Respiratory Medicine 172 (2020) 106119

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Clinical Trial Paper

# Effects of peripheral and different inspiratory muscle training methods in coronary artery disease patients with metabolic syndrome: A randomized-controlled trial

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ARTICLE INFO

*Keywords:*
Coronary artery disease
Metabolic syndrome
Neuromuscular electrical stimulation
Inspiratory muscle training
Peripheral muscle training

ABSTRACT

Background
*Objective:* To investigate the effects of peripheral muscle training (PMT) and different inspiratory muscle training (IMT) methods on respiratory functions, exercise capacity, and biochemistry parameters in coronary artery disease patients with metabolic syndrome.
*Methods:* This prospective, single-blind, randomized-controlled study included 60 patients of stable coronary artery disease with metabolic syndrome (New York Heart Association [NYHA] Class I-II, left ventricular ejection fraction >40%). Patients were randomly divided into three groups: neuromuscular electrical stimulation (NMES) plus PMT group (NMES + PMT group, n = 20), IMT plus PMT group (IMT + PMT group, n = 20) and PMT group (PMT group, n = 20). Treatment continued for six weeks for all groups. The NMES was applied to rectus abdominis, IMT was applied with 30% of maximal inspiratory pressures, and PMT was applied at home. Spirometry, maximal inspiratory and expiratory pressure, dyspnea scores, exercise stress test, and biochemistry parameters were measured before and after training.
*Results:* There were significant improvements in spirometric tests, respiratory muscle strength, dyspnea scores, exercise capacity, fasting blood glucose, and antistreptolysin O after treatment in all groups ($p < 0.05$). Significant improvements in C-reactive protein and erythrocyte sedimentation rate were observed in NMES + PMT and IMT + PMT groups ($p < 0.05$). Among the groups, there was a significant difference in maximal inspiratory pressure ($p = 0.02$) and erythrocyte sedimentation rate ($p = 0.037$) in favor of NMES + PMT group ($p < 0.05$).
*Conclusion:* Our study results showed significant improvements in respiratory functions, exercise capacity, and biochemistry markers in all groups. Different IMT methods can be used in cardiopulmonary rehabilitation to improve exercise intolerance in coronary artery disease patients with metabolic syndrome.
*Clinical Trial registration number:* NCT03523026.

## 1. Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities characterized by insulin resistance, obesity, diabetes, dyslipidemia, hypertension, coronary artery disease (CAD), and hypercoagulability [1]. Its incidence has been increasing globally and is an important public health issue worldwide [2]. According to the National Cholesterol Education Program (NCEP) definition, the diagnosis of MetS is made based on three of the five criteria: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein (HDL), hypertension, and hyperglycemia [3].

Currently, it is considered that MetS is an important health problem and increases cardiovascular damage and mortality with increasing cardiopulmonary risks. It has been shown that MetS, which includes multiple risk factors for cardiovascular diseases, causes atherosclerotic process [2,4,5]. Higher morbidity and mortality rates have been also found in MetS patients with CAD [6]. The association of MetS with CAD has been shown in many previous studies, and more than half of CAD is also diagnosed with MetS. It has been reported that the risk of CAD increases three times and the risk of cardiovascular mortality increases five times in patients with MetS [7]. In recent studies, MetS risk factors have been shown to adversely affect respiratory function and that each

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https://doi.org/10.1016/j.rmed.2020.106119
Received 2 June 2020; Received in revised form 8 August 2020; Accepted 10 August 2020
Available online 22 August 2020

of risk factors may be associated with respiratory functions [8–12]. This relationship between MetS and pulmonary dysfunction is also similar in some other studies [13–15]. Furthermore, patients with MetS have lower forced expiratory volume ($FEV_1$), forced vital capacity (FVC), and total lung capacity (TLC) compared to healthy individuals [10,11,16]. This relationship between restrictive respiratory disorder and MetS increases with age, sex, body mass index, smoking, and physical inactivity [17]. Recent evidence has shown a strong relationship between MetS and lower respiratory functions and exercise capacity [9,13–15,18,19].

In MetS, therapeutic lifestyle changes and exercise are recommended as the first-line treatment. In recent clinical studies in patients with MetS, aerobic, strengthening, and combined exercise training increase exercise capacity [4,20–30]. However, there is only one study showing that aerobic exercise training increases exercise capacity in patients of both MetS and CAD [26]. Peripheral muscle training (PMT) and inspiratory muscle training (IMT) methods are also used in exercise training to increase cardiovascular capacity [31]. Although there are studies which support the potential benefits of respiratory muscle training in different patient populations [32–34], there is no study available investigating respiratory muscle training and its effects in CAD patients with MetS.

In our hypothesis, CAD patients with MetS have a significant limitation in respiratory functions and exercise capacity, resulting in exercise intolerance. We, therefore, hypothesized that these risks could be eliminated by improving respiratory functions in these patients. In the present study, we aimed to investigate the effects of PMT and IMT on respiratory functions, exercise capacity, and biochemistry markers in CAD patients with MetS. Our secondary objective was to examine the availability of neuromuscular electrical stimulation (NMES) as an alternative treatment in respiratory muscle training.

## 2. Methods

### 2.1. Study design and study population

This prospective, single-blind, randomized-controlled study was conducted at Cardiopulmonary Physiotherapy and Rehabilitation Department, Cardiology Institute, Istanbul University-Cerrahpasa between May 2017 and June 2018 Medical data of the patients were obtained from archive records and outpatient online database between 2012 and 2017. A total of 69 patients with CAD and MetS were included in the study. Inclusion criteria were as follows: the New York Heart Association (NYHA) Class I (cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath while walking, climbing stairs, etc.) and Class II (mild symptoms; mild shortness of breath and/or angina, and slight limitation during ordinary activity), left ventricular ejection fraction (LVEF) above 40% and clinical stability. Exclusion criteria were as follows: having chronic obstructive pulmonary disease, pulmonary, neurological, renal, liver, gastrointestinal, endocrine, orthopedic and oncologic patients, new or suspected thromboembolic event, patients with severe resistant hypertension, having acute myocardial infarction within the past six months, pulmonary edema, previous valve surgery, coronary artery revascularization (percutaneous transluminal coronary angioplasty and coronary artery bypass surgery) within the past six months, and having cardiac pacemaker. Finally, a total of 60 patients were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Medipol University, Ethics Committee (Protocol No:10840098–604.01.01-E.201). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### 2.2. Randomization

This study was conducted in a single-blind design in which the assessors were blinded. The clinical status, exercise stress test, and biochemistry markers of all patients included in the study were evaluated by the cardiologist. The patients who met the inclusion criteria were randomly allocated into three equal groups: (1) NMES plus PMT group (NMES + PMT group, n = 20), (2) IMT plus PMT group (IMT + PMT group, n = 20), and (3) the PMT group (PMT group, control group, n = 20). All patients were evaluated by a single physiotherapist before and after treatment at the Cardiopulmonary Physiotherapy and Rehabilitation Department. Each group received the treatment program for a total of six weeks. In all patients, pulmonary functions, respiratory muscle strength, dyspnea scores, exercise stress test, and biochemistry markers were measured before and after training. All patients were allowed to continue their standard medical treatment during exercise training (acetylsalicylic acid, beta blocker, statin, angiotensin-converting enzyme-I, metformin, diuretic).

### 2.3. Measurements

#### 2.3.1. Pulmonary function tests

Pulmonary functions were evaluated by spirometry (Spiro USB, CareFusion Inc., CA, USA) according to the guidelines of the American Thoracic Society and European Respiratory Society. Using pulmonary function tests, forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_1$), forced expiratory volume in 1 s/forced vital capacity ($FEV_1$/FVC), forced expiratory flow (FEF) 25–75%, and peak expiratory flow (PEF) were measured [35].

#### 2.3.2. Respiratory muscle strength

Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were evaluated using a respiratory pressure meter (Micro-RPM; Micro Medical, UK) [36]. The tests were performed in the sitting position. Measurements were made by taking the disposable cardboard mouthpiece attached to the device into the mouth and tightly closed by lips. Meanwhile, the nose was closed with a clip. During the tests, all patients were verbally encouraged for the best performance. The measurement was repeated 10 times and the patient was allowed to rest for 30–60 s during repetitions. The variability among measurements was intended to be less than 5cm$H_2O$. The measured maximal value was recorded. To calculate the expected values, the equations of Black and Hyatt were taken as reference [37].

#### 2.3.3. Exercise stress test

The Bruce protocol was applied in the exercise stress test. The test was performed by reaching 85% of the maximal heart rate [38].

#### 2.3.4. Biochemistry markers analysis

The blood samples were taken from the antecubital vein with at least 8 h of fasting before and after treatment. The fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), hemoglobin (Hb), uric acid, creatinine, lipid parameters (total cholesterol, triglyceride, HDL, low-density lipoprotein [LDL] cholesterol), alanine transaminase (ALT), aspartate transaminase (AST), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antistreptolysin O (ASO), creatine phosphokinase (CPK), complete blood count, and brain natriuretic peptide (Pro-BNP) levels were measured.

#### 2.3.5. Modified Medical Research Council dyspnea scale

Dyspnea of patients in daily life were evaluated using the modified Medical Research Council (mMRC) scale [39].

### 2.4. IMT methods

**NMES Muscle Training**: Adjustable neuromuscular stimulator (NeuroTracTM ETS, Veritiy Medical Ltd., UK) was used to stimulate the rectus abdominis muscle. Stimulation was achieved by placing two pairs of electrodes (40 mm × 60 mm) on the muscle. The patient was 30° head high, sitting long, with arms sideways. In the first sessions, the application was provided by electrocardiography. The NMES was applied for

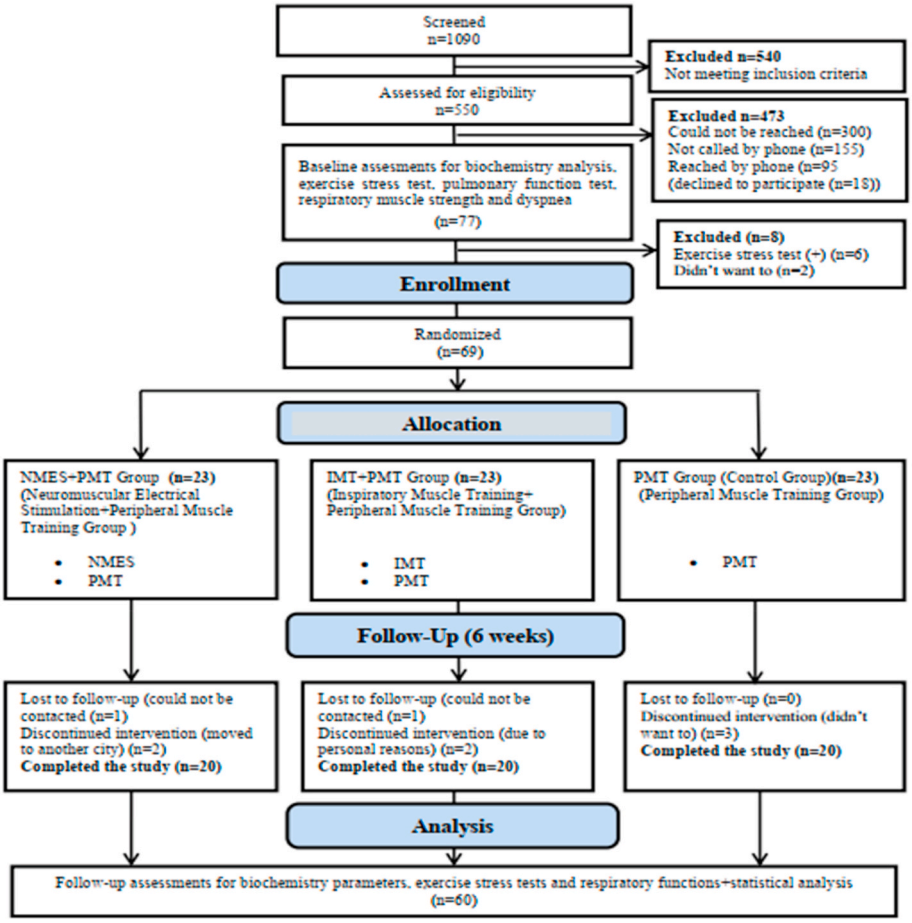


**Fig. 1.** Study flow diagram.

30 min at maximum intensity that the patient could tolerate by providing 10 s contraction/20 s relaxation, 30 Hz frequency (cycles per sec). The patient was coordinated with active deep diaphragmatic breathing exercises requested by the patient following electrical stimulation contractions. The NMES was applied under the supervision of the physiotherapist three days a week for a total of six weeks.

**IMT**: The IMT was performed by an exercise tool (Threshold IMT, Respironics, USA). The IMT was administered to the patients at 30% of the measured maximal inspiratory pressure (MIP), seven days a week, with 15 min twice a day for a total of six weeks. The patients were instructed to visit the physiotherapy department once a week. The measurements of the patients were repeated, new training loads were adjusted, and IMT was given under supervision. All patients used a nose-clips during training and were told to take five deep breaths to maintain diaphragmatic breathing with the device and, then, they were instructed to take the device out and rest for 5–10 s.

**PMT**: PMT was administered as a home-based exercise program three days per week under supervision one day per two weeks. Each group received the PMT program for a total of six weeks. The PMT follow-up was provided with an exercise follow-up form. In addition, an exercise follow-up card was made where other treatments were followed.

#### 2.4.1. PMT training components

***Patient education***. One-to-one patient education was given before exercise training. In the education program, the components of CAD and MetS, the importance and effects of exercise were explained in detail.

***Diaphragmatic respiration training***. Deep diaphragmatic breathing was given to all patients before exercise training. The anatomy of the lung and diaphragm, its neighborhood with other organs, the mechanics of breathing and exhalation were explained with prepared videos.

***Flexibility and stretching exercises***. Flexibility and stretching exercises to the upper and lower extremities are given to all patients. Exercises were performed before and after PMT every other day, three times a week, two to four repetitions, stretching for 5–10 min. Six exercises were applied to the shoulders, arms, neck, chest and trunk of the upper extremity, hip flexors, quadriceps, back extensors and hamstring muscles of the lower extremities were prepared with four exercises with illustrated templates. Flexibility and stretching exercises were applied to the patient during the training. After exercise training, the prepared exercise charts were given to the all patients.

***Selection of elastic band and proprioceptive neuromuscular facilitation (PNF) exercises***. Elastic band selection depends on the patient's tolerance and, according to the muscle strength, Borg scale was performed based on subjective perception. The patient was first asked to perform an exercise with 15 repetitions using the lowest elastic band. The perceived severity was determined as the correct elastic band between 11 and 14. When the patient did the exercises without any difficulty in 12 repetitions and three sets, the color of the elastic band was changed to the next level band [40]. The PNF exercises were given which were the basic movement patterns in combination with diaphragmatic breathing exercises with an elastic band for four to five repetitions [41]. The PMT was advanced three times a week every other day with 8–12 repetitions, one to three sets, 2 min rest between each set for a total of 30 min. Blood pressure was measured with a digital automatic blood pressure device (Omron Electronics B.V., Hoofddorp, Netherlands), and peripheral saturation and heart rate were checked with pulse oximetry before and after exercise. For the correct application of the PNF exercises at home, the exercise bouquet prepared with application pictures taken to a patient was sent to the patients via

**Table 1**
Baseline demographic and clinic characteristics of the groups.

| | NMES + PMT (n = 20) (Min-Max) | IMT + PMT (n = 20) (Min-Max) | PMT (n = 20) (Min-Max) | p[a] value |
|---|---|---|---|---|
| ***Demographic characteristics*** | | | | |
| Age (year), adult (39–74) | 55,95 ± 9,01 (39–74) | 56,90 ± 5,16 (48–69) | 56,40 ± 7,87 (41–70) | 0,92 |
| Gender Male (M) | 18 (90%) | 15 (75%) | 18 (90%) | 0,31[b] |
| (*n* (%) Female (F) | 2 (10%) | 5 (25%) | 2 (10%) | |
| Total M/F 51/9 (85%/15%) | | | | |
| BMI (kg/m$^2$) | 32,55 ± 3,33 (29–40) | 32,23 ± 3,37 (26–38) | 31,27 ± 4,04 (24–37) | 0,51 |
| LVEF (%) | 54,35 ± 7,67 (40–60) | 56,65 ± 7,01 (40–62) | 55,10 ± 6,32 (41–60) | 0,58 |
| NYHA Class I/II | 1,59 ± 0,62 | 1,56 ± 0,65 | 1,58 ± 0,55 | 0,89 |
| ***Risk factors*** | | | | |
| Smoking,pack-years | 22,63 ± 30,26 (0,5–132) | 25,78 ± 19,44 (12,5–60) | 33,63 ± 24,44 (10–80) | 0,37 |
| Smoking (non/ex-smoker/n (%) | 6/14 (30%/70%) | 5/15 (25%/75%) | 2/18 (10%/90%) | 0,28 |
| Hypertension (n) | 18 (90%) | 16 (80%) | 17 (85%) | 0,68 |
| Diabetes (n) | 13 (65%) | 17 (85%) | 13 (65%) | 0,27 |
| Hyperlipidemia(n) | 20 (100%) | 19 (95%) | 20 (100%) | 0,36 |
| Previous MI (n) | 12 (60%) | 9 (45%) | 12 (60%) | 0,55 |
| Heredity (n) | 17 (85%) | 15 (75%) | 14 (70%) | 0,52 |
| CABG(n)/ | 10 (50%) | 8 (40%) | 7 (35%) | 0,62[b] |
| PTCA(n) | 10 (50%) | 12 (60%) | 13 (65%) | |
| ***Respiratory functions*** | | | | |
| FVC (%) | 86,10 ± 14,28 (55–112) | 87,20 ± 18,99 (49–117) | 88,90 ± 11,75 (70–124) | 0,84 |
| $FEV_1$ (%) | 89,25 ± 15,26 (66–114) | 89,30 ± 20,68 (49–115) | 91,15 ± 14,29 (63–117) | 0,92 |
| PEF (%) | 90,30 ± 18,47 (58–122) | 87,15 ± 21,04 (50–127) | 95,50 ± 22,84(61–162) | 0,45 |
| mMRC (0–4) | 0,95 ± 0,83 (1–3) | 0,60 ± 0,60 (1–2) | 0,70 ± 0,66 (1–2) | 0,27 |
| ***Respiratory muscle strength*** | | | | |
| MIP ($cmH_2O$) | 86,40 ± 24,21 (30–130) | 90,35 ± 25,04 (45–126) | 92,35 ± 18,04 (71–144) | 0,30 |
| MEP ($cmH_2O$) | 122,40 ± 37,18 (60–201) | 119,75 ± 23,24 (76–159) | 123,65 ± 35,32 (74–207) | 0,32 |
| ***Exercise stress test*** | | | | |
| Walking time (min) | 7,11 ± 2,47 (1,31–10) | 6,93 ± 1,68 (3,18–9,14) | 8,03 ± 1,77 (4,34–12,02) | 0,19 |
| MET | 8,63 ± 2,23 (3,7–11,5) | 8,43 ± 1,60 (4,9–10,3) | 9,60 ± 1,69 (6,4–13,3) | 0,12 |

[a] Anova test.
[b] Chi-square test, significance level $p < 0.05$. NMES: neuromuscular electrical stimulation, PMT: peripheral muscle training (control group), IMT: inspiratory muscle training, BMI: body mass index, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, MI: myocardial infarction, CABG: coronary artery bypass graft, PTCA: percutaneous transluminal coronary angioplasty, FVC: forced vital capacity, $FEV_1$: forced expiratory volume in 1 s, PEF: peak expiratory flow, mMRC: modified Medical Research Council Association dyspnea score, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, MET: metabolic equivalent.

smartphone WhatsApp application. Manual drawing was performed to two patients who did not use a smart phone. The patients were instructed to do the exercises in the afternoon or evening and three to 4 h after the meal to prevent muscle and soft tissue injuries.

### 2.5. Statistical analysis

Statistical analysis was performed using the SPSS version 20.0 software (IBM Corp., Armonk, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The normality distribution of the data was analyzed using the Kolmogorov-Smirnov Test. The paired samples *t*-test was used to compare the values before and after among the groups with normally distributed data. Analysis of variance (ANOVA) was used to compare significant differences among the groups. A repeated measures ANOVA was used to examine recurrent measurements. A p value of $<0.05$ was considered statistically significant.

## 3. Results

A total of 60 patients completed the study (Fig. 1). All patients were adults and 51 (85%) were males and 9 (15%) were females with a mean age of 56.42 ± 7.40 (range, 39 to 74) years. At baseline, there was no significant difference among the groups in terms of demographic and clinical features ($p > 0.05$) (Table 1). There was no statistically significant difference among the groups in terms of pulmonary functions, respiratory muscle strength, exercise stress test, and blood biochemistry parameters ($p > 0.05$). In our study, 31.7% of the patients (n = 60) had restrictive type disorder. The FBG, triglyceride, CRP, ASO, and ESR values were above normal and HDL cholesterol was measured at borderline in the majority of male patients (NCEP-III 2001). None of the patients had complications in our study.

### 3.1. Respiratory functions

There was a significant increase in the FVC, $FEV_1$ and PEF in the NMES + PMT and IMT + PMT groups and FVC and PEF in the PMT group ($p < 0.05$). The MIP, MIP%, MEP and MEP% increased after treatment in all groups ($p < 0.05$) and mMRC dyspnea score decreased ($p < 0.05$). Respiratory functions and respiratory muscle strength before and after the training in all groups are shown in Figs. 2 and 3, respectively. The MIP before and after the training in all groups is shown in Fig. 4. A significant difference was found in the MIP among the groups with significantly higher MIP values in the NMES + PMT group compared to the PMT group ($p = 0.02$) (Table 2).

### 3.2. Exercise capacity

After treatment in all groups, a significant increase in metabolic equivalent of task (MET), walking time ($p < 0.05$) and a decrease in the baseline heart rate and maximal heart rate ($p < 0.05$) were found in the exercise stress test, although there was no significant difference among

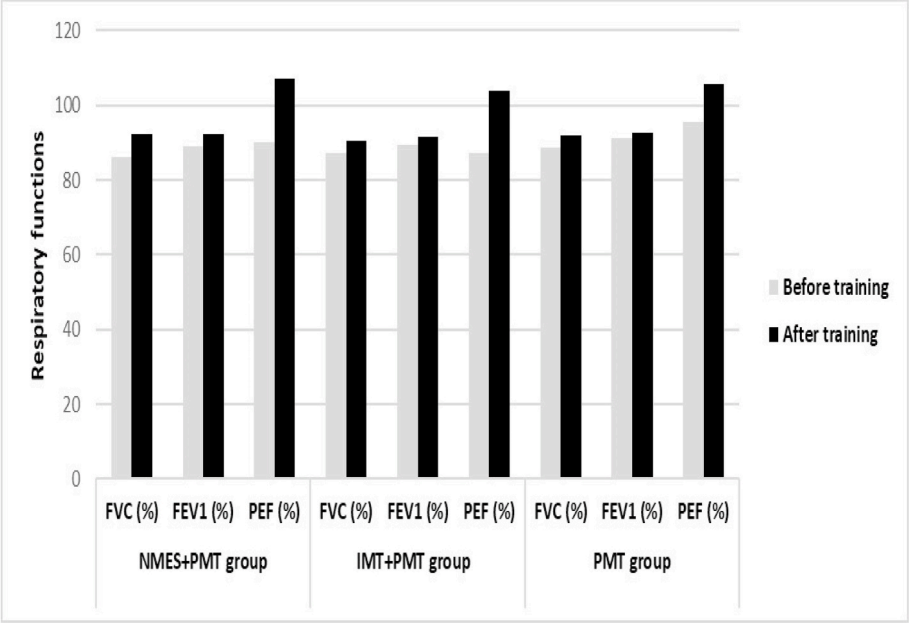


**Fig. 2.** Respiratory functions before and after training in all groups.

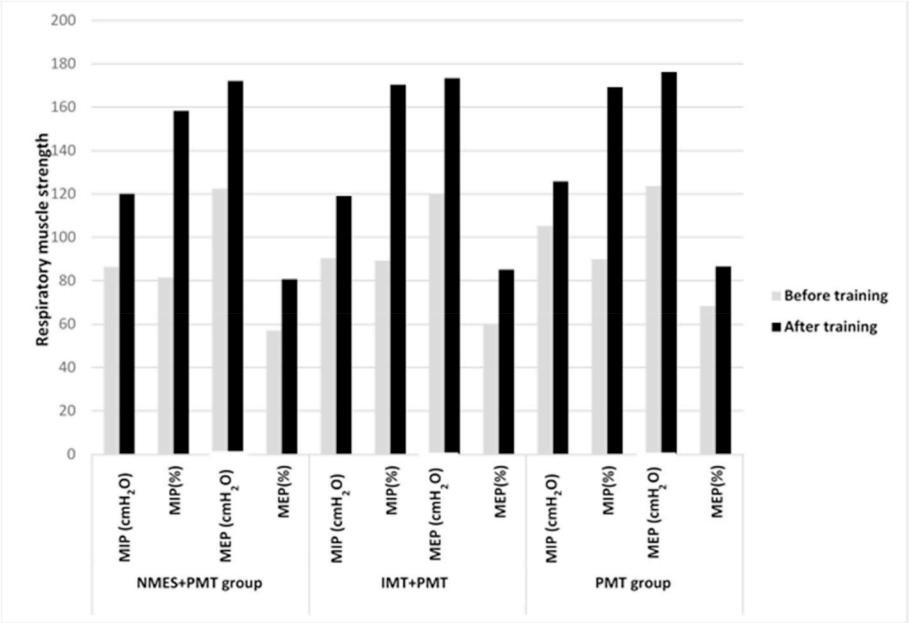


**Fig. 3.** Respiratory muscle strength before and after training in all groups.

the groups ($p > 0.05$) (Table 3). The MET before and after the training in all groups is shown in Figs. 5 and 6, respectively.

### 3.3. Biochemistry markers analysis

After treatment, there was a significant decrease in the FBG, CRP, ESR, and ASO ($p < 0.05$) in the NMES + PMT and IMT + PMT groups, in the FBG and ASO ($p < 0.05$) in the PMT group, and in the uric acid and ALT ($p < 0.05$) in the IMT + PMT group. In addition, there was a significant difference in the ESR value among the groups ($p < 0.05$). This difference was found to be significantly lower in the NMES + PMT group ($p = 0.037$) (Table 4).

## 4. Discussion

The main finding of this study is that exercise training on peripheral and respiratory muscles in CAD patients with MetS improves respiratory function resulting in clinical improvement, as evidenced by dyspnea scores and exercise stress test results. This finding was comparable among all three study groups, although there were some differences in the PMT findings. The improvement was more pronounced in the NMES + PMT group. With few exceptions, inflammation markers (CRP and ESR) were also positively influenced by exercise. This study is the first to apply PMT and different IMT methods and investigate their effects in CAD patients with MetS.

There is a limited number of studies investigating the effect of MetS on pulmonary functions. In a study, Bae et al. [11] examined the

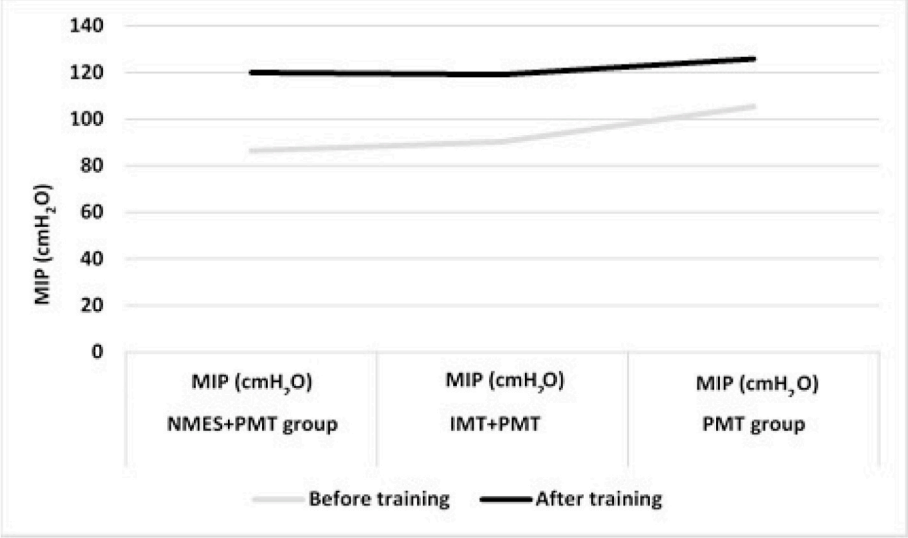


**Fig. 4.** MIP before and after training in all groups.

relationship between MetS and respiratory function and found that MetS patients had significantly lower respiratory functions (FVC, $FEV_1$) than healthy individuals. The authors also reported that all MetS components (waist circumference, triglyceride, and HDL cholesterol) had a linear relationship with pulmonary dysfunction. Rogliani et al. [10] investigated the pulmonary problems in patients with MetS and reported that FVC and $FEV_1$ in non-smoker MetS patients were lower than those in healthy individuals and concluded that MetS had a negative effect, independent of smoking ($p < 0.05$). The authors also reported a restrictive type rather than an obstructive type disorder in this specific group. These two studies indicate that MetS affects respiratory functions, regardless of smoking and age. In another study, Scarlata et al. [16] investigated pulmonary function disorders in patients with MetS and diabetes. In this study, there were restrictive and obstructive dysfunction in 18% and 20% of the patients, respectively, and there was a positive relationship between restrictive lung dysfunction and MetS and abdominal obesity ($p < 0.05$). Although the pulmonary function test results of our patients were within normal range, restrictive type respiratory disorder was found based on our patient-based examinations (32%). In relation to smoking, although our cases were similar to the cases in the study of Rogliani et al. [10], FVC and $FEV_1$ values were lower in our study. In addition, the mean waist circumference (100 ± 8.49 cm) was similar to the studies of Scarlata et al. [16] (98.8 ± 10.52 cm) and Rogliani et al. [10] (101.46 ± 11.80 cm). Lower respiratory function and higher prevalence of restrictive type disorder can be attributed to the fact that our patients had also CAD, which is the most

**Table 2**
Effects of exercise training on respiratory functions and differences among the groups.

| | NMES + PMTgroup (n = 20) | | | | IMT + PMTgroup (n = 20) | | | | PMT group (n = 20) | | | | CDAG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT X ± SS | AT X ± SS | Δ X ± SS | $p^a$ value | BT X ± SS | AT X ± SS | Δ X ± SS | $p^a$ value | BT X ± SS | AT X ± SS | Δ X ± SS | $p^a$ value | $p^b$ value |
| ***Respiratory functions*** | | | | | | | | | | | | | |
| **FVC (%)** | 86,10 ± 14,28 | 92,40 ± 12,20 | 6,30 ± 6,30 | **0,001** | 87,20 ± 18,99 | 90,70 ± 20,47 | 3,50 ± 5,21 | **0,007** | 88,90 ± 11,75 | 92,05 ± 10,61 | 3,15 ± 5,59 | **0,021** | 0,17 |
| **$FEV_1$ (%)** | 89,25 ± 15,26 | 92,35 ± 13,90 | 3,10 ± 3,39 | **0,001** | 89,30 ± 20,68 | 91,50 ± 19,35 | 2,20 ± 4,02 | **0,024** | 91,15 ± 14,29 | 92,65 ± 13,04 | 1,50 ± 5,06 | 0,20 | 0,49 |
| **$FEV_1$/FVC** | 83,75 ± 5,84 | 83,85 ± 6,36 | 0,10 ± 8,72 | 0,96 | 83,50 ± 4,97 | 83,40 ± 4,72 | −0,10 ± 4,18 | 0,92 | 84,20 ± 7,52 | 81,90 ± 6,97 | −2,30 ± 4,49 | 0,033 | 0,40 |
| **FEF25–75 (%)** | 81,70 ± 25,62 | 87,65 ± 26,44 | 5,95 ± 14,45 | 0,08 | 76,25 ± 35,98 | 83,15 ± 29,59 | 6,90 ± 32,32 | 0,35 | 89,85 ± 34,88 | 89,70 ± 33,82 | −0,15 ± 15,32 | 0,97 | 0,56 |
| **PEF (%)** | 90,30 ± 18,47 | 107,20 ± 18,04 | 17,90 ± 14,07 | **0,001** | 87,15 ± 21,04 | 103,95 ± 18,67 | 16,80 ± 13,07 | **0,001** | 95,50 ± 22,84 | 105,65 ± 24,89 | 10,15 ± 8,07 | **0,001** | 0,22 |
| ***Respiratory muscle strength*** | | | | | | | | | | | | | |
| **MIP ($cmH_2O$)** | 86,40 ± 24,21 | 120,05 ± 28,82 | 33,65 ± 14,11 | **0,001** | 90,35 ± 25,04 | 119,10 ± 31,58 | 28,75 ± 16,65 | **0,001** | 92,35 ± 18,04 | 118,85 ± 21,28 | 26,50 ± 12,65 | **0,001** | ***0,02** |
| **MIP(% predicted)** | 81,55 ± 27,29 | 158,40 ± 41,32 | 76,85 ± 28,43 | **0,001** | 89,25 ± 24,81 | 170,35 ± 30,76 | 81,10 ± 25,79 | **0,001** | 89,85 ± 11,15 | 169,25 ± 38,17 | 79,40 ± 36,64 | **0,001** | 0,78 |
| **MEP ($cmH_2O$)** | 122,40 ± 37,18 | 172,05 ± 49,24 | 49,65 ± 26,87 | **0,001** | 119,75 ± 23,24 | 173,55 ± 39,75 | 53,80 ± 29,09 | **0,001** | 123,65 ± 35,32 | 176,35 ± 39,15 | 52,70 ± 17,76 | **0,001** | 0,12 |
| **MEP (% predicted)** | 57,10 ± 80,65 | 80,65 ± 19,64 | 23,55 ± 12,79 | **0,001** | 60,10 ± 11,76 | 85,20 ± 15,84 | 25,10 ± 14,07 | **0,001** | 68,40 ± 16,94 | 86,50 ± 18,59 | 18,10 ± 8,49 | **0,001** | 0,16 |
| **mMRC** (0–4) | 0,95 ± 0,83 | 0,20 ± 0,52 | −0,75 ± 0,55 | **0,001** | 0,60 ± 0,60 | 0,05 ± 0,22 | −0,55 ± 0,60 | **0,001** | 0,70 ± 0,66 | 0,05 ± 0,22 | −0,65 ± 0,67 | **0,001** | 0,59 |

[a]Paired T test, $p < 0,05$.[b]Anova test, $p < 0,05$, NMES: neuromuscular electrical stimulation, PMT: peripheral muscle training, IMT: inspiratory muscle training, BT: before training, AT: after training, FVC: forced vital capacity, $FEV_1$: forced expiratory volume in 1 s, FEF25-75 forced expiratory flow 25%–75%, PEF: peak expiratory flow, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure, mMRC: modified Medical Research Council Association dyspnea score, CDAG: comparison of differences among the groups.
*$p < 0.02$ The difference in MIP ($cmH_2O$) was observed in NMES + PMT group by [b]Anova test with more improvement than PMT group.

**Table 3**
Effects of exercise training on exercise stress test and differences among the groups.

| | NMES + PMT group (n = 20) | | | | IMT + PMT group (n = 20) | | | | PMT group (n = 20) | | | | CDAG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | p[b] value |
| **Basal heart rate (min)** | 86.35 ± 12.11 | 84.60 ± 13.24 | 1.75 ± 2.35 | **0.001** | 87.75 ± 15.36 | 85.70 ± 12.81 | 2.05 ± 2.03 | **0.001** | 85.70 ± 14.71 | 84.50 ± 12.79 | 1.20 ± 1.85 | **0.001** | 0.30 |
| **Maximum heart rate (min)** | 157.45 ± 29.29 | 153.95 ± 14.43 | 3.5 ± 1.35 | **0.001** | 151.95 ± 12.08 | 149.85 ± 21.94 | 2.1 ± 1.42 | **0.001** | 152.95 ± 17.04 | 149.70 ± 13.37 | 3.25 ± 1.23 | **0.001** | 0.72 |
| **MET** | 8.63 ± 2.23 | 9.86 ± 2.45 | 1.23 ± 1.23 | **0.001** | 8.44 ± 1.60 | 9.76 ± 1.82 | 1.32 ± 1.06 | **0.001** | 9.60 ± 1.69 | 10.38 ± 1.97 | 0.78 ± 0.92 | **0.001** | 0.25 |
| **Walking time (min)** | 7.12 ± 2.47 | 8.26 ± 2.32 | 1.15 ± 1.20 | **0.001** | 6.94 ± 1.68 | 8.07 ± 1.52 | 1.13 ± 1.01 | **0.001** | 8.03 ± 1.77 | 9.11 ± 2.20 | 1.08 ± 1.77 | **0.013** | 0.99 |

[a] Paired T test, $p < 0,05$.
[b] Anova test, $p < 0,05$, NMES: neuromuscular electrical stimulation, PMT: peripheral muscle training, IMT: inspiratory muscle training, BT: before training, AT: after training, MET (Metabolic Equivalent) is a objective measure of oxygen uptake and shows the intensity of exercise (1 MET = 3,5 ml/kg/dk), CDAG: comparison of differences among the groups.

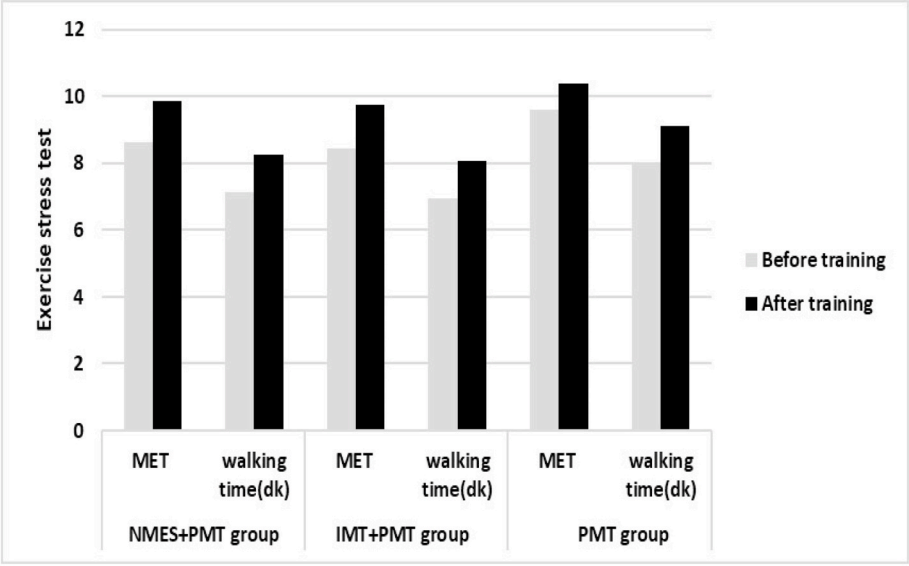


**Fig. 5.** MET before and after training in all groups.

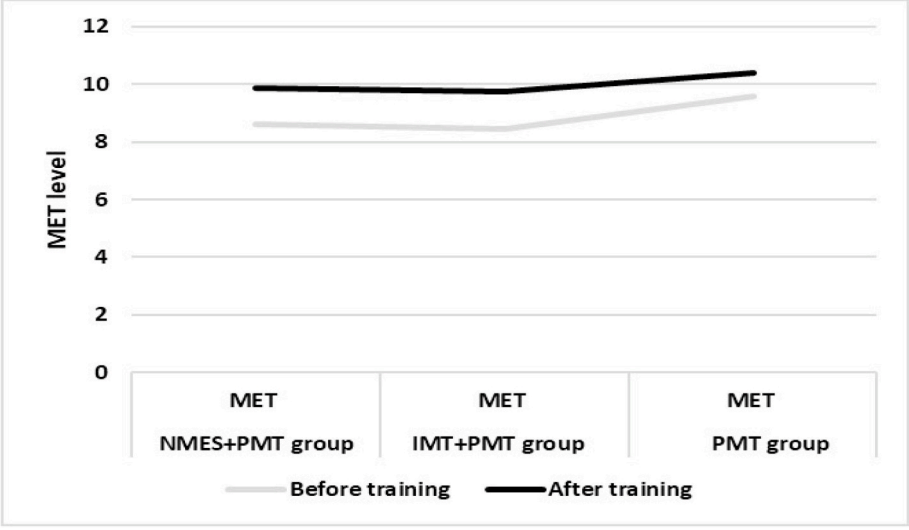


**Fig. 6.** MET before and after training in all groups.

**Table 4**
Effects of exercise training on blood biochemistry and differences among the groups.

| | NMES + PMTgroup (n = 20) | | | | IMT + PMT group (n = 20) | | | | PMT group (n = 20) | | | | CDAG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | BT X ± SS | AT X ± SS | Δ X ± SS | p[a] value | p[b] |
| **FBS** | 132,55 ± 64,76 | 122,65 ± 44,55 | −9,90 ± 25,02 | **0,003** | 133,99 ± 38,25 | 116,75 ± 24,07 | −17,24 ± 24,06 | **0,005** | 130,00 ± 54,11 | 121,05 ± 41,27 | −8,95 ± 18,97 | **0,048** | 0,46 |
| **TC** | 169,35 ± 32,66 | 165,00 ± 31,78 | −4,35 ± 21,49 | 0,377 | 172,30 ± 36,58 | 164,90 ± 37,66 | −7,40 ± 45,84 | 0,479 | 177,50 ± 54,36 | 173,40 ± 59,55 | −4,10 ± 31,27 | 0,565 | 0,94 |
| **TG** | 229,90 ± 164,88 | 199,15 ± 99,28 | −30,75 ± 128,57 | 0,298 | 170,85 ± 90,59 | 146,85 ± 43,54 | −24,00 ± 66,90 | 0,125 | 221,45 ± 146,22 | 211,75 ± 144,94 | −9,70 ± 80,68 | 0,597 | 0,78 |
| **HDL** | 41,35 ± 12,13 | 44,35 ± 10,84 | 1,00 ± 5,19 | 0,399 | 42,75 ± 8,40 | 43,35 ± 9,10 | 0,60 ± 4,17 | 0,528 | 42,95 ± 13,76 | 43,30 ± 8,99 | 0,35 ± 6,63 | 0,816 | 0,93 |
| **LDL** | 107,80 ± 34,00 | 100,40 ± 31,90 | −7,40 ± 26,08 | 0,220 | 113,75 ± 29,68 | 106,95 ± 38,71 | −6,8 ± 46,43 | 0,520 | 109,35 ± 48,23 | 103,75 ± 46,24 | −5,60 ± 25,02 | 0,330 | 0,99 |
| **Uric acid** | 6,28 ± 2,24 | 6,09 ± 2,09 | −0,18 ± 0,85 | 0,354 | 5,88 ± 1,70 | 5,34 ± 1,46 | −0,54 ± 0,89 | **0,013** | 4,89 ± 1,47 | 4,89 ± 1,42 | 0,00 ± 0,96 | 1000 | 0,16 |
| **Creatinine** | 0,99 ± 0,24 | 1,01 ± 0,34 | 0,03 ± 0,18 | 0,538 | 1,41 ± 1,91 | 0,89 ± 0,17 | −0,52 ± 1,93 | 0,269 | 0,92 ± 0,22 | 0,91 ± 0,22 | −0,02 ± 0,11 | 0,510 | 0,25 |
| **ALT** | 25,00 ± 14,63 | 24,30 ± 11,87 | −0,70 ± 6,42 | 0,631 | 28,85 ± 20,49 | 25,15 ± 17,68 | −3,70 ± 6,63 | **0,022** | 27,63 ± 11,94 | 27,89 ± 12,02 | 0,26 ± 8,81 | 0,898 | 0,22 |
| **AST** | 21,05 ± 8,14 | 20,20 ± 6,73 | −0,85 ± 5,40 | 0,490 | 22,70 ± 13,50 | 19,30 ± 7,50 | −3,40 ± 8,74 | 0,098 | 22,42 ± 7,54 | 22,21 ± 7,18 | −0,21 ± 5,67 | 0,873 | 0,30 |
| **Pro-BNP** | 242,82 ± 466,99 | 191,67 ± 280,55 | −51,15 ± 218,70 | 0,309 | 247,67 ± 569,90 | 234,16 ± 655,5 | −13,51 ± 140,59 | 0,672 | 97,37 ± 90,03 | 91,44 ± 60,20 | −5,94 ± 46,33 | 0,573 | 0,61 |
| **Sedim.** | 18,35 ± 23,99 | 12,25 ± 8,77 | −6,10 ± 16,53 | **0,005** | 15,25 ± 12,06 | 12,70 ± 11,28 | −2,55 ± 3,03 | **0,001** | 11,30 ± 10,16 | 14,15 ± 16,99 | 2,85 ± 8,15 | 0,134 | **0037** |
| **ASO** | 115,15 ± 84,59 | 100,50 ± 69,96 | −14,65 ± 19,24 | **0,003** | 98,00 ± 88,41 | 88,85 ± 73,68 | −9,15 ± 18,04 | **0,035** | 76,15 ± 90,43 | 68,25 ± 85,94 | −7,90 ± 7,28 | **0,001** | 0,37 |
| **CRP** | 7,28 ± 18,51 | 2,69 ± 2,87 | −4,58 ± 18,25 | **0,002** | 9,66 ± 13,27 | 6,11 ± 8,66 | −3,56 ± 5,67 | **0,011** | 10,01 ± 29,25 | 3,74 ± 3,97 | −6,28 ± 25,76 | 0,290 | 0,90 |
| **CPK** | 128,70 ± 94,28 | 138,55 ± 75,10 | 9,85 ± 64,39 | 0,502 | 171,20 ± 144,15 | 166,75 ± 135,7 | −4,45 ± 108,37 | 0,856 | 125,90 ± 64,31 | 137,45 ± 93,28 | 11,55 ± 78,46 | 0,518 | 0,81 |
| **Leukocyte** | 8,04 ± 1,53 | 8,18 ± 2,05 | 0,14 ± 0,99 | 0,533 | 8,50 ± 1,80 | 8,45 ± 2,28 | −0,05 ± 1,94 | 0,902 | 8,44 ± 2,95 | 8,57 ± 2,97 | 0,14 ± 1,40 | 0,670 | 0,90 |
| **Neutrophil** | 4,67 ± 1,30 | 4,60 ± 1,09 | −0,07 ± 0,83 | 0,705 | 4,91 ± 1,62 | 4,80 ± 1,72 | −0,11 ± 1,80 | 0,797 | 4,76 ± 1,84 | 5,01 ± 1,26 | 0,25 ± 1,32 | 0,406 | 0,67 |

[a] Paired T test, $p < 0.05$.
[b] Anova test, $p < 0.05$. NMES: neuromuscular electrical stimulation, PMT: peripheral muscle training, IMT: inspiratory muscle training, BT: before training, AT: after training, FBS: fasting blood sugar, TC: total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, ALT: aspartate aminotransferase, AST: alanine aminotransferase, Pro-BNP: brain natriuretic peptide, Sedim: sedimantation, ASO: antistreptolysin O, CRP: C-reactive protein, CPK: creatine phosphokinase, CDAG: comparison of differences among the groups.

specific aspect of this study. In the current study, the mean MIP was within normal limits, but found to be below 80 $cmH_2O$ in 30% of our patients. According to American Thoracic Society/European Respiratory Society, MIP below 80 $cmH_2O$ indicates inspiratory muscle weakness [42]. After exercise training, MIP increased by 38.9% in the NMES + PMT group, 31.82% in the IMT + PMT group, and 28.70% in the PMT group ($p < 0.001$). Likewise, MEP significantly increased in the NMES + PMT group by 40.56%, in the IMT + PMT group by 44.93%, and in the PMT group by 42.62% ($p < 0.001$). Given the fact that pulmonary functions are affected to this degree in a low-risk population with NYHA Class I-II (asymptomatic-mildly symptomatic), monitoring of respiratory functions is important in patients in CAD with MetS. In our study, a significant improvement in the pulmonary function and respiratory muscle strength was found in all groups ($p < 0.05$). This can be attributed to the fact that deep diaphragmatic breathing combined with PNF for PMT seems to be beneficial in all groups. Of note, the difference was found to be higher in the NMES + PMT group and the PMT group ($p = 0.02$), indicating a significant difference compared to the IMT + PMT group. One explanation for this may be that diaphragm is further supported mechanically by the increasing muscle mass by NMES, resulting in improvement of respiratory functions. We believe that the high compliance and tolerance to NMES in our study is a definite advantage. Therefore, it can be speculated that NMES can be used as an alternative method in the respiratory muscle training, being more effective than IMT. Based on these findings, we suggest that it is a safe and useful approach, particularly in patients who are not suitable for IMT and who cannot participate in cardiopulmonary rehabilitation programs, inpatient patients with exercise intolerance who cannot participate in traditional exercise or cardiopulmonary rehabilitation programs. Hence, NMES can be applied safely to patients with CAD and MetS patients with exercise intolerance.

The studies showing the effects of different exercise trainings on functional capacity are widely performed for changing risk factors in MetS patients [29,30,40]. In these studies, aerobic, strengthening, and combined exercise training were given, and the results showed that functional capacity increased ($p < 0.05$) [30,40]. Bateman et al. [25] reported that functional capacity increased in aerobic, strengthening, and combined exercise training for eight months in MetS patients ($p < 0.05$). In this study, however, strengthening training did not make a significant change, while functional capacity increased even in the PMT group in our study ($p < 0.05$). Of note, there was an increase in the exercise capacity in all groups and this increase was higher in the NMES + PMT and IMT + PMT groups. However, there was no significant difference among the groups. In our patients with low cardiorespiratory functions, we achieved an increase in functional capacity through PMT and IMT, which we performed with high compliance and safety. We believe that this significant increase in all groups contributes to deep diaphragmatic breathing exercises combined with PMT. Similarly, it has been shown that the addition of breathing exercises to all applied exercises improves the functional capacity.

In the treatment of MetS and risk factors, glycemia, lipid profile, and analysis of inflammatory markers in blood biochemistry are important for clinical follow-up. In several studies, the effects of different exercise trainings (aerobic, strengthening and combined) with a duration of 3–12 months on blood biochemistry for changing MS and risk factors were investigated [20,23,26,28,30]. Balducci et al. [28] showed that exercise reduced $HbA_1c$, HDL cholesterol, and CRP in patients with MetS + type 2 diabetes ($p < 0.05$). Perez et al. [26] showed a significant decrease in total cholesterol and triglyceride and increase in HDL cholesterol with exercise training applied to patients with MetS and coronary heart disease ($p < 0.05$). In the study of Colombo et al. [20] which provided exercise training to patients with MetS, a significant decrease in CRP ($p < 0.05$) and increase in HDL cholesterol ($p < 0.05$) were observed. Casella-Filha et al. [23] found a significant decrease in the FBG and LDL cholesterol through exercise training in patients with MetS ($p < 0.05$). In contrast to these studies, Stensvold et al. [30] found no significant

change in the FBG, total and HDL cholesterol in patients with MetS ($p > 0.05$). In our study, a decline in the FBG, CRP, ESR, ASO, uric acid, and ALT was observed ($p < 0.05$). There was a significant improvement in ESR in the NMES + PMT group, compared to the other groups. Although total cholesterol, triglyceride, and LDL cholesterol tended to decrease, the difference was not significant ($p > 0.05$). Based on these findings, we believe that improved respiratory functions and increased exercise capacity had a positive impact on blood biochemistry, despite the relatively short study duration. This finding has a hypothesis-generating value and further large-scale, long-term studies would provide better improvements in blood biochemistry.

### 4.1. Limitation

The main limitation of this study is the lack of a placebo group in which exercise training is not applied. However, a placebo group is unable to be formed due to ethical issues.

### 4.2. Clinical relevance and future directions

The results of our study showed that CAD patients with MetS substantially benefited from exercise training targeting the peripheral and respiratory muscles, confirming our hypothesis. Based on these results, we can suggest that the CAD patients with MetS benefit from all methods of exercise training. To the best of our knowledge, this is the first study to demonstrate that the method of NMES in cardiac patients for respiratory muscle training can be used safely as an alternative treatment to IMT. In addition, this is the first clinical study involving PMT and different IMT in CAD patients with MetS. We believe that the complications which may be seen in the advanced stage of CAD with MetS can be prevented by respiratory muscle training in the early stages and our study would contribute to increase the awareness of the clinicians on this issue.

## 5. Conclusions

In conclusion, a six-week PMT and IMT methods improve respiratory functions, exercise capacity, and biochemistry markers in CAD patients with MetS. We can recommend different respiratory muscle training methods before traditional exercise training in complicated CAD with lower exercise capacity to tolerate exercise well. However, NMES for respiratory muscle training is a safe method and can be recommended also in patients with lower cardiovascular functions and exercise intolerance who cannot participate in traditional cardiopulmonary rehabilitation programs. More importantly, positive results can be achieved with PMT.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## CRediT authorship contribution statement

**Kıymet Muammer:** Conceptualization, Methodology, Resources, Investigation, Writing - original draft, Writing - review & editing. **Fatma Mutluay:** Supervision, Project administration, Writing - review & editing, Visualization. **Rengin Demir:** Investigation. **Alev Arat Özkan:** Resources, Writing - review & editing.

## Declaration of competing interest

The authors declare that they have no conflict of interests.

## Acknowledgements

We are thankful to our patients who participated in the study.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106119.

## References

[1] R.H. Eckel, S.M. Grundy, P.Z. Zimmet, The metabolic syndrome, Lancet 365 (9468) (2005) 1415–1428.
[2] S. Mottillo, K.B. Filion, J. Genest, L. Joseph, L. Pilote, P. Poirier, et al., The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis, J. Am. Coll. Cardiol. 56 (14) (2010) 1113–1132.
[3] S.M. Grundy, J.I. Cleeman, C.N.B. Merz, H.B. Brewer, L.T. Clark, D. B. Hunninghake, et al., Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines, Circulation 110 (2) (2004) 227–239.
[4] M. Sadeghi, A. Salehi-Abargouei, Z. Kasaei, H. Sajjadieh-Khajooie, R. Heidari, H. Roohafza, Effect of cardiac rehabilitation on metabolic syndrome and its components: a systematic review and meta-analysis, J. Res. Med. Sci.: Off. J. Isfahan. Univ. Med. Sci. 21 (2016).
[5] K. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K.A. Donato, et al., Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity, Circulation 120 (16) (2009) 1640–1645.
[6] P.D. Savage, et al., Prevalence of metabolic syndrome in cardiac rehabilitation/secondary prevention programs, Am. Heart J. 149 (4) (2005) 627–631.
[7] C. Sarti, J. Gallagher, The metabolic syndrome: prevalence, CHD risk, and treatment, J. Diabetes Complicat. 20 (2) (2006) 121–132.
[8] M.-K. Breyer, M.A. Spruit, C.K. Hanson, F.M. Franssen, L.E. Vanfleteren, M. T. Groenen, et al., Prevalence of metabolic syndrome in COPD patients and its consequences, PloS One 9 (6) (2014), e98013.
[9] E. Clini, E. Crisafulli, A. Radaeli, M. Malerba, COPD and the metabolic syndrome: an intriguing association, Internal and emergency medicine 8 (4) (2013) 283–289.
[10] P. Rogliani, G. Curradi, M. Mura, D. Lauro, M. Federici, A. Galli, et al., Metabolic syndrome and risk of pulmonary involvement, Respir. Med. 104 (1) (2010) 47–51.
[11] M.-S. Bae, J.-H. Han, J.-H. Kim, Y.-J. Kim, K.-J. Lee, K.-Y. Kwon, The relationship between metabolic syndrome and pulmonary function, Korean journal of family medicine 33 (2) (2012) 70–78.
[12] C.W. Baffi, L. Wood, D. Winnica, P.J. Strollo, M.T. Gladwin, L.G. Que, et al., Metabolic syndrome and the lung, Chest 149 (6) (2016) 1525–1534.
[13] B. Naveed, M.D. Weiden, S. Kwon, et al., Metabolic syndrome biomarkers predict lung function impairment: a nested case-control study, Am. J. Respir. Crit. Care Med. 185 (4) (2012) 392–399.
[14] H.Y. Park, S.Y. Lim, J.H. Hwang, et al., Lung function, coronary artery calcification, and metabolic syndrome in 4905 Korean males, Respir. Med. 104 (9) (2010) 1326–1335.
[15] F.C. Hsiao, C.Z. Wu, S.C. Su, et al., Baseline forced expiratory volume in the first second as an independent predictor of development of the metabolic syndrome, Metabolism 59 (6) (2010) 848–853.
[16] S. Scarlata, F.L. Fimognari, M. Cesari, R. Giua, A. Franco, P. Pasqualetti, et al., Lung function changes in older people with metabolic syndrome and diabetes, Geriatr. Gerontol. Int. 13 (4) (2013) 894–900.
[17] W.Y. Lin, C.A. Yao, H.C. Wang, K.C. Huang, Impaired lung function is associated with obesity and metabolic syndrome in adults, Obesity 14 (2006) 1654–1661.
[18] C.-C. Liu, et al., Sex differences in relationships between metabolic syndrome components and factors associated with health-related quality of life in middle-aged adults living in the community: a cross-sectional study in Taiwan, Health Qual. Life Outcome 16 (1) (2018) 76.
[19] C.-H. Chen, et al., Benefits of exercise training and the correlation between aerobic capacity and functional outcomes and quality of life in elderly patients with coronary artery disease, Kaohsiung J. Med. Sci. 30 (10) (2014) 521–530.
[20] C.M. Colombo, RMd Macedo, M.M. Fernandes-Silva, A.M. Caporal, A.E. Stinghen, C.R. Costantini, et al., Short-term effects of moderate intensity physical activity in patients with metabolic syndrome, Einstein (Sao Paulo). 11 (3) (2013) 324–330.
[21] N. Pattyn, V.A. Cornelissen, S.R.T. Eshghi, L. Vanhees, The effect of exercise on the cardiovascular risk factors constituting the metabolic syndrome, Sports Med. 43 (2) (2013) 121–133.
[22] I. Gutwenger, G. Hofer, A.K. Gutwenger, M. Sandri, C.J. Wiedermann, Pilot study on the effects of a 2-week hiking vacation at moderate versus low altitude on plasma parameters of carbohydrate and lipid metabolism in patients with metabolic syndrome, BMC Res. Notes 8 (1) (2015) 103.
[23] A. Casella Filho, A.C.P. Chagas, R.C. Maranhão, I.C. Trombetta, F.H. Cesena, V. M. Silva, et al., Effect of exercise training on plasma levels and functional properties of high-density lipoprotein cholesterol in the metabolic syndrome, Am. J. Cardiol. 107 (8) (2011) 1168–1172.

[24] M. Gayda, P.A. Ribeiro, M. Juneau, A. Nigam, Comparison of different forms of exercise training in patients with cardiac disease: where does high-intensity interval training fit? Can. J. Cardiol. 32 (4) (2016) 485–494.
[25] L.A. Bateman, C.A. Slentz, L.H. Willis, A.T. Shields, L.W. Piner, C.W. Bales, et al., Comparison of aerobic versus resistance exercise training effects on metabolic syndrome (from the studies of a targeted risk reduction intervention through defined exercise-STRRIDE-AT/RT), Am. J. Cardiol. 108 (6) (2011) 838–844.
[26] I.P. Pérez, M.Á. Zapata, C.E. Cervantes, R.M. Jarabo, C. Grande, R. Plaza, et al., Cardiac rehabilitation programs improve metabolic parameters in patients with the metabolic syndrome and coronary heart disease, J. Clin. Hypertens. 12 (5) (2010) 374–379.
[27] L.H.S. Tenório, A.C. Santos, J.B. Câmara Neto, F.J. Amaral, V.M.M. Passos, A.M. J. Lima, et al., The influence of inspiratory muscle training on diaphragmatic mobility, pulmonary function and maximum respiratory pressures in morbidly obese individuals: a pilot study, Disabil. Rehabil. 35 (22) (2013) 1915–1920.
[28] S. Balducci, S. Zanuso, A. Nicolucci, F. Fernando, S. Cavallo, P. Cardelli, et al., Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss, Nutr. Metabol. Cardiovasc. Dis. 20 (8) (2010) 608–617.
[29] M. Rubenfire, L. Mollo, S. Krishnan, S. Finkel, M. Weintraub, T. Gracik, et al., The metabolic fitness program: lifestyle modification for the metabolic syndrome using the resources of cardiac rehabilitation, J. Cardpulm. Rehabil. Prev. 31 (5) (2011) 282–289.
[30] D. Stensvold, A.E. Tjønna, E.-A. Skaug, S. Aspenes, T. Stølen, U. Wisløff, et al., Strength training versus aerobic interval training to modify risk factors of metabolic syndrome, J. Appl. Physiol. 108 (4) (2010) 804–810.
[31] M.A. Spruit, S.J. Singh, C. Garvey, et al., An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 188 (2013) e13–64.
[32] S.-J. Lin, J. McElfresh, B. Hall, R. Bloom, K. Farrell, Inspiratory muscle training in patients with heart failure: a systematic review, Cardiopulm. Phys. Ther. J. 23 (3) (2012) 29.
[33] L.F. Neves, M.H. Reis, R.D. Plentz, et al., Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review, Respir. Care 59 (2014) 1381–1388.
[34] M.Y. Liaw, Y.H. Wang, Y.C. Tsai, et al., Inspiratory muscle training in bronchiectasis patients: a prospective randomized controlled study, Clin. Rehabil. 25 (2011) 524–536.
[35] J. Wanger, J. Clausen, A. Coates, O. Pedersen, V. Brusasco, F. Burgos, et al., Standardisation of the measurement of lung volumes, Eur. Respir. J. 26 (3) (2005) 511–522.
[36] R. Pellegrino, G. Viegi, V. Brusasco, R. Crapo, F. Burgos, R. Casaburi, et al., Interpretative strategies for lung function tests, Eur. Respir. J. 26 (5) (2005) 948–968.
[37] L.F. Black, R.E. Hyatt, Maximal respiratory pressures: normal values and relationship to age and sex, Am. Rev. Respir. Dis. 99 (5) (1969) 696–702.
[38] T.S. Bakanlığı, A.H. Koordinatörü, M. Yenigün, M. Kendir, Treadmill Stress Test Laboratuarında Değerlendirilen Hastalarda Efor Test Sonuçlarının Test Öncesi Ve Sonrası Alınan hsCRP Ve NT-proBNP Düzeylerine Göre Değerlendirilmesi, SmyrnaTıp Dergisi, 2012.
[39] D.A. Mahler, C.K. Wells, Evaluation of clinical methods for rating dyspnea, Chest 93 (3) (1988) 580–586.
[40] F.M. Wise, J.M. Patrick, Resistance exercise in cardiac rehabilitation, Clin. Rehabil. 25 (12) (2011) 1059–1065.
[41] G. Areas, A. Borghi-Silva, A.N. Lobato, A.A. Silva, R.C. Freire Jr., F.Z. Areas, Effect of upper extremity proprioceptive neuromuscular facilitation combined with elastic resistance bands on respiratory muscle strength: a randomized controlled trial, Braz. J. Phys. Ther. 17 (6) (2013) 541–546.
[42] J. Stoller, G. Snider, M. Brantly, R. Fallat, R. Stockley, G. Turino, et al., American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency, Pneumologie 59 (1) (2005) 36.