Tzu Chi Medical Journal 2024; 36 (1): 76-82

Original Article

High-intensity aerobic exercise training improves exercise capacity, dyspnea, and fatigue in patients with severe asthma using triple inhaler

*Lun-Yu Jao[a,b], Po-Chun Hsieh[c], Yao-Kuang Wu[a,b], I-Shiang Tzeng[d], Mei-Chen Yang[a,b], Wen-Lin Su[a,b], Chou-Chin Lan[a,b]**

[a]Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan, [b]School of Medicine, Tzu Chi University, Hualien, Taiwan, [c]Department of Chinese Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan, [d]Department of Research, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan

Submission : 04-Jul-2023
Revision : 01-Aug-2023
Acceptance : 19-Sep-2023
Web Publication : 12-Jan-2024

Abstract

Objectives: Asthma is a chronic respiratory disease that affects millions of people worldwide and causes severe symptoms such as wheezing, coughing, and breathing difficulty. Despite modern treatments, 3%–10% of patients develop severe asthma, which requires high-dose medications, and they may still experience frequent and severe symptoms, exacerbations, and psychological impacts. This study aimed to investigate the effects of high-intensity aerobic exercise training (HIAET) in patients with severe asthma. **Materials and Methods:** Patients with severe asthma were recruited, and cardiopulmonary exercise tests, dyspnea, and leg fatigue scores were performed before HIAET. Participants underwent a 12-week hospital-based HIAET, which involved exercising twice weekly to reach 80% of their peak oxygen uptake (VO_2). **Results:** Eighteen patients with severe asthma underwent HIAET, which resulted in significant improvement in peak VO_2 (1214.0 ± 297.9–1349.4 ± 311.2 mL/min, $P = 0.004$) and work rate (80.6 ± 21.2–96.2 ± 24.8 watt, $P < 0.001$) and decrease in dyspnea (5.1 ± 1.8–4.1 ± 1.2, $P = 0.017$) and fatigue scores (5.2 ± 2.3–4.0 ± 1.2, $P = 0.020$) at peak exercise. No significant changes were observed in spirometry results, respiratory muscle strength, or circulatory parameters. **Conclusion:** HIAET can lead to improved exercise capacity and reduced dyspnea and fatigue scores at peak exercise without changes in spirometry, respiratory muscle strength, and circulatory parameters.

Keywords: *Asthma, Exercise capacity, Pulmonary rehabilitation, Quality of life*

Introduction

Asthma is a chronic respiratory disease affecting the airway. It affects many people worldwide and has a significant impact [1]. According to the World Health Organization, approximately 339 million individuals worldwide are affected by asthma, with the majority of deaths occurring in older adults [2]. The Global Initiative for Asthma (GINA) reported that the prevalence of asthma varies between 1% and 18% in different countries and that its incidence is increasing globally [2]. Overall, asthma is a major public health issue requiring attention and resources from health-care providers [1,2].

Asthma can cause severe symptoms, such as wheezing, coughing, and difficulty in breathing, which can lead to hospitalization and even death [3]. Asthma symptoms and airflow limitations can fluctuate in pattern and intensity over time and are triggered by factors such as exercise, exposure to allergens or irritants, weather changes, and respiratory infections [3]. These triggers can lead to exacerbations, further complicating its management. Therefore, asthma can significantly affect daily life, causing impaired physical activity and daily work [3].

Even with modern treatments for asthma, a significant proportion of patients have poorly controlled asthma despite optimal treatment, with approximately 3%–10% of patients having severe asthma [4]. Severe asthma is a subtype of asthma that requires high-dose medications, including inhaled corticosteroids (ICS), long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and oral corticosteroids. However, patients with severe asthma may still experience frequent and severe symptoms as well as exacerbations [4]. In addition, severe asthma can have

****Address for correspondence:*** Dr. Chou-Chin Lan, Division of Pulmonary Medicine, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation 289, Jianguo Road, Xindian, New Taipei, Taiwan. E-mail: bluescopy@yahoo.com.tw

Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_171_23

How to cite this article: Jao LY, Hsieh PC, Wu YK, Tzeng IS, Yang MC, Su WL, *et al.* High-intensity aerobic exercise training improves exercise capacity, dyspnea, and fatigue in patients with severe asthma using triple inhaler. Tzu Chi Med J 2024;36(1):76-82.

a significant psychological impact, with patients often experiencing anxiety, depression, and other mental health issues related to frequent medication [5]. They may require frequent hospitalizations, emergency department visits, and even intensive care unit stays, and they may consume more health-care resources than other patients with asthma [4]. Therefore, it is necessary to provide additional interventions for these patients.

Patients with severe asthmatics often experience deconditioning of peripheral skeletal muscles and cardiovascular impairments, which collectively contribute to reduced exercise capacity and physical activity [6]. Deconditioning of peripheral skeletal muscles results from multiple factors, including prolonged periods of inactivity, and the systemic effects of chronic inflammation [6]. The deconditioning process involves a decline in muscle strength, endurance, and flexibility, leading to difficulties in performing physical activities [6]. Peripheral cardiovascular impairments are also reported in patients with asthma [7]. These impairments further exacerbate the physical limitations experienced by severe asthmatics. Severe asthma is also associated with impaired cardiovascular function [8]. In these patients with severe asthma attacks, the bronchospasm increases the workload on the heart, leading to an increased heart rate (HR) and potential arrhythmias [8]. Reduced oxygen supply during exacerbations can temporarily compromise cardiac performance. Chronic inflammation associated may contribute to endothelial dysfunction and increased risk of cardiovascular dysfunction [8]. Since patients with severe asthma may experience deconditioning of peripheral skeletal muscles and cardiovascular impairments, exercise training may be beneficial for these individuals.

Pulmonary rehabilitation (PR) is a comprehensive program aimed at improving exercise capacity and health related quality of life (HRQoL) [9]. The program typically involves a comprehensive approach, combining exercise training, breathing techniques, and education on asthma triggers, medications, inhaler technique, action plans, and lifestyle management [9]. PR can be an effective adjunct to standard asthma treatments to improve HRQoL, dyspnea, and exercise capacity [9]. Although there have been some studies on the effects of PR on asthma, the majority of the study populations had moderate asthma, with only a few patients having severe asthma. Exercise training is an important part of PR for asthma. Because severe asthma is a significant and challenging condition having a profound impact on patients and society, it is crucial to investigate the effects of exercise training in patients with severe asthma who are already receiving optimal triple-inhaler therapy. Therefore, we conducted this study to explore the effects of high-intensity aerobic exercise training (HIAET) in patients with severe asthma.

Materials and methods

Study design and patient recruitment

Patients with asthma were recruited from the outpatient department. As the GINA guidelines, severe asthma is diagnosed when asthma symptoms persist despite adhering to maximal high-dose ICS-LABA treatment and effectively managing all contributing factors [2]. The inclusion criteria in this study were severe asthma with persistent dyspnea despite being on optimal triple inhalation medication (ICS + LABA + LAMA), but no acute exacerbation of severe dyspnea, and the ability to fully perform the cardiopulmonary exercise test (CPET). The duration from triple inhalation medication to exercise training ranged from 28 to 1517 days (average: 480 days). The exclusion criteria were patients with orthopedic or neurological impairments that prevented them from performing CPET, a history of other lung diseases (e.g., chronic obstructive pulmonary disease, pneumoconiosis, and tuberculosis) or documented heart disease (e.g., congestive heart failure and coronary heart disease). This study was approved by the Ethics Committee of Taipei Tzu Chi Hospital (IRB no: 12-X-087). Informed consent was obtained from all the participants. All patients underwent spirometry, CPET, respiratory muscle strength testing, and symptom evaluation during maximal exercise. The CPET was conducted both 1 week before and 1 week after the exercise training. This allowed for the assessment of changes in exercise capacity before and after the intervention, providing valuable insights into the impact of exercise training on the study participants.

Pulmonary function test

Pulmonary function was assessed using a spirometer (Medical Graphics Corporation, St. Paul, MN, USA), in accordance with the guidelines recommended by the American Thoracic Society [10]. Spirometric reference values in these adults in Taiwan were derived from a previous study conducted by Wang *et al*. [11].

Cardiopulmonary exercise test

A bicycle ergometer (Lode Corival, the Netherlands) was used to perform the CPET. An incremental protocol was employed for CPET. Breath analysis was conducted using Breeze Suite 6.1 (Medical Graphics Corporation) to measure variables such as oxygen uptake (VO_2), carbon dioxide output (VCO_2), tidal volume (V_T), and respiratory frequency (Rf). Blood pressure (BP), HR, and oxygen saturation in the arterial blood (SpO_2) were monitored during CPET [12].

These patients underwent individualized incremental CPET with a personalized ramp protocol [13]. The load was set up to finish between the 10 and 12 min of exertion. Patients underwent a 2-min warm-up phase (unloaded cycling), following which the work rate (WR) was continuously increased in increments of 10, 15, or 20 watts per min, depending on the patient's estimated subjective functional capacity. During the exercise test, patients were asked to maintain a cycling frequency of approximately 60 revolutions per min [13]. VO_2 at the anaerobic threshold (AT) was determined using the V-slope method, which plots VO_2 against VCO_2 [12]. The work efficiency (WE) was assessed using data obtained during the approach to peak exercise, where we determined the slope of VO_2 versus WR using linear regression analysis [14]. Oxygen pulse (O_2P) was calculated by dividing VO_2 by HR [15]. Assuming that oxygen extraction remains constant during maximal exercise, O_2P is considered a stroke volume parameter [15]. The evaluation of ventilatory equivalent for carbon dioxide (VEqCO_2) was performed at the nadir point of its value during CPET.

Respiratory muscle strength

Maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were measured using a respiratory pressure meter (Micro Medical Corp, England). MIP was determined by measuring the pressure when patients exhaled to the residual volume and then performed rapid maximal inspiration. MEP was measured when patients inhaled to the total lung capacity and then exhaled with maximal effort [14].

Dyspnea and leg fatigue score during maximal exercise

The dyspnea and leg fatigue scores were assessed at rest and at peak exercise using the Borg scale, which employs a 10-point scoring scale. A higher score indicated a more severe symptom presentation [16].

Pulmonary rehabilitation program

In the 12-week hospital-based PR program, all participants underwent two sessions per week. These sessions aimed to educate patients on medications and self-management skills. HIAET with lower-limb cycle ergometer exercise training was included, with a targeted intensity of 80% peak VO_2. The training program consists of a 2-min warm-up period, followed by 10 min of exercise at 50% intensity, then another 10 min at 60% intensity, 20 min at 80% intensity, and finally, a 2-min cool-down period. Each exercise training session was supervised by an experienced and qualified respiratory therapist who monitored vital signs such as SpO_2, Rf, HR, and BP. The flow chart shows patient recruitment and exercise training program [Figure 1].

Statistical analysis

All parameters are reported as mean ± standard deviation. Statistical analyses were conducted using the Statistical Product and Service Solutions, version 24.0 (SPSS Inc., Chicago, IL, USA). A paired *t*-test was used to compare the parameters of the patients before and after PR. The threshold for statistical significance was set at $P < 0.05$.

Results

Baseline clinical and demographic characteristics

Eighteen patients with severe asthma completed the CPET and HIAET. The clinical characteristics of the patients are summarized in Table 1. The mean age was 57.8 ± 17.4 years, mean body weight was 63.8 ± 12.2 kg, and mean body height was 159.5 ± 7.9 cm. The mean forced expiratory volume in the first 1 s (FEV_1)/forced vital capacity (FVC) was 73.4% ± 11.6%, FVC was 2.54 ± 0.74 L (90.2% ± 23.7%), and FEV_1 was 1.92 ± 0.80 L/min (82.8% ± 28.9%). All patients with severe asthma were prescribed triple-inhaler medications that included ICS, LABAs, and LAMAs.

Effects of high-intensity aerobic exercise training on exercise capacity and symptoms during exercise

The effects of HIAET on exercise capacity were assessed using VO_2 and WR during peak exercise. Figure 2 shows the changes in peak VO_2, WR, exertional dyspnea, and leg fatigue at peak exercise in individual patients. HIAET improved both VO_2 and WR at peak exercise ($P < 0.05$). After HIAET, there was a significant decrease in dyspnea (5.1 ± 1.8–4.1 ± 1.2, $P < 0.05$) and fatigue scores (5.2 ± 2.3–4.0 ± 1.2, $P < 0.05$) at peak exercise.

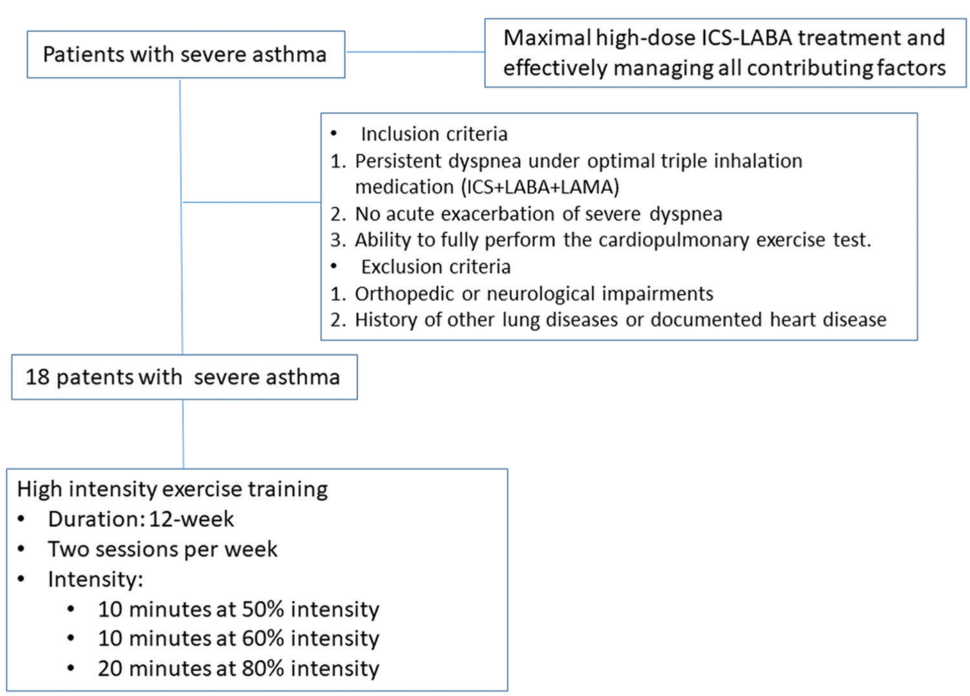

Figure 1: Flow chart of patient recruitment and exercise training program. ICS: Inhaled corticosteroids, LABA: Long-acting beta-agonist, LAMA: Long-acting muscarinic antagonist

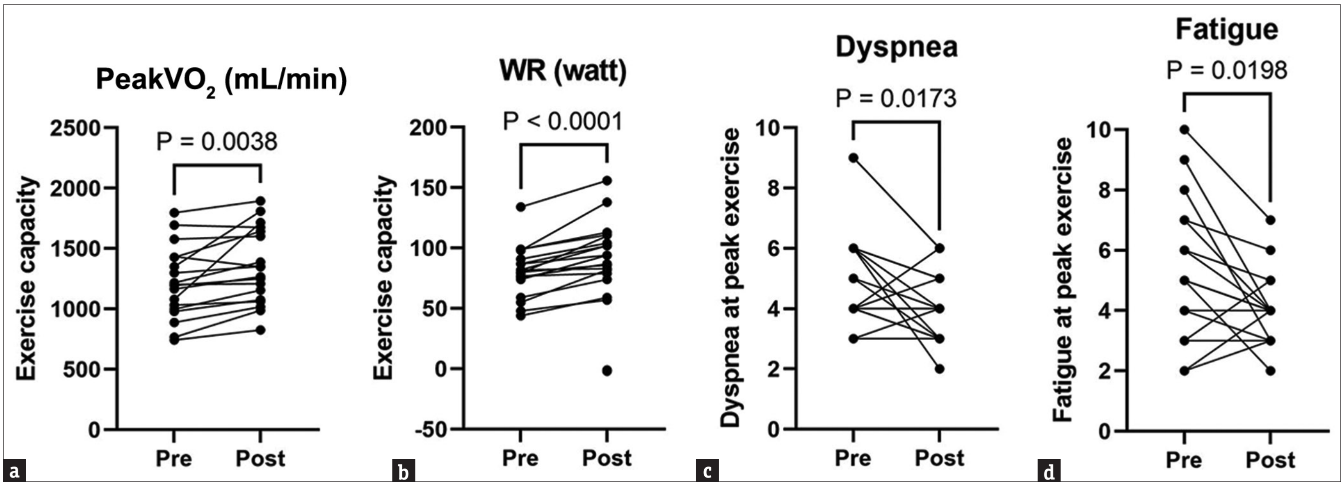

Figure 2: Effects of high-intensity aerobic exercise training (HIAET) on exercise capacity, dyspnea, and fatigue at peak exercise. After HIAET, peak oxygen uptake, (a) showed significant improvements from 1214.0 ± 297.9 mL/min to 1349.4 ± 311.2 mL/min ($P = 0.004$) and work rate, (b) showed significant improvements from 80.6 ± 21.2 watts to 96.2 ± 24.8 watts ($P < 0.001$). Patients also reported reduced exertion dyspnea scores, (c) decreasing from 5.1 ± 1.8 to 4.1 ± 1.2 ($P = 0.017$), as well as leg fatigue scores, (d) decreasing from 5.2 ± 2.3 to 4.0 ± 1.2 ($P = 0.020$) after HIEAT. VO_2: Oxygen uptake, WR: Work rate, HIAET: High-intensity aerobic exercise training, Pre: Pre-HIAET, Post: Post-HIAET

Table 1: Baseline characteristics

Characteristics	Mean±SD or *n* (%)
Age (years)	57.8±17.4
BW (kg)	63.8±12.2
BH (cm)	159.5±7.9
Sex	
Male	9 (50)
Female	9 (50)
Smoking	
Current smokers	0
Ex-smokers	2 (11)
Nonsmokers	16 (89)
FEV_1/FVC (%)	73.4±11.6
FEV_1 (% predicted)	82.8±28.9
FVC (% predicted)	90.2±23.7
MIP (cm H_2O)	72.0±25.1
MIP (%)	78.2±24.6
MEP (cm H_2O)	121.8±33.8
MEP (%)	71.5±16.0
ICS + LABA + LAMA	100%

BW: Body weight, BH: Body height, BMI: Body mass index, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, MIP: Maximal inspiratory pressure, MEP: Maximal expiratory pressure, ICS: Inhaled corticosteroids, LABA: Long-acting beta-agonists, LAMA: Long-acting muscarinic antagonists, SD: Standard deviation

Effects of high-intensity aerobic exercise training on respiratory parameters in patients with severe asthma

HIAET did not result in significant changes in spirometric parameters (FEV_1/FVC, FVC, and FEV_1), respiratory muscle strength (MIP and MEP), or ventilation parameters (Rf, V_T, $VEqCO_2$, and SpO_2) at rest or during exercise in patients with severe asthma [$P > 0.05$; Table 2].

Effects of high-intensity aerobic exercise training on circulatory parameters

No significant changes in HR or systolic and diastolic BP were observed after HIAET in patients with severe asthma ($P > 0.05$). In addition, HIAET did not result in significant changes in cardiac response parameters, such as O_2P, WE, and VO_2 at AT in these patients [$P > 0.05$; Table 3].

Discussion

This study enrolled patients with severe asthma who experienced exertional dyspnea despite receiving triple-inhaler medication comprising ICS, LABA, and LAMA. Our study demonstrated that high-intensity training sessions of 40 min per session twice a week for 12 weeks aimed at achieving 80% of peak VO_2 led to an increase in exercise capacity and a reduction in dyspnea and fatigue scores at peak exercise. However, HIAET did not produce significant changes in respiratory or circulatory parameters in these patients. These findings imply that HIAET can be an effective intervention for enhancing exercise tolerance in patients with severe asthma who are already on optimal inhaler medications.

Some previous studies have reported on exercise training in patients with asthma. Cochrane and Clark conducted a study involving patients with mild asthma, in which exercise training was implemented at a level of 75% maximum HR for 30 min per session, three times a week, for a total of 12 weeks [17]. The results indicated improvements in lung function and peak VO_2, O_2P, AT, and $VEqCO_2$ [17]. In a study conducted by Türk *et al*., patients with moderate asthma and obesity underwent exercise training, aiming to achieve 90% of peak VO_2 for 40–60 min per session, three times a week, over a period of 12 weeks [18]. The study findings indicated improved peak VO_2 and decreased Asthma Control Questionnaire (ACQ) scores, body mass index, and fat mass [18]. However, it should be noted that the intervention group in these two studies had less severe asthma than our study population. In a study by Ricketts *et al.*, exercise training was conducted once a week for 8 weeks using leg extensions, bicep curls, sit-to-stand movements, step-ups, pole raises, and knee lifts in patients with difficult-to-treat asthma and obesity [19]. The results indicated improved Asthma Quality of Life Questionnaire (AQLQ) score, decreased ACQ score,

Table 2: Effect of pulmonary rehabilitation on respiratory response to exercise

	Pre-HIAET	Post-HIAET	Mean difference	*P*
FEV_1/FVC (%)	73.4±11.6	72.2±11.7	−1.2±3.5	0.153
FEV_1 (% predicted)	82.8±28.9	84.4±24.6	1.61±11.1	0.548
FVC (% predicted)	90.2±23.7	93.4±19.1	3.2±12.1	0.273
MIP (cm H_2O)	72.0±25.1	75.3±24.9	3.3±13.0	0.292
MIP (%)	78.2±24.6	81.9±24.0	3.8±14.3	0.277
MEP (cmH_2O)	121.8±33.8	120.4±32.5	−1.4±28.3	0.838
MEP (%)	71.5±16.0	71.2±15.4	−0.3±15.5	0.928
V_T (mL) at rest	627.8±250.8	676.0±389.2	48.2±430.5	0.141
V_T (mL) at exercise	1348.3±336.9	1429.2±318.3	80.9±267.2	0.216
Rf (breaths/min) at rest	17.4±4.0	18.1±6.0	0.6±4.6	0.583
Rf (breaths/min) at exercise	33.6±9.5	32.2±6.7	−1.4±7.8	0.443
SpO_2 (%) at rest	96.4±1.9	96.2±2.0	−1.2±1.8	0.698
SpO_2 (%) at exercise	96.3±1.9	96.3±3.4	−1.0±2.7	0.135
VEqCO_2	35.2±4.9	33.3±4.4	−1.9±3.4	0.028

P values: Comparison between pre-HIAET and post-HIAET. HIAET: High-intensity aerobic exercise training, FEV_1: Forced expiratory volume in 1 s, FVC: Forced vital capacity, MIP: Maximal inspiratory pressure, MEP: Maximal expiratory pressure, V_T: Tidal volume, Rf: Respiratory frequency, SpO_2: Oxygen saturation of arterial blood, VEqCO_2: Ventilatory equivalent for carbon dioxide

Table 3: Effect of pulmonary rehabilitation on cardiovascular response to exercise

	Pre-HIAET	Post-HIAET	Mean difference	*P*
O_2P (mL/beat)	9.5±3.3	9.7±3.0	0.2±1.0	0.507
O_2P (%)	97.0±24.2	99.1±21.9	2.1±12.8	0.505
WE (mL/min/watt)	8.6±1.1	8.9±0.9	0.3±1.3	0.409
AT (mL/min)	725.5±145.7	753.0±141.9	27.5±103.6	0.276
AT (%)	47.4±11.4	49.1±10.2	1.7±9.5	0.468
HR (beats/min) at exercise	132.7±23.8	137.8±21.6	5.1±13.9	0.137
HR response (%)	81.8±13.2	85.1±12.1	3.3±8.0	0.99
SBP (mmHg) at rest	126.2±27.0	124.9±16.9	–1.3±21.1	0.801
SBP (mmHg) at exercise	158.4±39.0	166.6±30.1	8.2±36.3	0.353
DBP (mmHg) at rest	77.4±12.6	73.6±13.6	–3.8±12.1	0.197
DBP (mmHg) at exercise	80.0±11.2	78.2±12.8	–1.8±12.9	0.566

P values: Comparison between pre-HIAET and post-HIAET. HIAET: High-intensity aerobic exercise training, HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure AT: Anaerobic threshold, O_2P: Oxygen pulse, WE: Work efficiency

decreased Modified Medical Research Council Dyspnea Scale score, and increase 6-min walk distance [19]. However, the study did not evaluate VO_2, fatigue, or dyspnea scores at peak exercise. Majd *et al*. performed exercise training, achieving 60%–80% of peak VO_2 for 20 min per session, twice a week for a duration of 12 weeks in patients with severe asthma and showed improvement in HRQoL parameters, such as Chronic Respiratory Disease Questionnaire, Hospital Anxiety and Depression Scale, and AQLQ [20]. However, there was no improvement in peak VO_2 in this study [20]. Although the severity of asthma in the patients in Majd *et al*.'s study was comparable to that in our current study, their exercise training program had a lower intensity and duration than ours. A summary of these studies and the current study is provided in Table 4.

Several factors contribute to poor exercise capacity and exertional dyspnea in patients with asthma. Airway inflammation and obstruction aggravate dyspnea during exercise [12]. Exercise-induced bronchospasm is also a common trigger for shortness of breath during exercise [12]. Patients with severe asthma have reduced dynamic hyperinflation and are likely to have poor exercise capacity [21]. Anxiety and depression can worsen asthma symptoms and cause shortness of breath during activities [22]. Patients with asthma may avoid exercise because of the fear of triggering symptoms, which can lead to a cycle of reduced fitness and worsening of symptoms during physical activity [23].

Exercise training has the potential to enhance exercise capacity and decrease exertional dyspnea through various mechanisms, including improvement of respiratory function, airway inflammation, bronchial hyperresponsiveness, and cardiovascular fitness. A previous study showed that exercise training can improve lung function and VEqCO_2 [17]. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma [24]. França-Pinto *et al*. showed that exercise training reduced bronchial hyperresponsiveness and serum pro-inflammatory cytokines, such as interleukin 6 and monocyte chemoattractant protein 1, in patients with asthma [24]. Exercise-induced bronchoconstriction also contributes to exercise intolerance, and exercise training has been shown to mitigate this effect, leading to improved exercise capacity [25]. Combined respiratory muscle training and aerobic exercise training can also improve respiratory muscle strength and endurance, which can help patients with severe asthma to breathe more efficiently during exercise and reduce dyspnea [26]. According to previous evidence, there is substantial support for the diverse physiological adaptations resulting from aerobic exercise training [27]. These adaptations encompass increased oxygen extraction by trained muscles, ultimately leading to lower blood lactate levels, reduced carbon dioxide production, and decreased ventilatory requirements during exercise [27]. Consequently, these adaptations contribute to a reduction in exertional dyspnea.

Exercise training can also positively impact psychological factors such as anxiety, which can contribute to a sense of

Table 4: Studies on pulmonary rehabilitation in patients with asthma

Reference	Severity of asthma	Case numbers	Frequency	Intensity (%)	Time (min)	Duration (weeks)	Outcomes
Our study	Severe	18 PR	Twice a week	80% peak VO_2	40	12	Improved peak VO_2, fatigue, and dyspnea at exercise
Cochrane and Clark [17]	Mild to moderate	18 PR 18 UC	Three times a week	75% maximum HR	30	12	Improved FEV_1, peak VO_2, O_2P, AT, $VEqO_2$
Türk *et al*. [18]	Moderate, obesity	14 PR 9 PR+SMS 11 UC	Three times a week	90% peak VO_2	40–60	12	Improved peak VO_2, ACQ, BMI, fat mass
Ricketts *et al*. [19]	Difficult-to-treat asthma, obesity	33 PR 44 UC	Once a week			8	Improved AQLQ, ACQ, mMRC, 6MWD
Majd *et al*. [20]	Severe	17 PR 6 UC	Twice a week	60–80% peak VO_2	20	12	Improved CRQ, HADS, AQLQ No improvement in peak VO_2

PR: Pulmonary rehabilitation, UC: Usual care, SMS: Self-management support program, VO_2: Oxygen uptake, O_2P: Oxygen pulse, AT: Anaerobic threshold, HR: Heart rate, FEV_1: Forced expiratory volume in 1 s, $VEqO_2$: Ventilatory equivalent for oxygen, ACQ: Asthma Control Questionnaire, BMI: Body mass index, CRQ: Chronic respiratory questionnaire, HADS: Hospital Anxiety and Depression Scale, AQLQ: Asthma Quality of Life Questionnaire, mMRC: Modified medical research council, 6MWD: 6-min walk distance

breathlessness and reduced physical activity levels [28]. Regular exercise can help reduce anxiety, leading to improvements in overall well-being, quality of life, and exertional dyspnea [28]. Overall, the mechanisms by which exercise training improves exertional dyspnea or exercise capacity are multifactorial and include airway inflammation, respiratory muscles, and psychological factors.

Clinical implications

HIAET in severe asthma is significant, as it can provide valuable intervention for patients who experience exertional dyspnea despite receiving optimal inhaler medication. Our study demonstrated that HIAET can lead to an improvement in exercise capacity and a reduction in dyspnea and fatigue scores at peak exercise. Although HIAET did not produce significant changes in the respiratory or circulatory parameters, it still provides a promising approach for improving the overall quality of life of patients with severe asthma. Therefore, health-care providers should consider HIAET as a complementary treatment option to optimize exercise tolerance in this patient population.

Study limitations

This study has some limitations that should be considered. First, this was a single-center study, and the number of cases was relatively small, which could potentially lead to bias. However, given the low prevalence of severe asthma among patients with asthma, recruitment of a large number of patients with severe asthma can be challenging. Nevertheless, the study findings are still relevant. Multicenter studies with larger sample sizes are necessary to confirm the findings of the present study. Second, as this was a retrospective study and not a randomized controlled trial, conducting prospective randomized controlled studies would be essential to provide additional robust evidence. Randomized controlled trials are designed to minimize biases that may arise from researchers or participants, thus offering more reliable conclusions regarding the effectiveness of the intervention. Third, dynamic hyperinflation was not assessed in patients during the exercise test. As a result, we lacked an understanding of the effects of PR on dynamic hyperinflation in patients with severe asthma.

Conclusion

HIAET can be an effective intervention for enhancing exercise tolerance in patients with severe asthma who experience exertional dyspnea despite receiving optimal inhaler medication. We demonstrated that high-intensity training can improve exercise capacity and reduce dyspnea and fatigue scores at peak exercise.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Financial support and sponsorship

This study was supported by grants from Taipei Tzu Chi Hospital (TCRD-TPE-112-10).

Conflicts of interest

There are no conflicts of interest.

References

1. Song P, Adeloye D, Salim H, Dos Santos JP, Campbell H, Sheikh A, et al. Global, regional, and national prevalence of asthma in 2019: A systematic analysis and modelling study. J Glob Health 2022;12:04052.
2. Alomary SA, Al Madani AJ, Althagafi WA, Adam IF, Elsherif OE, Al-Abdullaah AA, et al. Prevalence of asthma symptoms and associated risk factors among adults in Saudi Arabia: A national survey from global asthma network phase I. World Allergy Organ J 2022;15:100623.
3. Kharaba Z, Feghali E, El Husseini F, Sacre H, Abou Selwan C, Saadeh S, et al. An assessment of quality of life in patients with asthma through physical, emotional, social, and occupational aspects. A cross-sectional study. Front Public Health 2022;10:883784.
4. Roche N, Garcia G, de Larrard A, Cancalon C, Bénard S, Perez V, et al. Real-life impact of uncontrolled severe asthma on mortality and healthcare use in adolescents and adults: Findings from the retrospective, observational RESONANCE study in France. BMJ Open 2022;12:e060160.
5. Dafauce L, Romero D, Carpio C, Barga P, Quirce S, Villasante C, et al. Psycho-demographic profile in severe asthma and effect of emotional mood disorders and hyperventilation syndrome on quality of life. BMC Psychol 2021;9:3.
6. Cordova-Rivera L, Gibson PG, Gardiner PA, Hiles SA, McDonald VM. Extrapulmonary associations of health status in severe asthma and

bronchiectasis: Comorbidities and functional outcomes. Respir Med 2019;154:93-101.

7. Yao CW, Shen TC, Lu CR, Wang YC, Lin CL, Tu CY, et al. Asthma is associated with a subsequent risk of peripheral artery disease: A longitudinal population-based study. Medicine (Baltimore) 2016;95:e2546.

8. Kreslová M, Kirchnerová O, Rajdl D, Sudová V, Blažek J, Sýkorová A, et al. Bronchial asthma as a cardiovascular risk factor: A prospective observational study. Biomedicines 2022;10:2614.

9. Osadnik CR, Gleeson C, McDonald VM, Holland AE. Pulmonary rehabilitation versus usual care for adults with asthma. Cochrane Database Syst Rev 2022;8:CD013485.

10. Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. Am J Respir Crit Care Med 2017;196:1463-72.

11. Wang WT, Ko HK, Lin CC, Shu JH, Hsu HC, Liang Y, et al. Spirometric reference values in heathy Chinese adults in Taiwan: The secular changes and comparison with other Asian populations. J Formos Med Assoc 2020;119:290-9.

12. Boutou AK, Daniil Z, Pitsiou G, Papakosta D, Kioumis I, Stanopoulos I. Cardiopulmonary exercise testing in patients with asthma: What is its clinical value? Respir Med 2020;167:105953.

13. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun XG, et al. Principles of exercise testing and interpretation. 5th ed. Philadelphia, USA: Lippincott Williams and Wilkins; 2012. p. 17.

14. Yang SH, Yang MC, Wu YK, Wu CW, Hsieh PC, Kuo CY, et al. Poor work efficiency is associated with poor exercise capacity and health-related quality of life in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2021;16:245-56.

15. Wu CW, Hsieh PC, Yang MC, Tzeng IS, Wu YK, Lan CC. Impact of peak oxygen pulse on patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2019;14:2543-51.

16. Jao LY, Hsieh PC, Wu YK, Yang MC, Wu CW, Lee C, et al. Different responses to pulmonary rehabilitation in COPD patients with different work efficiencies. Int J Chron Obstruct Pulmon Dis 2022;17:931-47.

17. Cochrane LM, Clark CJ. Benefits and problems of a physical training programme for asthmatic patients. Thorax 1990;45:345-51.

18. Türk Y, Theel W, van Huisstede A, van de Geijn GM, Birnie E, Hiemstra PS, et al. Short-term and long-term effect of a high-intensity pulmonary rehabilitation programme in obese patients with asthma: A randomised controlled trial. Eur Respir J 2020;56:1901820.

19. Ricketts HC, Sharma V, Steffensen F, Goodfellow A, Mackay E, MacDonald G, et al. A pragmatic randomised controlled trial of tailored pulmonary rehabilitation in participants with difficult-to-control asthma and elevated body mass index. BMC Pulm Med 2022;22:363.

20. Majd S, Apps L, Chantrell S, Hudson N, Eglington E, Hargadon B, et al. A feasibility study of a randomized controlled trial of asthma-tailored pulmonary rehabilitation compared with usual care in adults with severe asthma. J Allergy Clin Immunol Pract 2020;8:3418-27.

21. van der Meer AN, de Jong K, Hoekstra-Kuik A, Bel EH, Ten Brinke A. Targeting dynamic hyperinflation in moderate-to-severe asthma: A randomised controlled trial. ERJ Open Res 2021;7:00738-2020.

22. Stubbs MA, Clark VL, Gibson PG, Yorke J, McDonald VM. Associations of symptoms of anxiety and depression with health-status, asthma control, dyspnoea, dysfunction breathing and obesity in people with severe asthma. Respir Res 2022;23:341.

23. Cordova-Rivera L, Gibson PG, Gardiner PA, Powell H, McDonald VM. Physical activity and exercise capacity in severe asthma: Key clinical associations. J Allergy Clin Immunol Pract 2018;6:814-22.

24. França-Pinto A, Mendes FA, de Carvalho-Pinto RM, Agondi RC, Cukier A, Stelmach R, et al. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: A randomised controlled trial. Thora×2015;70:732-9.

25. Feng Z, Wang J, Xie Y, Li J. Effects of exercise-based pulmonary rehabilitation on adults with asthma: A systematic review and meta-analysis. Respir Res 2021;22:33.

26. Yang S, Zhang Z, Liu Y, Liu E, Luo Z. The effects of combined respiratory muscle and exercise training in children with bronchial asthma: A randomised controlled study. J Asthma Allergy 2023;16:293-303.

27. Cifu DX. Braddom's physical medicine and rehabilitation. 6th ed. Elsevier: Georgia, USA; 2021. p. 600-2.

28. O'Neill C, Dogra S. Reducing anxiety and anxiety sensitivity with high-intensity interval training in adults with asthma. J Phys Act Health 2020;17:1-5.