



## **Modified Arm Swing Exercise Improves Oxidative Stress and Heart Rate Variability in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial**

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### **ABSTRACT**

**Tunkamnerdthai O, Auvichayapat P, Punjaruk W, Manimmanakorn A, Leelayuwat N, Boonsawat W, Patjanasoonorn B.** Modified Arm Swing Exercise Improves Oxidative Stress and Heart Rate Variability in Patients with Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. **JEPonline** 2018;21(4):41-53. The purpose of this study was to evaluate the effects of modified arm swing exercise (MASE) training on oxidative stress, dynamic lung volumes, and heart rate variability (HRV) in patients with chronic obstructive pulmonary disease (COPD). Fifty-six stable COPD patients were each randomly allocated to either the Training Group (TG) (n = 28) or the Control Group (CG) (n = 28). Participants in the TG performed MASE for 30 min·d<sup>-1</sup>, 6 d·wk<sup>-1</sup> for 12 wks; whereas, the subjects in the CG had no exercise intervention. Outcome variables of oxidative stress, dynamic lung volumes, and HRV were assessed before and after the study period. None of the parameters differed significantly between the two groups at baseline and there was

no statistical change in the CG. After undergoing training, the TG showed significant improvement in superoxide dismutase, malondialdehyde, square root of the mean squared differences of successive normal-to-normal intervals, and high frequency (HF) ( $P < 0.05$ ). In addition, all variables that had changed in the TG also differed significantly from those in the CG ( $P < 0.05$ ), except for HF. However, forced expiratory volume in the first second ( $FEV_1$ ), forced vital capacity (FVC), and  $FEV_1/FVC$  ratio did not change significantly after the intervention nor did they differ significantly between the two groups. These results demonstrate that the MASE training improves oxidative stress and HRV in patients with COPD.

**Key Words:** Antioxidant, Cardiac Autonomic Activity, Low-Intensity Exercise Training, Oxidant

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities (16). It is currently the fourth leading cause of mortality worldwide, and it is expected to rise to the third leading cause of mortality by 2020 (16,24). Oxidative stress resulting from cigarette smoking plays an important role in the pathogenesis of COPD (25). An imbalance between oxidants and antioxidants caused by increased malondialdehyde (MDA) and reduced superoxide dismutase (SOD) and glutathione peroxidase (GPx) has been found in patients with COPD (1). Increased oxidative stress contributes to airway, lung parenchyma, and pulmonary vasculature inflammation leading to impaired lung function (23). Inflammatory mediators in the lungs also spread into the circulatory system and cause systemic inflammation (3). Additionally, increased oxidative stress may contribute to autonomic nervous system dysfunction, which is characterized by sympathetic dominance (11). Previous studies have indicated that COPD patients exhibited a decrease in heart rate variability (HRV), a marker of autonomic system dysfunction (4,36).

Pursed-lip breathing has been used to alleviate and control dyspnea that is one of the most common symptoms in COPD patients. This type of breathing helps to prevent airway narrowing during expiration (12). Furthermore, pursed-lip breathing helps to improve ventilation (37), exercise capacity (5), exercise tolerance, breathing pattern, and arterial oxygenation at submaximal intensity exercise (8). It also improves autonomic cardiac modulation that is reflected by an increase in HRV in patients with COPD (32).

Exercise training is a well-recognized method for improving exercise capacity, dyspnea, and functional capacity in individuals with COPD (17). Previous studies have demonstrated that low-intensity aerobic exercise training could increase lung function, exercise capacity, and quality of life in these patients (10,38). Endurance exercise training combined with strength exercise training at low-intensity improves exercise endurance in COPD patients (13). Furthermore, arm endurance and strength training at low-intensity reduces exertional dyspnea in these patients (26). However, there are no studies that report about the effects of low-intensity aerobic exercise on oxidative stress and HRV in patients with COPD.

Arm swing exercise (ASE) that is low-intensity aerobic exercise is an interesting exercise modality for people as it is easy to perform regularly without the use of any equipment and minimizes the risk of injury to bone and muscle. Previous studies have shown that ASE improved glycemic control (21), oxidative stress (21,28), and lung function (35). However, one study found that ASE did not improve autonomic nervous system function in sedentary young adults (30). Therefore, we created the modified arm swing exercise (MASE) to increase the effort required. The modifications include clenching both hands, kneeling during arm swinging, and stretching the knees until both arms were straightened overhead in combination with pursed-lip breathing. In addition, none of the previous studies have focused on the beneficial effects of this exercise in patients with COPD. Thus, this is the first study to investigate the effects of MASE on oxidative stress, dynamic lung volumes, and HRV in these patients. We hypothesized that the MASE training could improve oxidative stress, lung function, and cardiac autonomic activity in COPD patients.

## **METHODS**

### **Subjects**

The patients were all diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines (16). They were recruited from Khon Kaen province in Thailand. The inclusion criteria were the following: age 45 to 75 yrs, post-bronchodilator of a ratio of forced expiratory volume in the first second to forced vital capacity ( $FEV_1/FVC$ ) <70%, post-bronchodilator of  $FEV_1$   $\geq$ 30% of predicted value, clinical stability, and not engaging in regular exercise (<3 times $\cdot$ wk $^{-1}$  and <30 min $\cdot$ d $^{-1}$ ). The exclusion criteria included acute exacerbation within two months before starting the study, congestive heart failure, angina pectoris, third degree A-V block, and presence of orthopedic or neuromuscular conditions interfering with the ability to perform the MASE. Written informed consent forms were obtained from all subjects. This study was approved by the Khon Kaen University Ethics Committee for Human Research in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines (HE571478).

### **Study Design**

This study was a randomized controlled trial (RCT) with single-blinded assessment. It was performed in a research laboratory room at Khon Kaen University's Faculty of Medicine.

### **Power Calculation**

The sample size was calculated based on the change in square root of the mean squared differences of successive normal-to-normal intervals (rMSSD) after exercise training in patients with COPD (9). It was determined to require a power of 80% and a significance level of 5%. Accordingly, the sample size of 28 subjects per group (including 10% drop out) was indicated.

### **Experimental Design and Protocol**

All subjects received the screening tests before participating in this study, which included an assessment of their medical history, anthropometric assessment, electrocardiography, physiological measurement (respiratory rate, heart rate, and blood pressure), pulmonary function test, and physical examination. After passing the screening tests, all subjects were randomly allocated into either the Control Group (CG) or the Training Group (TG) with matching the stage of their disease. The subjects in the TG were instructed to carry out the

MASE  $30 \text{ min} \cdot \text{d}^{-1}$ ,  $6 \text{ d} \cdot \text{wk}^{-1}$  for 12 wks. Subjects in the CG were asked to continue with their usual physical activities during the study period. A researcher supervised the MASE in the TG according to the intervention protocol. The MASE was performed by clenching both hands, kneeling about  $15^\circ$  during arm swinging, and stretching the knees until both arms were straightened overhead. Subjects performed pursed-lip breathing while swinging both arms forward until they reached head level and then lowering them down. Each subject was given a guide to perform the MASE. Performance of the MASE was checked for accuracy at the 2nd wk and follow-ups were conducted by telephone on a weekly basis. Oxidative stress, dynamic lung volumes, and HRV were measured in both groups before and after the 12-wk study period.

## **Outcome Measurements**

### ***Oxidative Stress***

Blood (3 mL) was drawn from the median cubital vein and contained in EDTA tube. It was then centrifuged at  $3,000 \text{ rev} \cdot \text{min}^{-1}$  at  $4^\circ\text{C}$  for 10 min in order to separate fresh plasma. The upper plasma layer (1.5 mL) was transferred to a new tube and was then stored at  $-80^\circ\text{C}$  until analysis for the MDA and the SOD. Plasma MDA levels were measured indirectly from concentrations of thiobarbituric acid reactive substances by using Draper's method (14). Plasma SOD levels were measured following the manufacturer's instructions (SOD Assay Kit; Cayman Chemical, Ann Arbor, MI, USA).

### ***Dynamic Lung Volumes***

The subjects'  $\text{FEV}_1$ , FVC, and  $\text{FEV}_1/\text{FVC}$  were measured using a Vyntus<sup>®</sup> spirometer (CareFusion, UK). The pulmonary function test was carried out according to the criteria of the American Thoracic Society/European Respiratory Society (2). Measurement of dynamic lung volumes was performed at least three times to get the three highest close values, which did not differ more than 5%. The best value of dynamic lung volumes was chosen.

### ***Heart Rate Variability***

HRV was measured in a quiet room with air temperature and humidity that ranged from  $25$  to  $27^\circ\text{C}$  and 48 to 65%, respectively. All subjects were instructed to avoid stimulant drinks such as tea or coffee and to stop using bronchodilators at least 12 hrs prior to the autonomic evaluation. They were also requested to breathe regularly and as smoothly as possible after resting for 30 min. The electrocardiographic recording was conducted for 5 min with the subject in the sitting position using electrocardiogram electrodes. The results were then analyzed using a PowerLab<sup>®</sup> (ADInstruments). Analysis of HRV in the time domain consisted of standard deviation of all normal-to-normal intervals (SDNN) and rMSSD. Analysis of HRV in the frequency domain consisted of total power (TP), very low frequency (VLF), low frequency (LF), high frequency (HF), and LF/HF ratio.

## **Statistical Analyses**

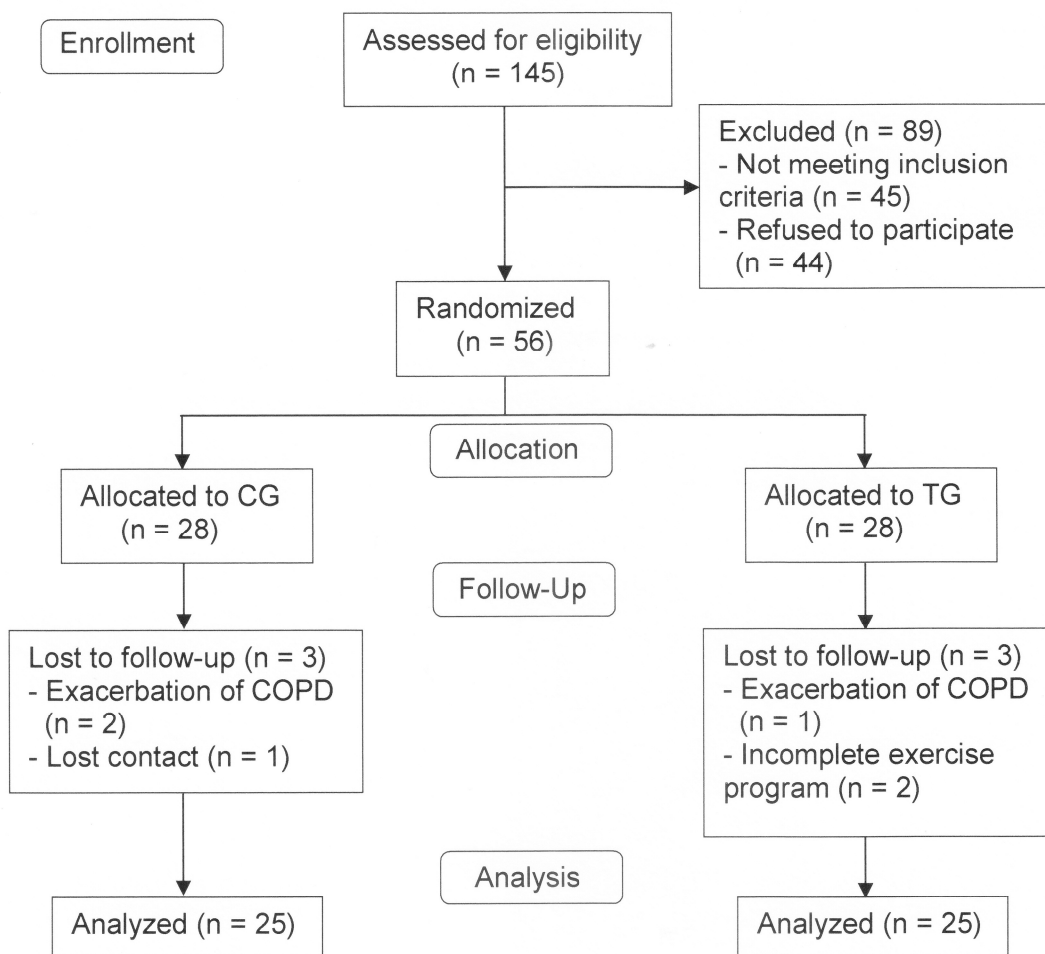
The data were analyzed using the SPSS software package version 19.0. The results were expressed as mean  $\pm$  standard deviation (SD). The normal distribution of all data was analyzed using the Kolmogorov-Smirnov test. The dependent samples *t*-test was used to compare differences in variables with paired samples. The independent samples *t*-test was used to evaluate inter-group changes in parameters at baseline. The analysis of covariance

(ANCOVA) was used to detect differences in parameters between the two groups after the study period. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Subject Characteristics

A total of 56 patients with mild to severe COPD were recruited for this study. They were randomized into either the CG or the TG. Six of them dropped out during the study period due to exacerbation of COPD, failure to complete the exercise program, or loss of contact. Therefore, 50 male subjects aged between 48 and 75 yrs completed the study (Figure 1). At baseline, there were no significant differences between the two groups in anthropometry, physiological characteristic, and lung function (Table 1).



**Figure 1. Flowchart of Study Protocol.** CG = Control Group; TG = Training Group; COPD = Chronic Obstructive Pulmonary Disease.

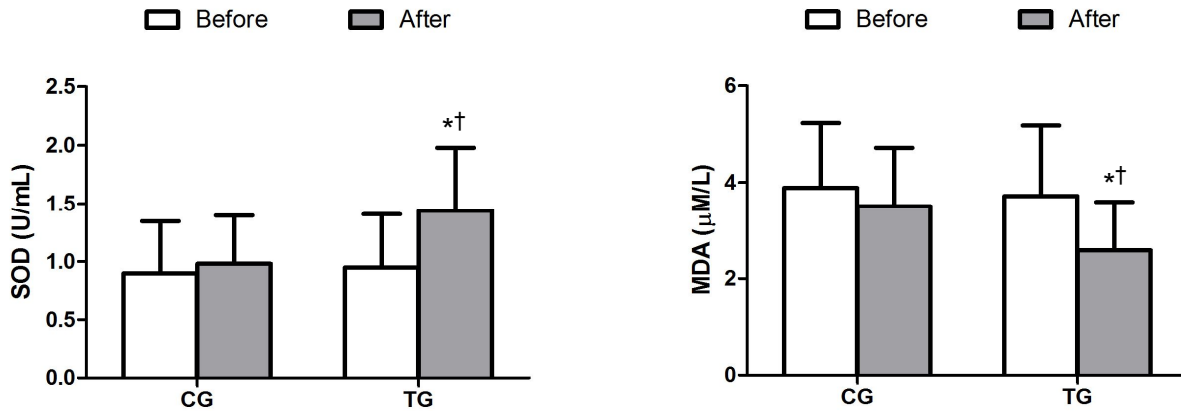
**Table 1. Baseline Characteristics of Subjects.**

<b>Parameters</b>	<b>CG (n = 28)</b>	<b>TG (n = 28)</b>	<b>P value</b>
<b>Age</b> (yrs)	65.47 ± 6.27	64.49 ± 6.69	0.535
<b>Weight</b> (kg)	56.88 ± 10.62	61.15 ± 9.87	0.403
<b>Height</b> (cm)	160.82 ± 6.04	161.52 ± 7.09	0.830
<b>BMI</b> (kg·m <sup>-2</sup> )	22.03 ± 4.10	23.49 ± 3.84	0.503
<b>RR</b> (breaths·min <sup>-1</sup> )	17.84 ± 2.64	18.00 ± 2.16	0.627
<b>PR</b> (beats·min <sup>-1</sup> )	76.88 ± 10.63	78.92 ± 10.79	0.646
<b>SBP</b> (mmHg)	126.28 ± 15.05	128.72 ± 12.64	0.297
<b>DBP</b> (mmHg)	74.76 ± 8.37	76.52 ± 6.60	0.495
<b>MAP</b> (mmHg)	91.93 ± 9.41	93.92 ± 8.13	0.350
<b>FEV<sub>1</sub></b> (L)	1.63 ± 0.54	1.68 ± 0.35	0.218
<b>FEV<sub>1</sub></b> (%predicted)	64.96 ± 20.26	65.76 ± 15.05	0.831
<b>FVC</b> (L)	3.01 ± 0.73	3.21 ± 0.45	0.097
<b>FVC</b> (%predicted)	84.36 ± 15.08	86.28 ± 12.66	0.088
<b>FEV<sub>1</sub>/FVC</b> (%)	53.86 ± 9.82	52.42 ± 9.42	0.580

Data are expressed as mean ± SD. **CG** = Control Group; **TG** = Training Group; **BMI** = Body Mass Index; **RR** = Respiratory Rate; **PR** = Pulse Rate; **SBP** = Systolic Blood Pressure; **DBP** = Diastolic Blood Pressure; **MAP** = Mean Arterial Pressure; **FEV<sub>1</sub>** = Forced Expiratory Volume in the First Second; **FVC** = Forced Vital Capacity.

### **Oxidative Stress**

The results of oxidative stress evaluations are presented in Figure 2. Before the study, levels of SOD and MDA did not differ significantly between the two groups. Following 12 wks of the MASE training, the SOD levels were significantly increased by  $0.49 \pm 0.45$  U/mL ( $0.95 \pm 0.46$  vs.  $1.44 \pm 0.54$  U/mL;  $P < 0.01$ ) and the MDA levels were significantly reduced by  $1.12 \pm 1.18$   $\mu$ M/L ( $3.72 \pm 1.46$  vs.  $2.59 \pm 1.01$   $\mu$ M/L;  $P < 0.01$ ). In addition, significant differences in SOD and MDA levels between the two groups were observed after the study period ( $P < 0.01$ ). However, no statistically significant changes in SOD and MDA levels were observed between before and after the study period in the CG [SOD:  $0.90 \pm 0.45$  vs.  $0.98 \pm 0.42$  U/mL ( $P = 0.476$ ); MDA:  $3.89 \pm 1.34$  vs.  $3.51 \pm 1.21$   $\mu$ M/L ( $P = 0.181$ )].



**Figure 2. Effect of MASE Training on Oxidative Stress in COPD Subjects.**

Data are expressed as mean  $\pm$  SD. N = 25 in each group. **CG** = Control Group; **TG** = Training Group; **SOD** = Superoxide Dismutase; **MDA** = Malondialdehyde. \*Significant differences between before and after the study period ( $P < 0.01$ ), †Significant differences after the study period between the two groups ( $P < 0.01$ ).

### Dynamic Lung Volumes

All data of dynamic lung volumes are shown in Table 2. Baseline variables of dynamic lung volumes did not differ significantly between the two groups. The subjects did not show changes in FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC, regardless of whether or not they underwent the training intervention.

**Table 2. Effect of MASE Training on Dynamic Lung Volumes in COPD Subjects.**

Parameters	CG (n = 25)		TG (n = 25)	
	Before	After	Before	After
<b>FEV<sub>1</sub></b> (L)	1.64 $\pm$ 0.59	1.70 $\pm$ 0.59	1.70 $\pm$ 0.37	1.79 $\pm$ 0.43
<b>FEV<sub>1</sub></b> (% predicted)	65.08 $\pm$ 23.35	68.04 $\pm$ 22.89	65.88 $\pm$ 12.98	68.68 $\pm$ 16.33
<b>FVC</b> (L)	2.98 $\pm$ 0.68	3.00 $\pm$ 0.68	3.27 $\pm$ 0.53	3.28 $\pm$ 0.47
<b>FVC</b> (% predicted)	84.24 $\pm$ 14.32	84.48 $\pm$ 14.67	87.48 $\pm$ 13.92	87.84 $\pm$ 11.21
<b>FEV<sub>1</sub>/FVC</b> (%)	54.46 $\pm$ 12.18	55.73 $\pm$ 11.42	52.85 $\pm$ 12.67	54.76 $\pm$ 11.59

Data are expressed as mean  $\pm$  SD. **FEV<sub>1</sub>** = Forced Expiratory Volume in the First Second; **FVC** = Forced Vital Capacity.

### Heart Rate Variability

The subjects' HRV values before and after the study period are presented in Table 3. Variables of HRV at baseline did not differ significantly between the two groups. There was a significant improvement in rMSSD after the intervention in the TG ( $P < 0.01$ ). In addition, rMSSD in the TG was significantly higher than that in the CG after the study period ( $P < 0.05$ ).

However, there was no significant difference in rMSSD between before and after the study period in the CG.

Moreover, there was a significant increase in HF after the intervention in the TG ( $P < 0.05$ ) but no significant difference between the two groups after the study period. In contrast, there was no significant difference in HF between before and after the study period in the CG. In addition, there were no significant differences in SDNN, TP, VLF, LF, and LF/HF between before and after the study period in either group.

**Table 3. Effect of MASE Training on HRV in Time and Frequency Domains in COPD Subjects.**

Parameters	CG (n = 25)		TG (n = 25)	
	Before	After	Before	After
<b>SDNN</b> (ms)	45.00 ± 24.09	44.14 ± 24.31	41.53 ± 23.32	39.91 ± 19.95
<b>rMSSD</b> (ms)	42.91 ± 15.13	43.42 ± 14.79	38.87 ± 12.51	53.99 ± 18.86**†
<b>TP</b> (ms <sup>2</sup> )	1033.01 ± 533.39	875.98 ± 584.42	1024.94 ± 425.39	838.00 ± 497.72
<b>VLF</b> (ms <sup>2</sup> )	279.54 ± 173.77	321.20 ± 193.03	311.38 ± 170.58	324.10 ± 217.39
<b>LF</b> (nu)	30.22 ± 11.51	31.21 ± 13.07	32.23 ± 15.60	31.17 ± 16.36
<b>HF</b> (nu)	41.08 ± 9.87	41.15 ± 13.07	40.93 ± 11.61	45.72 ± 16.57*
<b>LF/HF</b>	0.77 ± 0.57	0.80 ± 0.41	0.90 ± 0.67	0.82 ± 0.72

Data are expressed as mean ± SD. **CG** = Control Group; **TG** = Training Group; **SDNN** = Standard Deviation of all Normal-to-Normal Intervals; **rMSSD** = Square Root of the Mean Squared Differences of Successive Normal-to-Normal Intervals; **TP** = Total Power; **VLF** = Very Low Frequency; **LF** = Low Frequency; **HF** = High Frequency. \*Significant difference between before and after the study period ( $P < 0.05$ ), \*\*Significant difference between before and after the study period ( $P < 0.01$ ), †Significant difference after the study period between the two groups ( $P < 0.05$ ).

## DISCUSSION

To our knowledge, this is the first study to examine the effects of MASE on oxidative stress, dynamic lung volumes, and HRV in patients with COPD. The findings of this study partly supported our hypothesis as the subjects who engaged in the MASE training showed an improvement in oxidative stress and cardiac autonomic activity. However, the exercise program did not have any beneficial effects on the subjects' dynamic lung volumes.

Exercise training at low-intensity has been reported to have beneficial outcomes in patients with COPD that include improved dyspnea, exercise capacity, and exercise endurance (13,26). However, there has yet been no study to demonstrate the effect of low-intensity



aerobic exercise on oxidative stress in COPD patients. Several previous studies have shown an improvement in oxidative stress after 8 wks of low-intensity aerobic exercise training in terms of increased non-enzymatic antioxidant GSH levels and decreased levels of MDA and 8-IsoPGF $2\alpha$ , which are biomarker lipid peroxidation of oxidative stress. However, the subjects in those studies were patients with type 2 diabetes (21), older subjects with mild cognitive impairment (28), and sedentary people (20). Only one previous study in an animal model has shown the potential effect of aerobic exercise training at low-intensity on improved oxidative stress in terms of an up-regulation of antioxidant enzyme activities (SOD, catalase, and GPx) and reduced MDA (19). Therefore, the present study is the first to investigate the effect of the MASE training on oxidative stress in patients with COPD. This specific exercise program had a role in the alleviation of oxidative stress status. The improvement in antioxidant enzyme activity after regular exercise may be due to the transcription/translation process as exercise-induced reactive oxygen species (ROS) production stimulates the adaptive response to excessive ROS through redox signaling (15,31). Accordingly, activating antioxidant enzyme after exercise training maximizes the free radical scavenging system (18), which might lead to reduced lipid peroxidation.

The results of this study did not show any changes in dynamic lung volumes after the MASE training. These findings are inconsistent with those of previous studies (10,27,38). Chan et al. (10) found that two 60-min sessions of Tai chi Qigong per week for 3 months improved dynamic lung volumes in terms of increased FEV $_1$  and FVC in patients with COPD. Similarly, engaging in aerobic exercise training at low-intensity for 6 months has been shown to increase FEV $_1$  and FEV $_1$ /FVC in individuals with COPD (27,38). The discrepancies may be attributable to the differences in training protocol and duration of the exercise training.

According to the HRV data, there was only a significant improvement in rMSSD following the MASE training in patients with COPD. Interestingly, three previous RCT studies have shown a beneficial effect only on the time domain analyses of HRV (rMSSD and SDNN) in COPD patients, but these studies used high-intensity aerobic exercise training (6,7,9). Only one previous study by Logan et al. (22) found an improvement in cardiac autonomic function after low-intensity exercise training in pregnant women. Thus, this is the first study to show an increase in HRV after low-intensity aerobic exercise training combined with pursed-lip breathing in individuals with COPD. A potential explanation for the autonomic improvement is increased parasympathetic nervous system function. This is supported by a previous study, which showed an enhancement in vagus nerve activity after low-intensity exercise training (33).

Moreover, lung hyperinflation and respiratory pattern are associated with unbalanced sympathetic and parasympathetic nerve activity (29). Therefore, exercise training combined with pursed-lip breathing may lead to reduction in dynamic hyperinflation that less stimulated pulmonary stretch receptors result in an improvement in autonomic function in COPD patients. This explanation is supported by previous studies that pursed-lip breathing reduced dynamic hyperinflation (8) leading to improved cardiac autonomic activity by increasing in rMSSD and LF in patients with COPD (32,34).

## Limitations in this Study

Although this study demonstrated the benefits of MASE training, there were some limitations. First, all participants in this study suffered from mild to severe COPD. The results of this study cannot be extrapolated to cases in which COPD is very severe. Second, the subjects in this study were all male patients, and the results may differ in female patients. Lastly, factors, such as diet, which are associated with improved antioxidant in patients with COPD were not assessed.

## CONCLUSIONS

Based on the results from the present study, it can be concluded that the MASE training, which consists of a series of arm movements combined with pursed-lip breathing is effective for improving oxidative stress in patients with stable COPD. This improvement was demonstrated by an increase in SOD and a decrease in MDA. In addition, this specific exercise program can lead to improvement in cardiac autonomic function as demonstrated by the increase in rMSSD. However, the MASE training did not increase dynamic lung volumes in these patients.

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