (81.0–93.0)	85.0 (78.5–92.5)
PEF L	303.3 (250.2–368.3)	300.8 (287.1–358.8)
Aerobic fitness		
V'_{O_2peak} mL·min^{-1}	1341.3 (1218.2–1627.8)	1698.3 (1419.4–1958.1)
V'_{O_2peak} % predicted	87.5 (78.8–100)	87.9 (76.8–109)
Work rate W	100 (100–125)	125 (100–137)
Work rate % predicted	107.5 (86.1–133.0)	107.0 (86.1–131.8)
Clinical control		
ACQ-6 score	1.83 (0.70–2.33)	1.85 (1.33–2.41)
Medication		
Budesonide µg·day^{-1}	800 (500–1200)	800 (800–1500)

Data are presented as n, n (%) or median (interquartile range). CLE: constant-load exercise; HIIT: high-intensity interval training; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; V'_{O_2peak}: peak oxygen consumption; ACQ: Asthma Control Questionnaire.

Comparison of clinical asthma control between CLE and HIIT

Before the intervention, 62% *versus* 78% of all the participants presented with uncontrolled asthma (ACQ ⩾1.5). Both groups showed improved asthma control without a difference between them ($p>0.05$). However, a greater percentage of patients in the HIIT group with noncontrolled asthma before the intervention reached controlled asthma after the intervention compared with those in the CLE group (65% *versus* 35%, respectively; $p<0.05$) (figure 4a). In addition, the minimal clinically important difference (scores <0.5) was achieved in the HIIT group, but not in the CLE group (−0.52±0.73 *versus* −0.23±1.06) (figure 4b).

Effect size

The findings showed that the effect size ranged from small to large for all outcomes in both interventions. The results showed that the effect size was greater in three out of five outcomes in favour of HIIT (figure 5). The largest effect size observed in both groups was the reduction in SABA consumption. The ACQ-6, aerobic fitness outcomes (work rate) and PEF reached higher effect size values in HIIT than in CLE. However, the effect size in peak oxygen consumption (V'_{O_2peak}) was greater in CLE compared with HIIT.

Discussion

The present study showed that CLE and HIIT reduced the SABA consumption needed to perform the exercise and the total amount of SABA consumed during the intervention in individuals with moderate-to-severe asthma. In addition, we observed that individuals performing CLE presented lower PEF values after the exercise training sessions than the HIIT group. In addition, both interventions improved aerobic fitness and clinical control. However, only the HIIT group reached the minimal clinically important difference (MCID) on the ACQ-6.

Effect of HIIT and CLE on SABA consumption

Our data demonstrate a significant reduction in exercise-related SABA consumption during the intervention in both exercise modalities (figure 2, supplementary figure E2). SABA have been a mainstay of asthma treatment for a long time, but are currently recommended to relieve symptoms as needed [21]. The GINA guidelines recommend using pre-exercise reliever medication to avoid exercise-induced bronchoconstriction and symptoms [1, 18]; however, in recent years, GINA guidelines have undergone substantial changes. In previous editions, GINA [18] recommended SABA as a rescue measure, and in the more recent guideline [1], there was an important change, where the clinical medication is based on track 1, with as-needed low-dose ICS-formoterol as the reliever. Track 2, in which the reliever is a SABA or

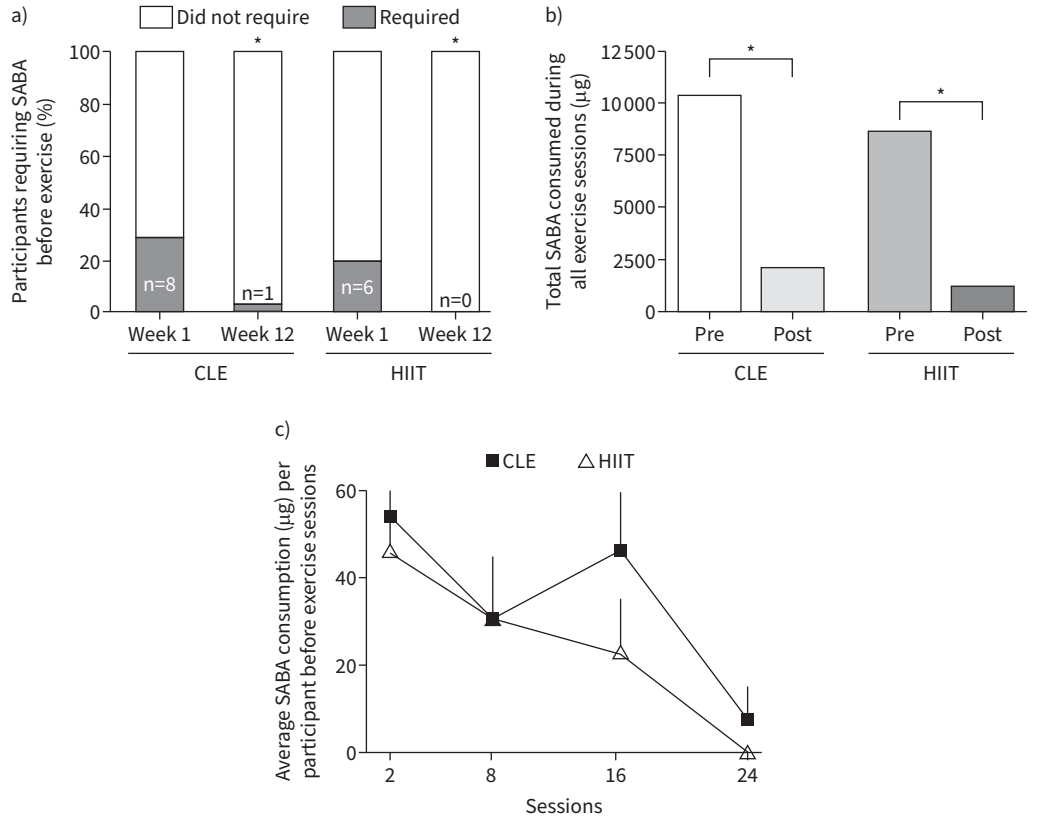

FIGURE 2 Effect of constant-load exercise (CLE) and high-intensity interval training (HIIT) on short-acting β_2-agonist (SABA) consumption. a) Number of participants who consumed SABA in the first and last weeks of intervention; b) total SABA consumption (µg) pre- and post-exercise in all sessions; c) average SABA consumption during interventions (µg). *: p<0.05 comparing the percentage of SABA users in the first *versus* last week of intervention.

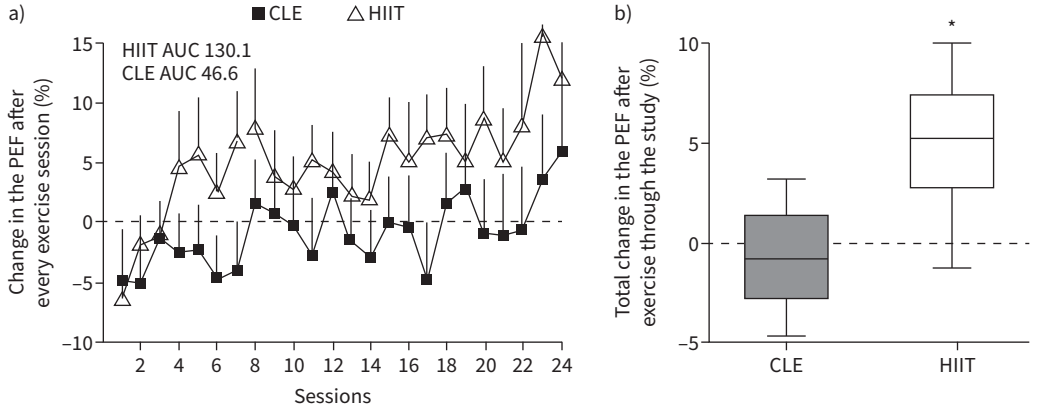

FIGURE 3 Effect of constant-load exercise (CLE) and high-intensity interval training (HIIT) on peak expiratory flow (PEF). a) Change (post – pre) in PEF during each exercise session in each exercise modality; data are presented as mean±SD. b) Change (post – pre) in PEF during all interventions; data are presented as median (confidence interval). The dashed line represents baseline values before each exercise session. AUC: area under the curve. *: p<0.05 comparing HITT *versus* CLE.

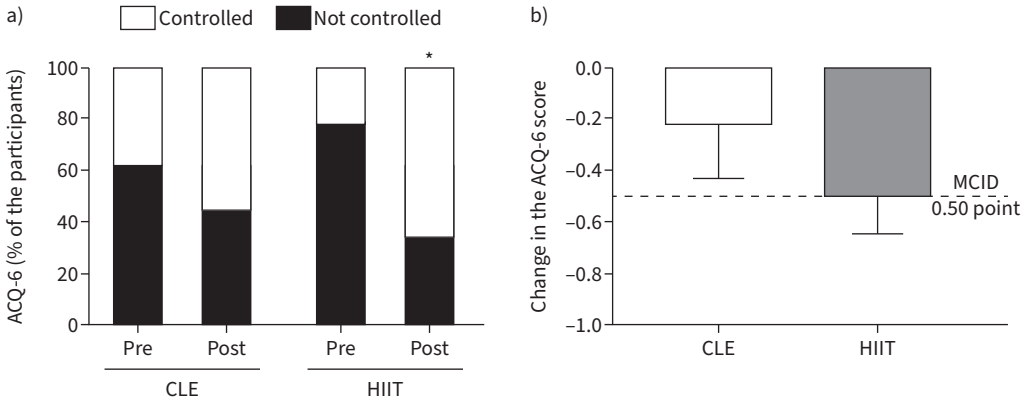

FIGURE 4 Effects of constant-load exercise (CLE) and high-intensity interval training (HIIT) on the Asthma Control Questionnaire (ACQ)-6. a) Percentage of participants with controlled and uncontrolled asthma before and after interventions. b) Subjects reaching the minimal clinically important difference (MCID) (⩾0.50 points) in the ACQ-6 are indicated by the dashed line [20]; data are presented as mean±SD. *: p<0.05 comparing HIIT with the baseline (within-group).

ICS-SABA, is an alternative if track 1 is not possible, or if a patient is stable, with good adherence and no exacerbations in the past year on their current therapy [1]. In poor or emerging countries such as Brazil, SABA are still widely used. Despite the extended use of SABA in asthma treatment, it is known that high consumption of SABA is associated with increases in exacerbation [22, 23] and mortality [2].

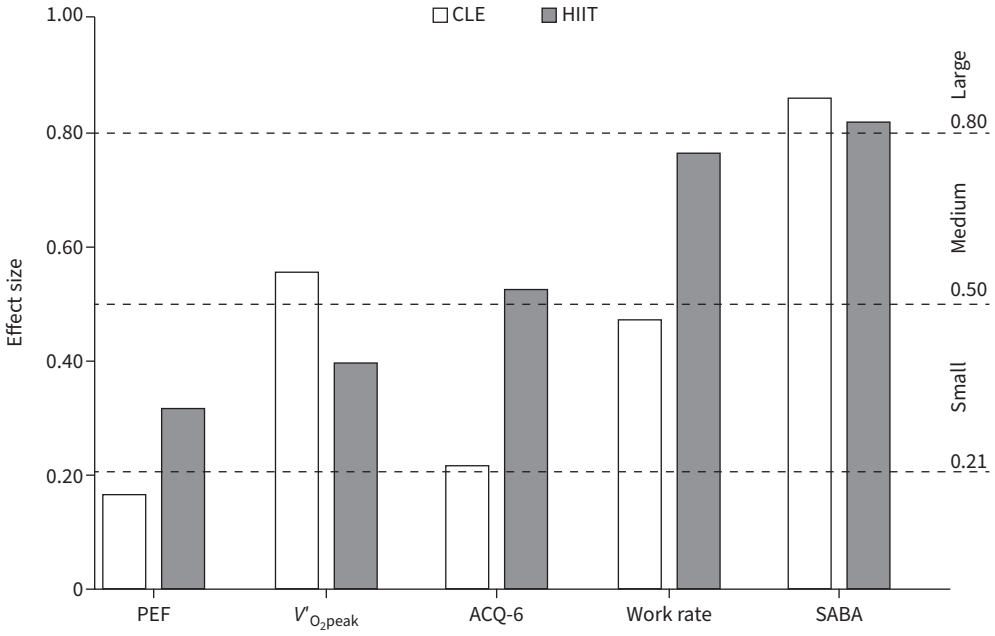

FIGURE 5 The effect size of constant-load exercise (CLE) and high-intensity interval training (HIIT) in the peak expiratory flow (PEF), aerobic fitness (peak oxygen consumption (V'_{O_2peak})), Asthma Control Questionnaire (ACQ)-6, work rate and short-acting bronchodilator (short-acting β_2-agonist (SABA)) consumption. The effect size was calculated using the Cohen method and classified as small (0.21–0.49), medium (0.50–0.79) and large (>0.80), represented by the dashed lines [13]. The effect size was used as a quantitative measure of the magnitude of the experimental effect. The effect size was expressed using Cohen's d index, which is determined by calculating the mean difference between the two groups and dividing the result by the pooled standard deviation.

Consequently, interventions that could reduce the consumption of reliever medication are extremely relevant for people with asthma [21]. Previous studies have demonstrated that CLE reduces ICS consumption in asthma participants [14, 15], and an elegant recent study showed that HIIT also reduced ICS consumption after a period of 12 months of intervention [16], but to the best of our knowledge, SABA consumption has never been evaluated. Therefore, our study provides new information by showing that individuals with asthma who required more SABA consumption reduced their pre-exercise consumption and their total consumption during the intervention. In addition, this effect was similar for participants performing CLE or HIIT, thus strongly suggesting that reduced SABA consumption occurs regardless of the exercise training modality. Interestingly, we observed that the total amount of pre-exercise SABA consumption was ∼10 mg in each group, while the post-exercise consumption was 2.5 mg, and that amount substantially decreased over time to almost none.

Effect of HIIT and CLE on PEF

A systematic meta-analysis suggested that aerobic exercise training has the potential to improve lung function [5]; however, studies with adults with moderate-to-severe asthma did not observe differences [10–12]. In the present study, we assessed PEF before and after exercise, and our results show that the CLE training improved the PEF values throughout the intervention; however, the post-exercise PEF changes were lower in the CLE group than in the HIIT group. Two previous studies demonstrated a significant change in lung function with exercise training; however, it is difficult to compare their results with the results of our study. Farid *et al*. [24] demonstrated a 25% improvement in forced expiratory volume in 1 s (FEV_1) after training. No other study observed this increase, probably related to other changes not properly controlled during the study, such as pharmacological treatment. Freitas *et al*. [9] also showed an improvement in expiratory reserve volume, but not in FEV_1, after exercise training; however, they studied obese individuals with asthma, and the change in lung function was related to weight loss. Our study assessed PEF, an outcome highly used in clinical practice to monitor airway calibre in individuals with asthma [1]. PEF has also been suggested as the best primary outcome for assessing lung function end-points for trials as a useful marker that shows the participant's daily condition [25]. Although PEF is an indirect lung function marker, it has been considered a reliable method to assess airway calibre before and after exercise sessions [1, 18]. The PEF difference observed between CLE and HIIT may have occurred due to the difference between both training modalities. Evidence shows that the minute ventilation during HIIT is lower than that during CLE in COPD patients [26–28]. Therefore, we hypothesise that HIIT induces lower airway drying and cooling, thereby reducing airway epithelium damage [27] and the vagal reflex initiated by the activation of afferent fibres [29]. Consequently, HIIT has a lower chance of inducing airway reactivity and constricting the airways.

Effect of HIIT and CLE on clinical control and aerobic fitness

Our results also show that both exercise training modalities improved clinical control and aerobic fitness (figure 5, supplementary figure E2). The improvement in aerobic fitness reached the MCID for V'_{O_2peak} ($1\ mL{\cdot}kg^{-1}{\cdot}min^{-1}$) [30]. However, only HIIT reached the MCID in the ACQ-6 score. Previous studies have shown improvement in clinical control by CLE [9, 13, 31, 32] and HIIT [7, 8], while other studies did not find improvements induced by both exercise modalities [8]. A possible explanation for the lower improvement in the ACQ-6 in the CLE group can be explained by the fact that more participants had good asthma control (score <1.50) before the intervention. This hypothesis is reinforced by previous studies showing a lower increase in patients with better clinical control [9, 13]. Another possible explanation for the lower improvement in the clinical control induced by the CLE is that the exercise was performed on a cycle ergometer instead of on a treadmill, the latter of which was used in most studies [9, 10, 11]. We conduct the exercise sessions on a cycle ergometer because it provides better control of exercise intensity and workload during HIIT. However, performing CLE on a cycle ergometer requires lower muscle mass and may reduce the systemic effect compared with using a treadmill. Some studies suggest that oxygen consumption varies between 10% and 20% between both ergometers [33]. Nevertheless, HIIT and CLE induced similar aerobic fitness improvements, reaching the MCID ($\geqslant 1.0\ mL{\cdot}kg^{-1}{\cdot}min^{-1}$) [30]. However, this increase resulted in values that were lower than those reported by a systematic review ($3.6\ mL{\cdot}kg^{-1}{\cdot}min^{-1}$) [34], in which most of the studies using CLE were performed using treadmills [35, 36].

Conclusion

CLE and HIIT similarly reduced SABA consumption in patients with moderate-to-severe asthma, but compared with HIIT, CLE decreased the post-exercise PEF during the intervention. In addition, both exercise modalities improved clinical control and physical fitness. HIIT induced a greater improvement in the PEF and lowered ACQ-6 below the MCID threshold. These results may suggest that HIIT might be a better choice for patients with greater airway hyperreactivity; however, this hypothesis remains to be confirmed by future studies.

Provenance: Submitted article, peer reviewed.

Ethics statement: The ethics review board at the School of Medicine, University of Sao Paulo (Sao Paolo, Brazil) approved the study (number 534 507).

This study is registered at www.clinicaltrials.gov with identifier number NCT02489383. All of the individual participant data collected during the trial will be shared, after deidentification.

Author contributions: Substantial contribution to the study concept and design: R.A. da Silva and C.R.F. Carvalho; data acquisition: R.A. da Silva, A. Cukier, R.M. Carvalho-Pinto and C.R.F. Carvalho; data analysis and/or interpretation: R.A. da Silva, A. Cukier, R.M. Carvalho-Pinto and C.R.F. Carvalho; significant manuscript writing and/or critical revisions for important intellectual content: R.A. da Silva, A. Cukier, R.M. Carvalho-Pinto and C.R.F. Carvalho. All the authors confirm that they read and approved the final version of the manuscript.

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