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Short Communication

Low-intensity aerobic cycle ergometer effects on lung function of myasthenia gravis patients: A randomized controlled trial

Nabila Amalina[1*], Dewi Poerwandari[1], Noor I. Handajani[1], Devi A. Sudibyo[2] and Soenarnatalina Melaniani[3]

[1]Department of Physical Medicine and Rehabilitation, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; [2]Department of Neurology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia; [3]Department of Epidemiology, Biostatistics, Population Studies and Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, Indonesia

*Corresponding author: nastitisoemarno@gmail.com

Abstract

Patients with generalized myasthenia gravis (MG) often show restrictive spirometry results. Although regular exercise and physical fitness are linked to better respiratory function, there is limited research assessing the effects of aerobic exercise on lung function in MG patients. The aim of this study was to analyze the effect of low-intensity aerobic exercise using a cycle ergometer on lung function parameters in MG patients. A randomized controlled trial with pre- and post-test was conducted at the Medical Rehabilitation Outpatient Clinic of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, in 2023. MG patients classified as I–IIb based on the Myasthenia Gravis Foundation of America (MGFA) classification were recruited and randomly divided into treatment and control groups. The treatment group was given low-intensity aerobic exercise using a cycle ergometer, education on lifestyle changes, and breathing exercises (deep and pursed lip breathing). Lung function parameters, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and forced expiratory volume ratio (FEVR), were then measured. Measurements were conducted before and after eight weeks of low-intensity aerobic cycle ergometer exercise and compared with those of a control group. A total of 17 MG patients were included in this study. The results showed a significant increase in FVC in the treatment group (p=0.003), whereas no significant change in the control group (p=0.068). A significant increase in FEV_1 was observed both in the treatment (p=0.029) and the control group (p=0.016). There was no improvement in FEVR in either group. After the intervention, significant differences were observed in FVC (p=0.009) and FEV_1 (p=0.029) between the treatment and control groups. There was no significant difference in FEVR values after the intervention between both groups (p=0.491). In conclusion, eight weeks of low-intensity aerobic cycle ergometer exercise led to significant improvements in FVC and FEV_1 among MG patients.

Keywords: Myasthenia gravis, pulmonary rehabilitation, aerobic exercise, cycle ergometer, lung function

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Introduction

Myasthenia gravis (MG) is an autoimmune disease targeting the post-synaptic membrane at the neuromuscular junction. Its primary manifestation is muscle weakness that worsens with repetitive muscle activity [1]. The symptoms fluctuate, with patients typically feeling at their best in the morning and gradually declining throughout the day [2]. Over the past seven decades, the

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prevalence rate of MG worldwide has increased significantly [3]. This rise occurred alongside to greater awareness of the disease, as well as advancements in diagnostic and therapeutic methods, which have improved the life expectancy of MG patients [3]. Currently, the prevalence of MG stands at 77.7 cases per one million people [4]. In Asian countries, the incidence of MG is 4.7 cases per million people per year [4]. However, there is no available epidemiological data on MG in Indonesia [4,5]. The incidence of MG in women has a bimodal distribution, peaking at ages 30 and 50 [3]. In contrast, the incidence in men increases with age, with the highest peak occurring between 60 and 89 years old [6,7].

Symptoms of muscle weakness and fatigue experienced by MG patients can vary for each individual, ranging from mild to severe. The Osserman and Genkins classification system divides MG into five classes based on how quickly symptoms develop, the extent of the patient's condition, and which muscle groups experience weakness [8]. Approximately 70% of MG patients fall into classes of IIa and IIb, which are collectively referred to as generalized MG [9]. In this early stage of the disease, respiratory muscle involvement is identified in only 1–4% of patients; however, in advanced stages, respiratory problems can occur in 60–80% of MG patients [10].

Manifestations of MG in the respiratory system are generally caused by weakness in the diaphragm muscle and other accessory respiratory muscles [9]. Patients with generalized MG often show restrictive patterns (forced vital capacity (FVC)<80%) on spirometry examination, showing a myasthenic pattern with a decrease in respiratory volume during maximum voluntary ventilation (MVV) [11]. A study demonstrated obstructive outcomes in the respiratory system of MG patients, with lower forced expiratory volume ratio (FEVR) compared to controls, even among patients managed with medication [12]. This was thought to be caused by the side effects of pyridostigmine [12]. Muscle weakness, exercise intolerance, and fatigue lead to reduced physical activity and a sedentary lifestyle in MG patients, which further exacerbates exercise intolerance and decreases functional capacity, and ultimately resulting in a lower quality of life [13-15].

Over the past five years, extensive studies have been conducted on exercise therapy for individuals with MG, demonstrating that aerobic exercise therapy is quite safe for stable MG patients [16-19]. Our study in 2023 showed that eight weeks of mild-intensity aerobic exercise using a cycle ergometer enhanced functional and aerobic capacity, as well as reduced depression and disease severity in adult patients with MG [16,17]. Another study in 2022 that compared the effects of resistance and breathing exercises, with and without aerobic exercise in the form of partial body weight-supported treadmill training (PBWSTT) on MG juveniles aged between 13–16 years, reported an increase in FVC and forced expiratory volume in 1 second (FEV_1) in both groups post-intervention, with a greater increase in the group that received PBWSTT [18]. However, a 2021 study that provided a home-based aerobic exercise in the form of a rowing ergometer to MG patients for 12 weeks showed no significant increase in FVC at evaluations of three, six, and nine months post-intervention [19]. These indicate that there are limited studies assessing the impact of aerobic exercise on lung function parameters in MG patients, with conflicting results. The aim of this study was to determine whether light-intensity aerobic exercise using a cycle ergometer could improve FVC, FEV_1, and FEVR in MG patients by conducting a randomized controlled trial.

Methods

Study design, setting and sampling

A randomized controlled trial with pre- and post-test was conducted at the Medical Rehabilitation Outpatient Clinic of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, in 2023. The sample size was determined using the two-sample Z-test sample size formula from a previous study [18] with an additional 20% dropout rate, resulting in a total of 20 patients, with 10 patients in each treatment group and control group. A random sampling technique was employed in this study.

Patients

This study included patients who met the following criteria: confirmed MG patients classified as

I–IIb based on the Myasthenia Gravis Foundation of America (MGFA) classification, aged 18–59 years, had normal cognitive function as evidenced by a Montreal Cognitive Assessment Indonesia Version (MoCA-INA) with a score of ≥26, receiving treatment for MG at Dr. Soetomo General Academic Hospital, and were able of engaging in 30 minutes of low-intensity aerobic exercise using a cycle ergometer. Patients with myasthenic crisis (MG complication characterized by worsened muscle weakness leading to respiratory failure that requires intubation and mechanical ventilation); currently engaging in a routine aerobic workout program 2–3 times per week within the past month.

Having a history of cardiorespiratory disease (such as ischemic heart disease, a resting heart rate of ≥120, stage II hypertension according to the Joint National Committee (JNC) VII criteria with systolic blood pressure >160 mmHg, arrhythmia, heart failure class II–IV according to the New York Heart Association (NYHA) criteria, uncontrolled restrictive or obstructive airway disease), a history of systemic disease such as kidney failure, liver disease such as liver cirrhosis, and uncontrolled diabetes mellitus with random blood sugar levels <80 or >250 mg/dL were excluded. In addition, those who have contraindications to spirometry (such as stroke or heart attack in the last three months, intracranial space-occupying lesion (SOL), cerebral aneurysm, retinal detachment, history of surgery (eye, brain, chest, and stomach) in the last three months, hemoptysis in the last month, pneumothorax, hernia (including scrotal, inguinal, umbilical, or hernia of the nucleus pulposus, and suspected or confirmed infectious disease like tuberculosis, influenza, and pneumonia), being pregnant, having a body mass index (BMI) of ≥30 (obese grade II), and experiencing pain in the lower extremities with a Wong-Baker Faces Scale (WBFS) >4 were also excluded from the study.

Patients were withdrawn from the study if they were unwilling to continue for any reason, failed to complete the exercise for two consecutive sessions, or were absent from training more than two sessions in a row or over 20% of total attendance (with a maximum of three absences allowed). Withdrawal also occurred if patients became sick, died, or developed cardiovascular, pulmonary, or musculoskeletal disorders during the study that prevented continued participation.

Intervention

The treatment group was given low-intensity aerobic exercise using a cycle ergometer (BTL stress test, Massachusetts, USA), education on lifestyle changes, and breathing exercises (deep and pursed lip breathing). During the initial session, patients were familiarized with the training protocol. The intervention consisted of three sessions every week for eight weeks, each lasting 30 minutes, including a 5-minute warm-up, a 20-minute core exercise period, and a 5-minute cooldown. In contrast, the control group did not receive aerobic exercise but still received education on lifestyle changes and breathing exercises.

The intensity of the aerobic exercise was measured using target heart rate (heart rate rest + 30% heart rate reserve) and aimed for a level of 11–12 on the Borg's rating of perceived exertion (RPE) scale. Both groups were instructed to continue their regular follow-up at the Medical Rehabilitation Outpatient Clinic of Dr. Soetomo General Academic Hospital for having the standard treatment as prescribed by a neurologist, including lifestyle modifications, physical activity, and breathing exercises (deep breathing and pursed lip breathing). Patients were also advised not to participate in other exercises, with compliance monitored through daily activity diaries.

Data collection

Characteristics data, such as age at onset, duration of treatment, dose of pyridostigmine, history of thymectomy, and comorbidity, were collected. BMI was determined by measuring body weight and height, and then categorized according to the Asia-Pacific classification. The type of MG was classified based on the patient's signs and symptoms. MG severity was assessed using the Myasthenia Gravis Composite (MGC) scale. Physical activity level was measured with the International Physical Activity Questionnaire (IPAQ), and patients were considered to have moderate physical activity if they engaged in at least 600 metabolic equivalent of task (MET) minutes of total activity per week. All of the mentioned information was collected after the

patients gave consent to participate in the study or at least one day before the initial intervention session.

Lung function parameters, including FVC and FEV_1, were assessed using a digital spirometer (CONTEC SP10, Contec Medical, China). Patients performed a forced expiratory maneuver while standing, exhaling as forcefully as possible after taking a deep breath [20]. The FVC and FEV_1 were measured as a percentage of the predicted value, which is based on the patient's age, gender, race/ethnicity, height, and weight. The FEVR was calculated using the FEV_1/FVC formula and expressed as a percentage [20]. Patients were categorized as restrictive respiratory patterns if their FVC was <80% of the predicted value, with normal or decreased FEV_1. An obstructive respiratory pattern was identified if the FEVR was <70% and FEV_1<80% of the predicted value. Patients were classified as having a mixed respiratory pattern if both FVC and FEV_1 were <80% of the predicted value and FEVR <70%.

The lung function parameters were measured twice in both groups. For the treatment group, measurements were taken one day before starting the initial session and one day after the last session of the intervention. For the control group, measurements were taken once after they gave consent to participate in the study and again eight weeks after. The scores of the lung function parameters (FVC, FEV_1, and FEVR) were compared between pre and post within each group and between the two groups after eight weeks.

Statistical analysis

All data analysis was performed using SPSS version 26 (SPSS Inc., Chicago, USA). A paired Student t-test was used to compare the lung function parameters (FVC, FEV_1, and FEVR) scores within each group pre- and post-intervention. An independent Student t-test test was used to compare the lung function parameters (FVC, FEV_1, and FEVR) scores between the two groups after intervention. A p-value of <0.05 was considered significant.

Results

Characteristics of the patients

A total of 20 MG patients were initially enrolled in the clinical trial and the detailed flow diagram of the patient's participation is presented in **Figure 1**. These patients were randomly divided into 2 groups consisting of 10 each, forming the treatment and control groups. One patient in the treatment group withdrew at the end of week 4 due to personal reasons. Additionally, two patients in the control group withdrew because they were unable to complete the post-test due to work commitments and travel distance. Throughout the 8-week, the treatment group received a total of 24 training sessions. Among the treatment group, 8 out of 9 patients (88.8%) completed all training sessions within the 8-week timeframe, with one patient finishing in 9 weeks. Importantly, all patients tolerated the exercise intervention well, with no exacerbations or adverse events reported during the study.

A total of 17 MG patients (12 females) were included in the study, as presented in **Table 1**. According to MGFA classification, 55.6% of subjects in the treatment group and 75% in the control group were classified as Type IIB. The mean MGC Scale was 4.89±2.89 for the treatment group and 5.63±3.20 for the control group. All subjects in the treatment group were receiving pyridostigmine at varying doses (60–300 mg/day), so does everyone but one subject in the control group. Only 22.2% and 12.5% of subjects already had thymectomy in treatment and control group, respectively. The majority of the subjects had no comorbidity, except hypertension and dyslipidemia in 44.4% of the treatment group's subjects and 25% in the control group. There was no significant difference in characteristics between both groups, which was measured using Chi-squared test, independent t-test and Mann-Whitney U test.

Comparison of lung function parameters between pre- and post-intervention

There was a significant difference in FVC (p=0.003) and FEV_1 (p=0.029) between the pre- and post-intervention phases in the treatment group, while no significant difference was observed in FEVR. In the control group, there was a significant difference in FEV_1 (p=0.016) between the pre- and post-intervention phases, and no significant differences were noted in FVC and FEVR (**Table 2**).

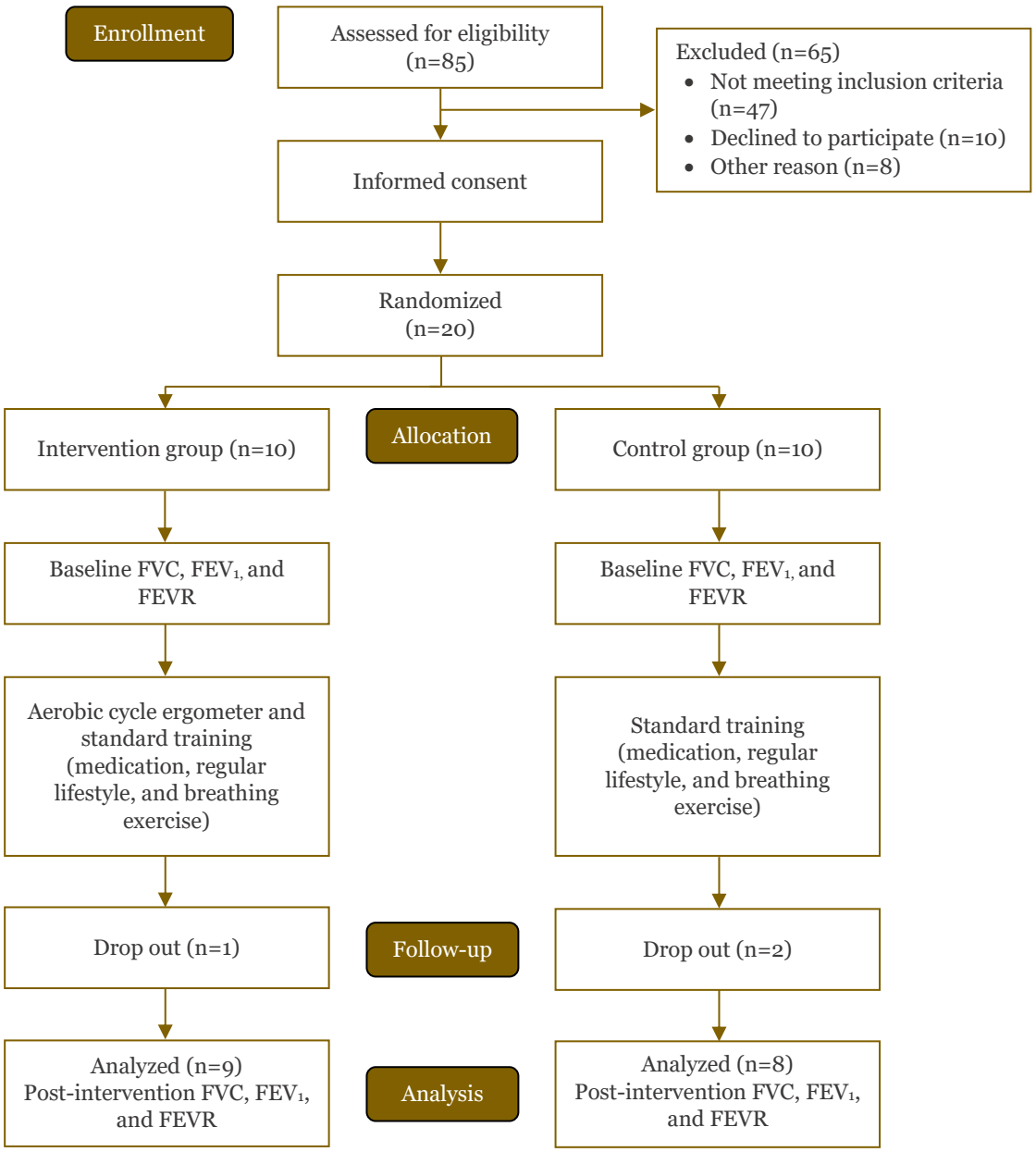

Figure 1. CONSORT diagram of the patient's participation. FEV1: forced expiratory volume in 1 second; FEVR: forced expiratory volume ratio; FVC: forced vital capacity.

Table 1. Characteristics of myasthenia gravis patients included in the study (n=17)

Characteristics	Treatment group (n=9) Frequency (%)	Control group (n=8) Frequency (%)	*p*-value
Sex			0.623 [a]
Male	2 (22.5)	3 (37.5)	
Female	7 (77.8)	5 (62.5)	
Age (years)	48.44±5.19	45.75±6.98	0.378 [b]
Body mass index (kg/m²), mean±SD	21.98±4.06	23.38±2.95	0.435 [a]
Age of onset (years), mean±SD	38.11±11.05	37.00±6.48	0.807 [b]
Myasthenia Gravis Foundation of America (MGFA) classification			0.522 [a]
Type IIA	4 (44.4)	2 (25)	
Type IIB	5 (55.6)	6 (75)	
Myasthenia Gravis Composite (MGC) scale score, mean±SD	4.89±2.89	5.63±3.20	0.626 [b]
Duration of treatment (years), mean±SD	10±7.34	6.38±4.98	0.288 [c]
Dose of pyridostigmine 60 mg/day (tab)			0.234 [a]
0	0 (0)	1 (12.5)	
1	1 (11.1)	1 (12.5)	
2	0 (0)	1 (12.5)	

Characteristics	Treatment group (n=9)	Control group (n=8)	*p*-value
	Frequency (%)	Frequency (%)	
3	4 (44.4)	1 (12.5)	
4	0 (0)	3 (37.5)	
5	4 (44.4)	1 (12.5)	
Thymectomy			0.427 [a]
No	7 (77.8)	7 (87.5)	
Yes	2 (22.2)	1 (12.5)	
Comorbidity			0.600 [a]
None	5 (55.6)	6 (75)	
Hypertension	3 (33.3)	1 (12.5)	
Dyslipidemia	1 (11.1)	1 (12.5)	
Physical activity (minutes/week), mean±SD	656.67±148.89	650.88± 136.25	0.663 [c]
Level of physical activity			0.573 [a]
Light	5 (55.6)	5 (62.5)	
Moderate	4 (44.4)	3 (37.5)	
Spirometry patterns			0.895 [a]
Restrictive	5 (55.6)	6 (75)	
Obstructive	1 (11.1)	0 (0)	
Mixed	2 (22.2)	1 (12.5)	
Normal	1 (11.1)	1 (12.5)	

[a] Analyzed using Chi-squared test
[b] Analyzed using independent t-test
[c] Analyzed using Mann-Whitney U test

Table 2. Comparison of lung function parameters (FVC, FEV_1, and FEVR) between pre- and post-intervention within group

Groups	Variables	Pre-intervention	Post-intervention	*p*-value	Effect size
		Mean±SD	Mean±SD		
Treatment group	FVC (% predicted value)	70.52±13.37	80.37±8.70	0.003*	1.37
	FEV1 (% predicted value)	67.30±18.45	76.85±9.23	0.029*	0.88
	FEVR (%)	77.89±11.25	79.33±6.53	0.665	0.15
Control group	FVC (% predicted value)	60.53±11.43	66.97±9.74	0.068	0.76
	FEV1 (% predicted value)	58.64±10.12	64.68±11.56	0.016*	1.11
	FEVR (%)	82.20±7.83	82.30±10.59	0.984	0.01

FEV_1: forced expiratory volume in 1 second; FEVR: forced expiratory volume ratio; FVC: forced vital capacity
[a] Analyzed using paired t-test
* Statistically significant at $p<0.05$

Comparison of lung function parameters between treatment and control groups

After 8 weeks of intervention, significant differences between the treatment and control groups were observed in FVC ($p=0.009$) with a large effect size (1.45) and FEV_1 ($p=0.029$) with a large effect size (1.17). However, no significant differences were found in FEVR between these groups ($p=0.491$; effect size 0.34) (**Table 3**).

Table 3. Comparison of lung function parameters (FVC, FEV_1, and FEVR) between groups

Groups	Variables	Treatment group	Control group	*p*-value	Effect size
		Mean±SD	Mean±SD		
Pre-intervention	FVC (% predicted value)	70.52±13.37	60.53±11.43	0.258	0.80
	FEV1 (% predicted value)	67.30±18.45	58.64±10.12	0.121	0.58
	FEVR (%)	77.89±11.25	82.20±7.83	0.380	0.44
Post-intervention	FVC (% predicted value)	80.37±8.70	66.97±9.74	0.009*	1.45
	FEV1 (% predicted value)	76.85±9.23	64.68±11.56	0.029*	1.17
	FEVR (%)	79.33±6.53	82.30±10.59	0.491	0.34

FEV_1: forced expiratory volume in 1 second; FEVR: forced expiratory volume ratio; FVC: forced vital capacity
[a] Analyzed using independent t-test
* Statistically significant at $p<0.05$

Discussion

This study found restrictive spirometry patterns in 64.7% of patients, followed by mixed patterns (17.6%), obstructive (5.9%), and normal (11.8%). Generalized MG patients often show restrictive results on pulmonary function examinations [10,11]. These results differ from a study that showed

only 2 out of 15 patients (13.3%) had abnormal spirometry results, even though both of them also had restrictive patterns [10]. The obstructive and mixed disorders observed in this study were likely due to the cholinergic effects of pyridostigmine, which caused airway spasms and increased mucus production, potentially contributing to obstructive respiratory disorders [12].

This study's findings revealed a significant increase in FVC (p=0.003) with a substantial effect size in the treatment group, whereas no notable increase was observed in the control group. This finding aligns with a study that also reported a significant post-intervention rise in FVC among MG patients following 30 minutes of exercise therapy, with or without PBWSTT, administered three times weekly over 12 weeks [18]. In contrast, a study found divergent results, noting no significant increase in post-intervention FVC after 30 minutes of self-determined aerobic exercise over 24 weeks, which included a geriatric cohort with patients averaging 56.1±8.6 years old, ranging from 40 to 70 years [21]. FVC is a lung function parameter that measures the volume of air expelled from the lungs after deep inspiration. Aerobic exercise enhances oxygen uptake and stimulates inactive alveoli. The repetitive breathing cycles during exercise can improve alveolar compliance, thereby increasing FVC [22].

This study demonstrated a significant increase in FEV_1 (p=0.029) with a large effect size observed in both the treatment and control groups. Notably, the treatment group exhibited a greater difference (9.55) compared to the control group (6.04). This result is similar to a study that reported a significant post-intervention increase in FEV_1 among MG patients following exercise therapy with or without PBWSTT [18]. Aerobic exercise increases exercise tolerance, respiratory muscle strength, and thoracic cavity volume, resulting in air exchange in the lungs [23]. At rest, expiratory muscles play a minor role in breathing since expiration is predominantly passive. However, during exercise, expiratory muscles are activated to increase tidal volume and expiratory airflow rate [24]. The significant increase in the FEV_1 of the control group, which did not receive intervention, may be attributed to a learning effect among patients familiarized with spirometry procedures repeated at the study's outset.

In this study, both groups were instructed to perform breathing exercises consisting of diaphragmatic breathing and pursed lip breathing. However, no follow-up was conducted to determine whether the subjects adhered to these exercises. A meta-analysis investigating the benefits of home-based breathing exercises in COPD subjects found significant increases in FEV_1 and FEVR compared to controls [25]. Another study compared the effects of pursed lip exercises and diaphragmatic breathing combined with bronchodilators versus bronchodilators alone in 60 COPD subjects. The treatment group showed a significant increase in FEV_1 (p=0.0005) and FVC (p=0.014) compared to the control group [26]. These findings parallel those of another study on COPD patients, where a significant rise in FVC and FEV_1 was observed after 30 minutes of cycle ergometer aerobic exercise three times per week for four weeks, although no change in FEVR was noted [27]. FEVR reflects the proportion of FEV_1 to FVC, where an increase doesn't always signify a positive outcome. A higher FVC relative to FEV_1 will result in a lower FEVR. The study demonstrates increases in FVC and FEV_1 variables, thereby clarifying that the lack of change in FEVR can be understood accordingly.

After the intervention, it was observed that the treatment group exhibited significantly higher FVC and FEV_1 levels (p=0.009 and p=0.029, respectively), indicating a substantial improvement. This suggested that low-intensity cycle ergometer aerobic exercise has a beneficial effect on increasing FVC and FEV_1 in MG patients. Conversely, there was no significant difference in FEVR values after the intervention between both groups, indicating that cycle ergometer aerobic exercise does not affect the FEVR. As previously explained, an increase in FEVR is not indicative of a positive outcome. Moreover, the changes in the FVC and FEV_1 of pre- and post-intervention were not significantly different between the groups in this study, resulting in minimal changes in FEVR. FEVR is crucial for assessing the degree of obstruction, and its interpretation hinges on obtaining a low FEV_1 result. In restrictive lung disorders where the FVC values are low, FEVR may show normal results or even increase.

This study had several limitations. Firstly, due to the nature of the intervention used, it was not possible to conduct it in a blinded manner, meaning that the patients were aware of the type of intervention they were receiving. Secondly, the post-intervention study results were assessed by the authors themselves without blinding, potentially introducing measurement bias,

specifically examiner bias. Thirdly, long-term post-intervention follow-up was not carried out, leading to a lack of documentation regarding the intervention's long-term effects.

Conclusion

Low-intensity aerobic cycle ergometer training combined with eight-week breathing exercises has been proven to increase FVC in MG patients. A combination of low-intensity cycle ergometer aerobic training with breathing exercises and breathing exercises alone for 8 weeks can increase FEV_1 in MG patients. Moreover, a significant improvement in FVC and FEV_1 was observed after low-intensity cycle ergometer aerobic exercise combined with breathing exercises for eight weeks in MG patients compared to breathing exercise alone.

Ethics approval

Ethical clearance for this study was issued by the Hospital Ethical Committee of Dr Soetomo General Academic Hospital with ethical clearance number 0601/KEPK/II/2023.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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