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Effect of combined high-intensity interval training and inspiratory muscle training on pulmonary function and exercise capacity in COPD patients

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ABSTRACT

The aim of this study was to investigate the effect of combined high intensity interval training (HIIT) and inspiratory muscle training (IMT) on pulmonary function and exercise capacity in patients COPD. This randomized, controlled trial study involved 100 COPD patients (GOLD stages II and III) aged between 40 and 70 years. Subjects were randomly assigned to one of two groups. The study group (n=50) underwent 8 weeks combined HIIT and IMT. The HIIT protocol involved four intervals, each lasting 4 minutes, beginning at 70% of maximum power and building to a target intensity of at least 85% HRmax. The IMT sessions included 2-3 sets of 30 breaths (totaling 60-90 breaths per session), with a two-minute rest between sets, three days per week starting with 30% of PI_{max} and reaching 60% of PI_{max}. The control group (n=50) performed an 8-week program of therapeutic education and 30-min self-based cycling or walking. Pulmonary function tests, incremental cycle ergometer tests, 6 min walk tests and inspiratory muscle strength were performed, and dyspnea and Halth-Related Quality of Life (HRQoL) were assessed before and after the intervention period. Results indicated that combined HIIT and IMT significantly improved exercise capacity, respiratory muscle strength, dyspnea, and quality of life in patients with COPD ($p<0.05$). There were no significant changes in pulmonary functions ($p>0.05$). This study suggests that integrating HIIT with IMT can effectively enhance the overall prognosis of patients with COPD.

KEYWORDS

COPD; HIIT; IMT; Exercise; Pulmonary Function

1. INTRODUCTION

Globally, chronic obstructive pulmonary disease (COPD) is the third leading cause of death, causing 3.23 million deaths in 2019, and consequently representing an increasingly significant public health concern (Zou et al., 2022). Patients with COPD show irreversible airflow obstruction accompanied by chronic cough, sputum production and dyspnea. Progressive pulmonary function deterioration, exercise intolerance and poor quality of life are commonly experienced by COPD patients (Chen et al., 2023). Multiple factors contribute to the decline in exercise capacity among COPD patients, including impairments in pulmonary, cardiovascular, and skeletal muscle function (Maltais et al., 2014).

Pulmonary rehabilitation has been widely recognized as the most effective nonpharmacologic COPD management method, supported by extensive evidence and multiple international guidelines (Bolton et al., 2013; Spruit et al., 2013). Exercise training is the cornerstone in the rehabilitation of lung diseases, particularly COPD aiming to relieve dyspnea and enhance pulmonary functions, aerobic capacity and health-related quality of life (HRQoL) (McCarthy et al., 2015; Lin et al., 2019). While exercise intensity is regarded as the most important aspect of any exercise training program, there is no consensus on the optimal intensity in patients with COPD (Morris et al., 2016). Although exercise intensity represents an important consideration in programs designed to enhance exercise capacity in COPD, due to symptoms of exercise intolerance such as dyspnea and muscle pain during exercise, patients fail to maintain high-intensity training for the intended duration (Gao et al., 2022). Therefore, strategies such as interval training have gained greater interest in providing an effective adaptive stimulus with a tolerable exercise load. HIIT may be an excellent approach to enhance tolerance, optimize workouts, shorten total exercise duration, improve adherence, and minimize dropout rates, ultimately contributing to improved exercise capacity and lung function (Sawyer et al., 2020).

HIIT is an exercise training method involving short intervals of high-intensity exercise, interspersed by lower-intensity or rest intervals (MacInnis & Gibala, 2017). Research indicates that in individuals with COPD, HIIT can enhance exercise tolerance, respiratory muscle function, and HRQoL while also reducing fatigue and dyspnea (Gao et al., 2022).

The primary inspiratory pump muscles leading to expansion of the chest wall are the diaphragm and parasternal intercostal muscles (Sieck et al., 2013). These muscles are overloaded in patients with COPD (Marchand & Decramer, 2000), and experience structural and functional changes leading to respiratory muscle dysfunction and reduced respiratory efficiency, exercise capacity and HRQoL

(Spruit et al., 2013). Inspiratory muscle training (IMT) is a means to exercise the inspiratory muscles using an inspiratory training device which provides consistent and specific pressure. This training method improves the strength and endurance of inspiratory muscle, alleviates dyspnea, and enhances exercise capacity in COPD patients particularly those with weak inspiratory muscles (Spruit et al., 2013).

Clinical trials investigating HIIT efficacy in COPD patients are scarce. A previous study reported that 16 weeks of 3-min HIIT lead to significant improvements in W peak, peak oxygen uptake, dyspnea, functional capacity, and HRQoL significantly in moderate and severe COPD patients (Arnardóttir et al., 2007). In a recent systematic review, it was indicated that when comparing HIIT to other exercises or standard care in COPD patients, it has been found that HIIT had more positive effects on pulmonary functions, exercise capacity, and HRQoL (Gao et al., 2022). Previous research work investigating the effects of IMT in patients with COPD are equivocal (Maltais et al., 2014). A previous systematic review showed that exercise capacity and pulmonary functions significantly increased in response to IMT without significant changes in dyspnea or HRQoL (Figueiredo et al., 2020). Nevertheless, it has been found that adding IMT to conventional pulmonary rehabilitation programs did not provide any additional benefits (Beaumont et al., 2018; Ammous et al., 2023).

No previous studies investigated the impact of combined HIIT and IMT in patients with COPD. Therefore, the present study aims to investigate the effect of combined HIIT and IMT on pulmonary function and exercise capacity in COPD patients.

2. METHODS

2.1. Study Design

The present study was performed as a randomized, controlled trial over 8 weeks and included two groups. Procedures of the study were performed in the Department of Rehabilitation and Health Sciences, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia between June 2024 and October 2024.

The study protocol was approved by the Standing Committee of Bioethics Research in Prince Sattam bin Abdulaziz University, Saudi Arabia (ID: SCBR-418/2025). The study was conducted in line with the principles of the Declaration of Helsinki. The study was registered on ClinicalTrials.gov (identifier: NCT06836895). A written informed consent form was obtained from each participant. The aim, procedures and potential risks of participating in the study procedures were explained carefully to all subjects.

2.2. Participants

This study recruited 144 patients with clinically stable COPD from local health facilities and nearby hospitals and clinics through advertisements to take part in this study and 100 were included in the study follow-up. Initially 120 patients with stable COPD (GOLD stage II, III) participated in this study as shown in Figure 1. Subjects were equally divided between the study and the control groups. Ten patients dropped from the study group because of intolerance (n=4), deterioration in respiratory function (n=3), lost in follow-up (n=2), or excluded from the statistical analyses (n=1). Also, ten patients dropped from the control group due to deterioration in respiratory function (n=5), lack of motivation (n=3), or excluded from the statistical analyses (n=2). Finally, one hundred patients completed the study with each group including 50 patients.

The inclusion criteria were: 1) moderate and severe COPD (GOLD II and III) according to guidelines criteria (Vogelmeier et al., 2017), 2) Age ≥40 but ≤70 years. Diagnosis of COPD was affirmed by irreversible airflow obstruction based on FEV1–FVC% <70% of predicted, FEV1 equal or more than 30% of predicted after bronchodilation. 3) Body mass index (BMI) >18 kg/m^2 and <30 kg/m^2.

Exclusion criteria were: 1) any musculoskeletal, cardiovascular, or neurologic diseases that prohibited participating in HIIT, 2) Exacerbation of COPD, 3) Participation in structured pulmonary rehabilitation programs or any organized exercise training within the past 6 months.

A specialized physician examined all participants to exclude ineligible subjects ensuring safe participation in the high-intensity exercise program. Written informed consent was obtained from each participant after an introductory session explaining the detailed evaluation and training procedures used in the study. All patients were instructed to maintain their medications and their regular physical activity during the intervention period. Participants in both groups were assessed for the study outcomes at baseline and following the 8-week intervention period.

Eligible subjects were randomly assigned to one of two groups, either the study group practiced HIIT and IMT or the control group who received a program of therapeutic education and 30-min self-based cycling or walking on cycle ergometers or on treadmills. Pulmonary function tests, cardiopulmonary exercise tests (CPET), functional exercise capacity (6 min walk tests) were performed, and inspiratory muscle strength, HRQoL was assessed pre- and post-intervention.

2.3. Sample Size Calculation

The estimated effect size (d = 0.65) derived from changes in maximal inspiratory pressure (PImax) observed in Larson's study was used to determine the sample size (Al-Rawaf et al., 2023). In order to reject the null hypothesis, the probability was set at 0.05, with a power of analysis at 90%, calculated using G*power 3.1.9.7 software (University of Dusseldorf, Dusseldorf, Germany). A total of 100 participants were initially recruited. However, to accommodate a projected dropout rate of up to 20%, the sample size was expanded to 120.

2.4. Randomization

A researcher, uninvolved in any other aspect of this study, conducted randomization by creating a block randomization schedule without stratifications. Initially, Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to generate randomization codes for all participants. Participants' allocation was then concealed in sequentially numbered, sealed, and non-transparent envelopes. A researcher responsible for overseeing treatment enrolled eligible participants and assigned them randomly to either the study or control group (Figure 1.)

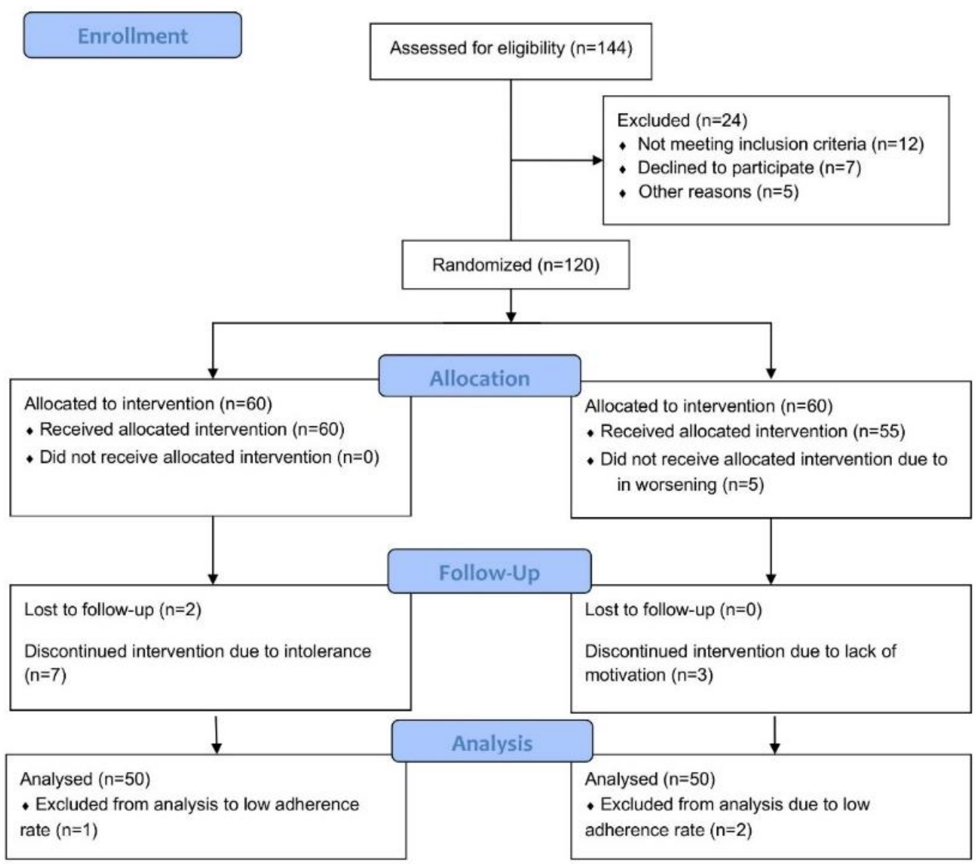

Figure 1. Consort flow diagram of the study

2.5. Anthropometrics Assessment

All participants were assessed for body weight and height using a weight and height scale (Detecto, made in USA). The body mass index (BMI) was calculated using the following formula:

$$BMI = weight (kg) / height (m)^2$$

2.6. Outcome Measures

2.6.1. Pulmonary function tests

Lung function test was carried out by the same experienced personnel using Master Screen Body® Jaeger–Carefusion spirometer (22745 Savi Ranch Parkway, Yorba Linda, CA, USA). The pulmonary function test procedures were conducted repeatedly until three satisfactory spirograms were obtained. A spirogram was considered acceptable if it was artifact-free, demonstrated adequate expiration, exhibited final forced expiratory phase plateau lasting 6 seconds, and reflected proper patient cooperation. Measurements of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), total lung capacity (TLC), and residual volume (RV) were taken (Graham et al, 2019). The single-breath technique was implemented to measure the diffusing capacity of the lung for carbon monoxide (DLco) using Master Screen Body® Jaeger–Carefusion spirometer (22745 Savi Ranch Parkway, Yorba Linda, CA, USA) (Graham et al., 2017). The pulmonary function parameters were recorded as absolute values and percentage of predicted according to participant’s height, age and sex based on summary equations (Cotes et al., 1993; Quanjer, 1993).

2.6.2. Exercise capacity

To measure peak workload (WR_{peak}), an incremental cycle ergometer test was conducted on a motorized cycle ergometer (Kettler ErgoRace, Virginia Beach, VA). Continuous ECG-registration was maintained throughout the test. The initial pedaling load was 20W, with the resistance increasing by 10W each minute until they reached exhaustion. The respiratory frequency and heart rare were recorded every minute throughout the test. Dyspnea (Borg CR-10 scale), perceived exertion (Borg RPE scale), and systolic blood pressure were assessed every two minutes. All variables were also measured before exercise and at 1, 2, 4, and 10 minutes post-exercise.

Maximal incremental cardiopulmonary exercise testing (CPET) with continuous ECG monitoring was performed to evaluate patients’ aerobic capacity using a Quark CPET metabolic cart (Cosmed, Rome, Italy) with a stationary cycle ergometer (800S, Ergoline, Bitz, Germany) in accordance with the ATS guidelines (Ross, 2003).

The test started with a warm-up period without resistance lasting 5 min by pedaling at intensity of 20W then every min the load was increased by 10W until exhaustion. CPET procedures were terminated when patients showed symptoms of maximal exercise such as extreme dyspnea or muscle fatigue. The criteria for test termination included inability of the patient to continue pedaling at <60 rpm in addition to fatigue signs, such as hyperpnea or excessive sweating and accompanied by a maximum heart rate exceeding 80% of the predicted heart rate, VO_{2peak} reaching more than 80% of the predicted, respiratory exchange ratio (RER) over 1.0, and/or reaching a VO_2 (Rowland et al., 2008; Wasserman, 2012). The measured cardiorespiratory parameters were heart rate, breathing frequency, minute ventilation, peak O_2 consumption, minute ventilation, oxygen uptake (VO_2), carbon dioxide output (VCO_2), and the anaerobic threshold. Every two minutes throughout the test, systolic blood pressure, dyspnea (using the Borg CR-10 scale), and subjective ratings of perceived exertion (using the Borg RPE scale) were recorded (Borg, 1982).

2.6.3. Functional exercise capacity

The six minute walk test (6MWT) was used to evaluate the functional exercise capacity. A 30 m long flat corridor was used to conduct the test according to the American Thoracic Society guidelines (American Thoracic Society, 2002). Assessment of heart rate, respiratory rate, oxygen saturation, and dyspnea were performed before and after testing. Before beginning the test, patients received instructions on the proper test procedures. Each patient was verbally encouraged every minute during the test. Patients performed the test twice, with the initial trial done to familiarize them with the test procedures and was not recorded (Hamilton & Haennel, 2000).

2.6.4. Respiratory muscle strength assessment

Respiratory muscle strength was evaluated by measuring PI_{max} with a digital mouth pressure meter (Micro RPM®, Micro Medical, United Kingdom). The highest value from three trials, each varying by less than 10% was recorded, with at least 30 seconds of rest between each attempt. A PI_{max} of 60 cm H_2O was set as the lower limit for normal (Evans & Whitelaw, 2009).

2.6.5. Health-Related Quality of Life (HRQoL)

Health-Related Quality of Life (HRQoL) was assessed using the St. George’s Respiratory Questionnaire (SGRQ) (Jones, 2005). It is a standardized questionnaire and is self-administered. It is designed to measure self-perceived health impairments and HRQoL in individuals with airway diseases. Symptoms, activity limitations, and disease impact are the domains being evaluated by the test. The test has 50 items with 76 weighted responses. The symptoms domain includes 8 items, the activity domain includes 16 items, and the disease impact domain includes 26 items. The questionnaire responses are rated from 0 to 100. 0 represents the best HRQoL while 100 represents the poorest HRQoL.

2.6.6. COPD assessment test

Participants' symptoms were documented using the COPD Assessment Test (CAT) (Jones et al., 2009). It is consisted of eight items covering topics such as cough, sputum production, chest tightness, breathlessness on hills or stairs, limitations in home activities, sleep quality, and fatigue. The higher the score of the test, the more significant is the influence of COPD on the participant's life (Jones et al., 2011).

2.6.7. Dyspnea

The severity of dyspnea was evaluated using the modified Medical Research Council Dyspnea Scale (mMRC). It is a 0–4 scale designed to measure the influence of dyspnea on physical activity in patients with respiratory conditions. When the score is 0 this means that dyspnea occurs only in response to intense physical exertion, while a score of 4 reflects severe breathlessness that prevents the individual from leaving the house or causes difficulty during activities such as dressing or undressing. Subjects are required to mark the level of activity at which they experience dyspnea (Singh, 2014).

2.7. Interventions

2.7.1. HIIT protocols

The exercise training was carried out on an outpatient basis for 8 weeks, with each session starting and ending with 10 minutes of cycling on an ergometer at 30%–40% of baseline peak power (WR_{peak}) for warm-up and cool-down. HIIT protocol involved four intervals, each lasting 4 minutes, beginning at 70% of maximum power (WR_{peak}) and building to a target intensity of at least 85% of the maximum heart rate (HR_{max}). Each interval is followed by a 3-minute active recovery period at 30% of WR_{peak}. The full interval block lasted 28 minutes, and the entire session was 42 minutes. A Polar heart rate monitor (Polar V800, Polar Electro Oy, Kempele, Finland) was used to continuously monitor heart rate. All exercise sessions were supervised, with verbal encouragement given during intervals. At the end of each interval, both heart rate and Borg scale ratings were recorded aiming for about 90% of the predicted HR_{max} and a Borg rating of 5–7 on the modified Borg scale. The targeted exercise intensity during the 3-minute active rest phases was 50–60% of the predicted HR_{max}. All training sessions were supervised by a respiratory physiotherapist to ensure exercise safety and to provide guidance and encouragement for the patients (Borg, 1982).

2.7.2. Inspiratory Muscle Training (IMT)

Prior to beginning IMT, study participants were provided with an overview of IMT by a trained physiotherapist. The maximum inspiratory pressure (PI_{max}) was recorded before starting the training. All sessions for both groups were held in a well-ventilated room and at the same time of day. Before the training session, each patient sat comfortably in a chair, and then the measures of systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation and Borg scale score were taken. Once clinical stability was confirmed, subjects rested for a minimum of five minutes and began the session when they felt ready.

The training session starts by placing the subject in a relaxed comfortable position ensuring their upper chest, shoulders, and arms are properly supported. Subjects were instructed to take the mouthpiece, seal their lips tightly and after applying the nasal clip they had to perform slow deep inspiration followed by full expiration with minimal effort. They were advised to keep their shoulders and legs relaxed throughout the maneuver through using diaphragmatic breathing. Subjects were closely monitored for symptoms of dyspnea, fatigue, or dizziness. Also, oxygen saturation and heart rate were tracked with a pulse oximeter. The IMT sessions used the Threshold IMT® device (Respironics New Jersey, Inc., USA) and included 2-3 sets of 30 breaths (totaling 60-90 breaths per session), with a two-minute rest between sets, three days per week. In the first week of training, IMT intensity was set at 30% of the subject’s PI_{max}. By the end of the first month, the exercise intensity reached 60% of the subject’s PI_{max} by gradually increasing the intensity by 10% weekly. Weekly PI_{max} assessments were conducted to ensure appropriate load adjustments. For the next four weeks, the exercise intensity was fixed at 60% of each subject’s PI_{max}. Throughout the last month, PI_{max} value and subsequently 60% are weekly updated according to the most recent PI_{max} measurement. All respiratory muscle strength assessments were performed by the same trained physiotherapist to maintain consistency.

2.7.3. Control group intervention

Control group intervention included 8 weeks (3 sessions weekly) of a supervised rehabilitation program. Subjects in the control group received therapeutic education as well as 30-min self-based cycling or walking on a treadmill or on a cycle ergometer. The RPE scale was measured following each session.

2.8. Statistical Analysis

Statistical analyses were conducted using SPSS software version 23 (Chicago, IL). Data from both groups were expressed as mean ± SD. To check for the normal distribution in continuous variables, the Shapiro–Wilk test was used. Chi-Square X^2 test and independent t-test were conducted to ascertain the homogeneity of fundamental characteristics of nominal and continuous data, respectively, between the study and the control groups. To test the pre- to post intervention differences before between the study and control groups, a two-way repeated measures analysis of variance (ANOVA) (2x2, group x time) was used. Independent t-tests were conducted to identify the group where the significant changes took place. The p-value was set at $p < 0.05$.

3. RESULTS

3.1. Patients' Characteristics

The statistical analyses results revealed no significant differences between the study and the control groups in the baseline characteristics of all measured variables (Table 1).

Table 1. Participants' baseline characteristics

Variable	Study group (n=49)		Control group (n=48)		*p*
Gender, M/F					
-Male	31		29		
-Female	19		21		0.465*
GOLD					
GOLD II	33		31		
GOLD II	17		19		0.149*
	Mean ±SD		**Mean ±SD**		
Age, *years*	61.32 ±6.51		62.17 ±5.63		0.41‡
Smoking exposure, pack-year	31 ±12		32 ±11		0.21‡
Duration of disease, *years*	5.42 ±5.33		6.12 ±4.82		0.32‡
BMI, *Kg/m²*	24.87 ±2.3	24.9 ±2.6	25.12 ±2.8	24.88 ±2.91	0.12‡

*Note. Mean ± SD, GOLD, Global Initiative for Chronic Obstructive Lung Disease; BMI: body mass index *: Non-significant difference p>0.05 (Chi-Square X^2 test) ‡: Non-significant changes between two groups p>0.05 (Independent t-test).*

The study group included 62% male patients compared to 58% in the control group. Patients at GOLD stage II represented 66% of the study group subjects while 34% were at stage III. Patients at GOLD stage II represented 62% of the control group subjects while 38% were at stage III. Subjects' BMI at baseline showed no significant difference between the study and control groups ($p > 0.05$).

At baseline, pulmonary functions values in both groups showed moderate obstruction, no significant difference between the study and control groups ($p > 0.05$). All subjects completed the training protocols without reporting any adverse events attributable to the study protocol. Subjects in both groups completed their sessions according to the proposed schedule. In the study group, patients performed 24 sessions over 8 weeks. The average work rate during each session in the study group was 80% of WR_{peak}.

3.2. Pulmonary function tests

All the pulmonary function parameters showed no significant changes among groups after training ($p > 0.05$) (Table 2).

Table 2. Pulmonary function at baseline and end of the intervention in the study groups

Variable	Study group (n=50) Mean ±SD		Control group (n=50) Mean ±SD		Group X Time interaction	
	Pre	Post	Pre	Post	*p*	$\eta^2_{Partial}$
FEV_1, *L*	1.7±0.69	1.7±0.6	1.7±0.7	1.6±0.6	0.14‡	-
FEV_1, %*pred*	56.5±14	56.8±11	55.6±12	54.7±12	0.21‡	-
FVC, *L*	3.2±0.7	3.3±0.6	3.1±0.6	3.2±0.5	0.11‡	-
FVC, %*pred*	88.2±11	89.1±9	87.5±10	88.4±11	0.10‡	-
FEV_1/FVC, %	53.1±11	52.3±10	52.7±10	51.4±9	0.31‡	-
TLC, *L*	6.3±0.8	6.2±0.7	6.1±0.6	6.1±0.7	0.33‡	-
TLC, %*pred*	110.3±12	107.5±13	111.8±11	110.2±10	0.61‡	-
IC, *L*	2.2±0.6	2.3±0.7	2.1±0.7	2.1±0.5	0.07‡	-
FRC, *L*	4.3±1.2	4.2±1.1	4.4±1.2	4.4±1.0	0.71‡	-
FRC, %*pred*	124.3±21	121.9±19	126.3±23	125.5±18	0.09‡	-
RV, *L*	3.1±0.8	3.0±0.7	3.2±0.7	3.2±0.9	0.07‡	-
RV, %*pred*	148±26	147±24	151±28	149±26	0.1‡	-
RV/ TLC, %	51.6±11	50.3±9	52.3±10	51.9±8	0.27‡	-
D_LCO, %	71.3±18	70.2±17	69.4±16	70.1±16	0.48‡	-
PaO_{2rest}*, *(mmHg)	71.9±9.2	73.1±10.3	69.8±11.5	70.9±10.8	0.09‡	-
$PaCO_{2rest}$*, *(mmHg)	42.1±5.2	40.3±4.4	43.3±5.6	42.6±6.1	0.32‡	-
SpO_{2rest}, %	94.2±3.4	94.5±3.1	93.7±4.1	93.5±4.6	0.45‡	-

Note. FEV_1: forced expiratory volume in 1s; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_LCO: diffusing capacity of carbon monoxide; PaO_{2rest}: arterial partial oxygen pressure at rest; $PaCO_{2rest}$: arterial partial carbon dioxide pressure at rest; $spO_{2rest,}$: arterial oxygen saturation at rest; $\eta^2_{Partial}$: Effect size of the difference;‡: Non-significant changes from pre- to post-intervention among study and control groups $p>0.05$.

3.3. Exercise capacity

A significant interaction of VO_{2peak} was observed pre- to post-intervention between the study and the control groups, $F (1, 98) = 43.22$, $p < 0.001$, $\eta^2 = 0.536$ (Table 3). In comparison with baseline values, VO_{2peak} was significantly increased in the study group ($p<0.001$) in response to the combined training program compared with the control group. The same for the WR_{peak}, there was significant interaction from pre- to post intervention between the study and the control groups, $F (1, 98) = 40.45$, $p < 0.001$, $\eta^2 = 0.488$. The WR_{peak} was significantly increased in the study group ($p<0.001$) compared with the control group. There were no significant changes in the other CPET parameters among groups ($p > 0.05$) (Table 3).

Table 3. Exercise capacity at baseline and end of the intervention in the study groups

Variable	Study group (n=50) Mean ±SD		Control group (n=50) Mean ±SD		Group X Time interaction	
	Pre	Post	Pre	Post	*p*	$\eta^2_{Partial}$
CPET at WR_{peak}						
HR, *b/min*	133.4±19	131.2±18	136.3±21	135.1±19	0.43‡	-
RR, breaths/min	37.2±7	36.7±6	37.8±9	37.9±8	0.32‡	-
VO_2, *L/min*	1.51±0.6	1.66±0.7†	1.47±0.5	1.48±0.6	P<0.001*	0.318
VO_2, *mL/min/kg*	21.4±6	26.1±9†	19.8±7	20.1±6	P<0.001*	0.536
VE, L/min	55.8±12	54.5±11	56.1±10	56.0±11	0.27‡	-
VE/VCO_2	33.5±7	33.1±6	33.7±8	33.3±6	0.51‡	-
O_2 pulse, *ml/beat*	11.6±4.2	11.9±3.8	11.5±4.1	11.5±4.2	0.62‡	-
SpO_2, %	93.3±3.6	93.8±3.4	92.8±4.1	92.9±3.9	0.23‡	-
WR_{peak}, *W*	86.5±31	95.3±23†	84.7±28	85.4±27	P<0.001*	0.488
Borg (dyspnea)	6.3±2.9	6.2±2.8	6.4±2.7	6.4±2.8	0.08‡	-
Borg (Leg fatigue)	6.1±2.3	5.9±2.2	6.2±2.5	6.2±2.4	0.07‡	-
Borg, RPE (6-20)	16.2±1.6	15.6±1.7	16.8±1.8	16.9±1.7	0.08‡	-
6-min walk test						
Distance, *m*	451.3±122.6	492.9±132.1 †	447.5±119.6	450.2±117.5	P<0.001*	0.391
Distance, *% pred*	73.2±16	79.5±13†	72.5±14	73.4±15	P<0.001*	0.356
Dyspnea at end of test	6.2±2.9	6.0±2.8†	6.3±3	6.2±3.1	0.01*	0.186
Leg fatigue at end of test	6.3±2.7	6.1±2.8†	6.4±2.9	6.4±3.1	0.04*	0.113

*Note. Mean ± SD, CPET: cardiopulmonary exercise test; WR_{peak}: peak work capacity; HR: heart rate; RR: respiratory rate; VO_2: oxygen uptake; VE: minute ventilation; VE/VCO_2: ventilatory equivalent; SpO_2: arterial oxygen saturation; $spO_{2rest,}$: arterial oxygen saturation; $\eta^2_{Partial}$: Effect size of the difference; *: Changes from pre- to post-intervention among study and control groups are significant at p<0.05; ‡: Non-significant changes from pre- to post-intervention among study and control groups p>0.05 †: Significant changes of post-tests between the two groups at p<0.05.*

3.4. Functional exercise capacity

The changes in the 6-min walk test between the study and control groups from pre- to post-intervention are shown in Table 3 above. The analysis of the results revealed significant interaction of 6-min walk distance and percent-predicted 6-min walk distance pre- to post-intervention between the study and the control groups, $F(1, 98) = 32.21$, $p < 0.001$, $\eta^2 = 0.391$ and $F(1, 98) = 28.63$, $p < 0.001$, $\eta^2 = 0.356$ respectively. When compared with baseline values, 6-min walk distance and percent-predicted 6-min walk distance were significantly increased in the study group ($p<0.001$) in response to the combined training program compared with the control group.

3.5. Respiratory muscle strength

Table 4 shows the changes in respiratory muscle strength between the study and control groups from pre- to post-intervention. A significant interaction of PI_{max} was observed pre- to post-intervention between the study and the control groups, $F(1, 98) = 29.51$, $p < 0.001$, $\eta^2 = 0.367$. When compared with the pre-intervention values, PI_{max} was significantly increased in the study group ($p<0.001$) in response to the combined training program compared with the control group.

Table 4. Respiratory muscle strength, CAT scores and SGRQ scores at baseline and end of the intervention in the study groups

Variable	Study group (n=50) Mean ±SD		Control group (n=50) Mean ±SD		Group X Time interaction	
	Pre	**Post**	**Pre**	**Post**	***p***	$\eta^2_{Partial}$
PI_{max}, *cmH_2O*	76.5±22	85.3±19	75.3±21	77.1±20	p<0.001*	0.367
CAT score	9.6±4.3	6.7±4.7	10.1±5.2	9.8±5.5	p<0.001*	0.329
SGRQ score	14.3±5.7	11.1±5.6	14.8±6.1	13.5±6.3	p<0.001*	0.311
mMRC score	1.9±0.5	1.7±0.4	2.1±0.6	2.0±0.7	P<0.001*	0.371

*Note. PI_{max}: maximum inspiratory pressure; CAT score: COPD Assessment Test; SGRQ score: St. George's Respiratory Questionnaire; mMRC score: The modified Medical Research Council Dyspnea Scale; $\eta^2_{Partial}$: Effect size of the difference; *: Changes from pre- to post-intervention among HIIT and control groups are significant at p<0.05; †: Significant changes of post-tests between the two groups at p<0.05.*

3.6. Health-related quality of life

Changes in the CAT and SGRQ scores between the study and control groups from pre- to post-intervention are shown in Table 4. The analysis of the results revealed significant interaction of the CAT and SGRQ scores pre- to post-intervention between the study and the control groups, $F(1, 98) = 26.41$, $p < 0.001$, $\eta^2 = 0.329$ and $F(1, 98) = 24.88$, $p < 0.001$, $\eta^2 = 0.311$ respectively. When compared with baseline values, the CAT and SGRQ scores were significantly increased in the study group ($p<0.001$) in response to the combined training program compared with the control group.

3.7. Dyspnea

Table 4 above also showed the changes in mMRC score between the two groups pre- and post-intervention. A significant interaction of mMRC was observed pre- to post-intervention between the study and the control groups, $F(1, 98) = 29.73$, $p < 0.001$, $\eta^2 = 0.371$. When compared with baseline values, mMRC was significantly increased in the study group ($p<0.001$) in response to the combined training program compared with the control group.

4. DISCUSSION

Poor exercise capacity is the main cause of disability for many patients with COPD (Oga et al., 2005). Growing evidence suggests that HIIT can enhance exercise capacity, pulmonary functions, and HRQoL in COPD patients (Gao et al., 2022). Additionally, research has demonstrated that IMT may alleviate dyspnea and improve inspiratory muscle strength in patients with COPD (Hill et al., 2010). The aim of the current study was to investigate the effect of combined HIIT and IMT on pulmonary function and exercise capacity in COPD. The analysis of results showed that combined HIIT and IMT significantly improved exercise capacity, dyspnea, respiratory muscle strength, and HRQoL in COPD. There were no significant changes in pulmonary functions.

With respect to exercise capacity, VO_{2peak} showed significant improvement in the exercise group. A recent meta-analysis that included 59 studies reported significant VO_{2peak} improved in COPD patients in response to HIIT (Ward et al., 2023). Similarly, HIIT brought about significant VO_{2peak} gain in male COPD patients (Gao et al., 2022). Also, 16 weeks of interval training with a training intensity ⩾80% of the baseline WR_{peak} enhanced VO_{2peak} in patients with moderate or severe COPD (Arnardóttir et al., 2007). Nevertheless, only continuous exercise training led to significant improvement in VO_{2peak} in patients with moderate and severe COPD, while 8-week interval training program with alternated intensity of 90% (1 min) and 45% (2 min) of the WR_{peak} didn't result in significant changes (Coppoolse et al., 1999).

Moreover, 12 weeks of interval training using 30-sec intervals at 100% of WR_{peak} intensity with 30-s recovery intervals) resulted in no change in VO_{2peak} (Vogiatzis et al., 2002). In the same domain, the subjects in the exercise group showed significant improvement in WR_{peak}. In line with this finding, a systematic review reported significant improvements in WR_{peak} in response to HIIT intervention when compared with the control (Gao et al., 2022). Interval training in patients with chronic respiratory disease has been found to be more effective than continuous training in enhancing peak exercise capacity with minimal dyspnea sensations (Alexiou et al., 2021). The results of the present study showed that exercise capacity significantly improved, as evaluated by 6MWD in the study group compared with the control group. Several previous studies have reported similar findings (Gao et al., 2022; Aakerøy et al., 2021). Also, an 8-week program of combined interval training and IMT significantly improved the 6MWD (Wang et al., 2017).

Regarding the effect of IMT on exercise capacity, a recent systemic review found that 6 of the 10 included studies indicated that IMT improves exercise tolerance in patients with COPD (Mota et al., 2023). Moreover, functional exercise capacity in COPD patients, has been found to be increased in response to IMT in a meta-analysis of 32 randomized controlled trials (Gosselink et al., 2011). On the contrary, several studies have reported that although isolated IMT improved inspiratory muscle function, it was not sufficient to significantly improve exercise capacity (Riera et al., 2011; Ramírez-Sarmiento et al., 2002; Hill et al., 2006). Moreover, it has been found that combined rehabilitation program and IMT did not significantly improve 6MWD in COPD patients without respiratory muscle weakness (Beaumont et al., 2015).

Repeated bouts of HIIT place stress on the ventilatory, cardiovascular, and skeletal muscle systems, triggering physiological adaptations. These include cardiac adaptations, such as improved cardiac output through increased stroke volume, and skeletal muscle adaptations, such as enhanced oxidative capacity and capillary density in the working muscles. These changes enhance oxygen delivery and utilization in the muscles during both peak and submaximal workloads. In COPD, the primary site of adaptation appears to be the skeletal muscles, where well-documented improvements in oxidative capacity and capillary density occur. These enhancements delay the onset of lactic acidosis to higher workloads. Consequently, after exercise training, COPD patients can perform the same submaximal workload with reduced lactate production, lower nonmetabolic carbon dioxide production, and decreased ventilatory demands (Morris et al., 2016). Exercise training in COPD patients has been suggested to partially reverse the slow-to-fast shift in muscle fibers (de Brandt et al., 2016). Moreover, HIIT has been shown to induce significant increase in muscle fiber size and type-I muscle fibers in trained muscles (Gouzi et al., 2013). Also, it stimulates muscular protein synthesis and muscular hypertrophy via promoting the expression of anabolic growth factors, such as myogenic differentiation factor-D and insulin-like growth factor-1 (Vogiatzis et al., 2010). Other mechanisms such as improved endothelial function (Polverino et al., 2017), improved ejection fraction (Brønstad et al., 2013) have been previously proposed as potential mechanisms explaining the exercise-induced improvement in exercise capacity.

However, the enhanced inspiratory muscle strength observed in this study could be an additional factor contributing to the positive impact of HIIT on exercise capacity as decreased inspiratory muscle strength is a contributing factor to dyspnea and exercise intolerance (Charususin et al., 2013).

The results of the current study revealed significant improvement in mMRC score for dyspnea in the study group in comparison with controls. Previous research work comparing the effect of HIIT to continuous training reported comparable findings (Vogiatzis et al., 2002; Arnardóttir et al., 2007).

Improvements in dyspnea observed in the current study may be due to improved aerobic capacity in the study group. Improved VO_{2peak} is associated with decreased ventilatory demands during exercise (Patessio et al., 1992). Moreover, improved exercise capacity may postpone ventilatory limitation at higher exercise intensities as subjects can increase aerobic metabolism with increased intensities (Casaburi & Zuwallack, 2009). Improvement of dynamic hyperinflation subsequent to improved IC may be another explanation for decreased dyspnea (Alexiou et al., 2021). Yet, the results of the present study showed nonsignificant change in IC in the study group. Regarding the effect of IMT on dyspnea, a recent systematic review of 16 studies on COPD have reported that IMT lead to significant improvement in dyspnea (Han et al., 2024). Furthermore, threshold IMT has been shown to be effective in alleviating dyspnea in patients with severe COPD. Also, a 12-months of daily home IMT program significantly improved dyspnea in mild to very severe COPD (Battaglia et al., 2009). dyspnea in COPD occurs due to tachypnea caused by pulmonary hyperinflation, resulting in rapid, shallow breathing. Respiratory muscle fatigue is aggravated, and gas exchange efficiency is reduced due to the abnormal breathing pattern. The result is increased respiratory effort and increased lactic acidosis in response to exercise (Han et al., 2024). IMT has been suggested to increase type II muscle fibers in the diaphragm which in turn can increase diaphragmatic velocity leading to shortened respiratory cycle time and improved hyperinflation (Beaumont et al., 2015). Further, improvement of inspiratory muscle strength and endurance, mainly diaphragm, and subsequent increase in ventilation capacity is a proposed mechanism by which IMT can encounter inspiratory muscle fatigue and alleviate dyspnea in COPD patients (Abedi Yekta et al., 2019). In contrast to the findings of the abovementioned studies, the results of a recent systematic review and meta-analysis showed that IMT did not significantly improve dyspnea in COPD patients (Huang et al., 2024). Furthermore, it has been shown that isolated IMT was not effective in improving dyspnea even in patients with inspiratory muscle weakness (Figueiredo et al., 2020). These inconsistent findings may be due to different IMT protocols, outcome measures, and limited sample size in the previous studies. Indeed, several factors such as the patient’s disease status, exercise mode, intensity, and frequency are crucial in determining the efficacy of IMT in improving dyspnea in patients with COPD (Han et al., 2024).

The results of the present study have shown significantly improved HRQoL in the study group. In line with this finding, a systemic review including 8 studies reported that interval training significantly improved HRQoL in patients with COPD (Beauchamp et al., 2010). Also, HRQoL has been found to be significantly improved above the clinically significant difference for following both 16 weeks of interval training in patients with COPD (Arnardóttir et al., 2007). A previous study revealed that only 12 to 15 supervised HIIT exercise sessions over 3 weeks that followed by exercise at home lead to significant improvement in HRQoL in patients with severe COPD with (Puhan et al., 2006). Significant improvements in HRQoL in the present study can be explained by improved exercise capacity and decreased dyspnea (Vogelmeier et al., 2017). However, recent systematic reviews reported no significant change following aerobic training despite significant improvement in exercise tolerance and respiratory muscle strength in patients with COPD (Figueiredo et al., 2020; Ward et al., 2020). It has been established that IMT positively affects HRQoL in patients with COPD (Han et al., 2024). As an independent intervention, IMT has the possibility of reducing dyspnea and enhancing exercise capacity and thereby improving the HRQoL in COPD patients by alleviating symptoms and limiting the progression of the pathophysiologic processes (Abedi Yekta et al., 2019). Management of dyspnea through IMT is the cornerstone in enhancing HRQoL (Han et al., 2024). Inspiratory muscle weakness in COPD patients is mainly affected by inspiratory muscle dysfunction and abnormal length-tension relationship (Singer et al., 2011).

The present study showed significant improvement in inspiratory muscle strength as measured by PI_{max}. A previous study used combined cycle ergometer training and IMT reported significant improvement in inspiratory muscle strength in patients with stable COPD (Wang et al., 2017). Moreover, the 8 weeks of HIIT significantly increased PI_{max} by 23% in patients with moderate and severe COPD (Coppoolse et al., 1999). On the other hand, a recent systemic review has reported significant inspiratory muscle strength improvement in response to IMT in patients with COPD (Han et al., 2024). Further, this improvement is attained whether the IMT is isolated or combined with other interventions (Figueiredo et al., 2020; Buran Cirak et al., 2022). Another meta-analysis of 32 randomized clinical trials demonstrated IMP brought about significant improvements in PI_{max} (+13 cmH_2O) in patients with COPD (Gosselink et al., 2011). Similarly, a randomized clinical trial implementing eight weeks of IMT showed significant increase in PImax of about 18cmH2O (Chuang et al., 2017). Moreover, it has been reported that in subjects with moderate and severe COPD, 8 weeks of interval high intensity IMT significantly increased PI_{max} by 29% (Hill et al., 2006). IMT in COPD patients has been found to result in functional improvement and adaptive changes in inspiratory muscle structures e.g., significant enlargement in the fast-twitch muscle fibers (Mota et al., 2023).

Regarding pulmonary function, the current study did not show significant change in any of the pulmonary functions in both groups. Indeed, it was expected that significant improvement in the respiratory muscle strength occurred in the present study to induce improvements in pulmonary function. At least, FEV1 that reflects disease severity could be improved through combined HIIT and IMT (Gao et al., 2022).

Research has shown that exercise training does not lead to significant improvements in lung volumes. In response to exercise, some pulmonary functions remain unchanged in both healthy individuals and patients with chronic lung diseases (Morris et al., 2016). While basic therapies and pulmonary rehabilitation can help slow disease progression, airflow obstruction remains irreversible. Airway obstruction is incompletely reversible, tissue damage is permanent, and the lungs cannot fully return to their normal state (Chen et al., 2023). However, the program intervention period implemented in the current study is relatively short, which might have limited the observation of potential effects on lung function parameters. It is possible that IMT requires a longer timeframe to show significant improvements in lung function. Further research, including more robust randomized controlled trials, is needed to thoroughly evaluate the effects of respiratory muscle training on lung function in COPD patients. Additionally, comprehensive treatment approaches—such as medication, rehabilitation programs, and respiratory support may have a more significant role in enhancing lung function in COPD patients (Huang et al., 2024).

Randomized design with adequate statistical power is one of the strengths of the present study. Second, the training program was conducted under full supervision, ensuring adherence and incorporating regular progressive increases in training intensity. Third, the sample size included in this study is relatively large. However, this study has some limitations. First, the lack of more study groups undergoing isolated HIIT or IMT may have limited the ability to determine the exact mechanism of outcome measures improvements. Second, the lack of long-term follow-up to monitor the improvements in the study group subjects. Third, the relatively short intervention duration (8weeks). Future studies should consider both isolated as well as combined intervention over longer durations.

5. CONCLUSIONS

This study demonstrated that 8 weeks of combined HIIT and IMT significantly improved exercise capacity, dyspnea, respiratory muscle strength, and quality of life in patients with COPD. There were no significant changes in pulmonary functions. The study recommends combining HIIT with IMT to comprehensively improve the prognosis of COPD patients.

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AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. Ahmed S. Ahmed contributed to the conception of the study, performed the work, participated in data collection, and was involved in manuscript preparation and revision for important intellectual content. Saud M. Alrawaili contributed to the performance of the work and data collection. Fahad H. Alahmadi contributed to data analysis, data interpretation, and manuscript preparation. Samah M. Ismail contributed to data analysis, data interpretation, manuscript preparation, and revision for important intellectual content.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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