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Original article

Effects of neuromuscular electrical stimulation in patients with pulmonary arterial hypertension: a randomized controlled pilot study

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ABSTRACT

Background: Patients with pulmonary arterial hypertension (PAH) present impairments in muscle strength and exercise capacity. There is growing evidence about the benefits of neuromuscular electrical stimulation (NMES) in patients with respiratory diseases, except in patients with PAH. The aim of this study was to investigate the effects of NMES on muscle strength, and other physical and psychosocial variables in patients with PAH.

Methods: Patients with PAH were randomly divided into two groups as NMES and control. The NMES was applied to the bilateral deltoid and quadriceps femoris muscles with 50 Hz for 3 days/week, 8 weeks for the NMES group. Muscle strength, muscle cross-sectional area and thickness, arterial stiffness, exercise capacity, functional mobility and balance, balance confidence, fatigue, physical activity, and quality of life were assessed at baseline and after 8 weeks by blinded assessors.

Results: There was no significant difference in the demographic and clinical characteristics between the patient groups ($p > 0.05$). The improvements in muscle strength, muscle cross-sectional area and thickness, pulse wave velocity, exercise capacity, functional mobility and balance, balance confidence, fatigue, physical activity, and quality of life were significantly higher in the NMES group compared to the control group ($p < 0.05$).

Conclusions: This study suggests that NMES intervention is safe and effective for patients with PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disease which is characterized by the combination of endothelial dysfunction and increased contractility in small pulmonary arteries, proliferation, and remodeling of endothelial and smooth muscle cells, and thrombosis causing progressive narrowing of blood vessels [1]. Muscle wasting and weakness in PAH present with a switch from “resistant” fiber I type to “fast” type II fiber, reduced muscle capillary density, lower aerobic enzyme activity, impaired mitochondrial content, and altered excitation-contraction coupling [2,3]. Exercise intolerance is a key symptom of PAH and the reduction in muscle strength in patients with PAH is considered to be one of the most important causes of exercise limitation [4]. A recent Cochrane review has suggested that exercise-based rehabilitation programs result in improvements in exercise capacity in patients with PAH without causing any serious adverse events [5]. The studies included in that review investigated the effects of aerobic exercise alone, combined with strength or respiratory exercises in patients with PAH [5]. Despite the benefits of exercise training in PAH, not every patient can be a candidate for an exercise training program because of concomitant symptoms.

Neuromuscular electrical stimulation (NMES) has been used as an alternative method to increase muscle strength and exercise capacity in patients who cannot/are unwilling to participate in

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exercise training programs [6,7]. The NMES is a preferred method because patients are more passive during treatment and require less motivation than traditional exercise training [8]. The NMES is also more tolerable for patients with breathlessness and decreased condition because of its low metabolic load on the cardio-respiratory system [9].

Although there is growing evidence about the benefits of NMES in patients with other diseases such as chronic obstructive pulmonary disease (COPD) and heart failure (HF) [6,7] to the best of our knowledge, the effects of NMES in patients with PAH have not been previously investigated. Therefore, this study aimed to determine the effectiveness of NMES on muscle strength, muscle cross-sectional area (CSA) and thickness, arterial stiffness, functional exercise capacity, functional mobility, and balance performances, balance confidence, fatigue perceptions, physical activity level, activities of daily living, and quality of life in patients with PAH.

Materials and methods

Participants

This assessor-blinded randomized controlled trial was conducted at pulmonary hypertension (PH) outpatient clinic of Dokuz Eylül University. Consecutive patients with PAH were included in this study. The inclusion criteria were as follows: elevated pulmonary artery pressures measured by right heart catheterization, New York Heart Association (NYHA) class II or III, 18 years or older, stable PAH-specific pharmaceutical therapy for the previous 3 months. Patients were excluded if they had an orthopedic problem, significant restrictive or obstructive pulmonary disease, and acute cor pulmonale.

Since our study was the first study to be undertaken in this regard, the findings of the study that examined the effectiveness of NMES in patients with COPD were taken into account in calculating *a priori* sample size [10]. *A priori* sample size was calculated as 15 participants for each group as $\alpha = 0.05$, and the power of the study is 0.80 using the G-Power software (Version 3.1.9.2, Düsseldorf University, Düsseldorf, Germany).

The study protocol was registered at ClinicalTrials.gov (Identifier: NCT03612115) and approved by the Noninvasive Research Ethics Board of Dokuz Eylül University. All the participants gave written informed consent before participation in the study.

Study protocol

The participants were divided into two groups as NMES and control groups by block randomization with a 1:1 allocation using random block sizes of two by an independent party. All assessors were blinded to the group allocation until study completion. To blind the assessors, the patients were informed not to tell assessors the treatment they received. In addition, no information was given to the assessors about which group the patients were and the assessors were not present during the treatment sessions. Outcome assessors included a cardiologist, physiotherapist, and radiologist.

The cardiologist screened patients for inclusion-exclusion criteria and performed arterial stiffness assessments. The physiotherapist evaluated physical and psychosocial functions. The radiologist evaluated ultrasound-related evaluations. Adequate rest periods were provided between the tests. The pre-intervention assessment was performed within one week before the day of the first session and a post-intervention assessment was performed within one week after the last intervention session after 8 weeks. The participants in the control group were evaluated twice with an interval of 8 weeks. The demographic data and clinical characteristics of the participants were recorded to describe the study sample.

The NMES was delivered with a four-channel Wireless Professional device (Chattanooga, DJO United Kingdom Ltd., Guildford, UK). The current was fixed at 50 Hz frequency in 350 μs pulses over an on: off duty cycle, which was increased on a weekly basis from 2:15 s to 5:20 s to 10:15 s, then remaining the same [6]. The intensity of the stimulation was increased to achieve a visible muscle contraction according to the patient's tolerance (i.e. not strong enough to cause discomfort). The 8-week intervention was administered as 40 min a day, 3 days per week. The NMES was applied to quadriceps and deltoid muscles of bilateral extremities by the same physiotherapist.

Study outcomes

The aim was to determine the effects of NMES in this study, so the primary outcome was determined by the changes in quadriceps muscle strength. Isometric muscle strength was measured by a handheld dynamometer (Lafayette Instrument, Lafayette, IN, USA) and handgrip (Jamar® dynamometer, Patterson Medical, Warrenville, IL, USA) in a standard position. Measurements were taken for peripheral muscle groups bilaterally: shoulder flexors and abductors, handgrip, and knee extensors. Each muscle group was tested 3 times, and the highest value was recorded [11]. Dominant and non-dominant extremity were recorded. Rectus femoris CSA and quadriceps femoris thickness assessed by superficial ultrasonic probe [12,13]. Arterial stiffness was measured with a non-invasive method using a device (SphygmoCor XCEL, AtCor Medical, Sydney, Australia) with applanation tonometry. Measurements were made by pulse wave velocity (PWV) over the carotid-femoral artery via a transducer. Results were obtained in meters/second for the PWV [14].

Six-minute walk test (6MWT) was used to assess functional exercise capacity. It was applied according to the European Respiratory Society/American Thoracic Society Technical Standard Guidelines [15]. Six-minute walk distance (6MWD) was recorded. Six-minute pegboard and ring test (6PBRT) was used to assess upper extremity functional capacity [16].

Functional mobility and balance performances were evaluated by the sit-to-stand test (STS) and timed up-go (TUG) test [17,18]. Balance confidence was assessed with the Activities-specific Balance Confidence (ABC) Scale [19].

Fatigue Impact Scale (FIS) was used to determine fatigue levels [20]. The physical activity level was assessed with the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [21]. Health-related quality of life was assessed using the Nottingham Health Profile (NHP) scale which includes six sub-domains: energy level, pain, emotional reactions, sleep, social isolation, and physical abilities [22]. The physiotherapist recorded adverse events after interventions.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software (Version 23.0, IBM Corp., Armonk, NY, USA). The normal distribution of the variables was assessed by examining the Shapiro-Wilk test results as well as the histogram and probability plots. Nonparametric test statistic was used because the variables did not show normal distribution. Continuous variables are expressed in median (interquartile range), while categorical variables are shown as frequency and percentage. Statistical significance of the differences between the groups in the categorical variables was assessed by the chi-square test. The difference between the two groups before the intervention was assessed by the Mann-Whitney *U* test. The difference between pre- and post-intervention outcomes between the groups (NMES vs. control group) was assessed by the Wilcoxon signed rank test. The

effect sizes were calculated as Cohen's *d* coefficient using the online impact size calculation software, and the *d* values larger than 0.8 were interpreted as the large effect size. The study's *post-hoc* power analysis was calculated using the G-Power software (Version 3.1.9.2, Düsseldorf University, Düsseldorf, Germany) using the knee extensor muscle strength effect size, the primary outcome measure. The statistical significance level was taken as $p < 0.05$.

Results

In total, 47 patients with PH were screened, and 22 patients (11 patients in each group) completed the follow-up (Fig. 1). No participant reported negative experiences or views during the intervention and the testing protocols. No adverse effect was recorded during the study.

There were no significant differences in demographic and clinical characteristics ($p > 0.05$) (Table 1). The right side was the dominant extremity for all patients. Most patients (n = 16; 66.7%) received oral PH medication; 2 (8.3%) received intravenous or subcutaneous infusions, and 6 (25%) received combination therapies. No significant difference was observed in the study outcome measures (except 6MWD) between the intervention and control groups ($p > 0.05$) at baseline (Table 2 and Table S1 in the supplemental file).

Shoulder flexion and extension, handgrip and knee extension muscles strength, rectus femoris muscle CSA and quadriceps femoris muscle thickness, PWV, 6MWD, TUG, 30s-STS, ABC, FIS, IPAQ-SF scores and NHP's energy level, emotional reactions, and physical activity sub-section scores were significantly improved from baseline at 8 weeks in the intervention group, represented by large effect sizes ($p < 0.05$, $d > 0.80$), except 6PBRT ($p \geq 0.05$, $d > 0.80$). No significant improvements in the study outcome measures were observed in the control group ($p > 0.05$) (Table 3 and Table S2 in the supplemental file). After the 8-week period, the NYHA functional class of the two patients (16.66%) from the NMES group improved and one patient (8.33%) from the control group got worse. There was no significant difference in the NYHA functional classes between the NMES and the control group ($p = 0.070$).

Significant differences were observed in the shoulder flexion and extension, handgrip and knee extension muscles strength, rectus femoris muscle CSA and quadriceps femoris muscle thickness, 6MWD, 6PBRT, TUG, 30s-STS, ABC, FIS, IPAQ-SF scores and NHP's energy level, emotional reactions and physical activity sub-section scores between the changes in the pre- and post-assessments in the intervention and control groups (Table 4 and Table S3 in the supplemental file).

The *post-hoc* power of the study, which was calculated based on the effect size of the primary outcome measure was found as 99.9%.

Discussion

To the best of our knowledge, this is the first randomized controlled pilot study to investigate the effects of NMES in patients with PAH. The results show that the NMES improved peripheral muscle strength, muscle CSA and thickness, arterial stiffness, exercise capacity,

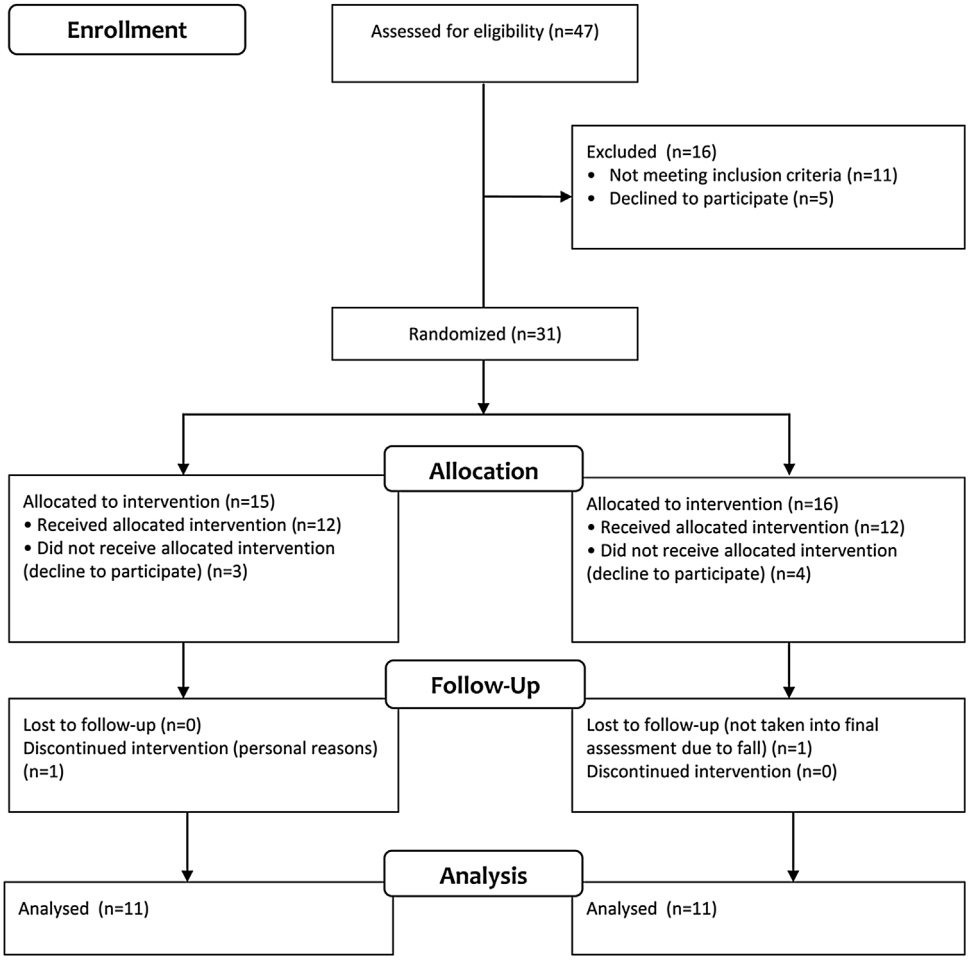

Fig. 1. Trial flow diagram.

Table 1
Baseline Characteristics of Study Patients.

	Intervention (n = 12)	Control (n = 12)	*p*
Age (years)[a]	52.50 (25.75–62.50)	47.50 (29.50–59.0)	0.977[a]
Sex, n (%)			
Women	9 (75)	9 (75)	0.999[b]
Men	3 (25)	3 (25)	
BMI (kg/m^2)[a]	26.47 (22.30–28.34)	25.94 (22.24–33.19)	0.686[a]
Duration of disease (years)[a]	4.5 (2–6)	5 (2–8)	0.333[a]
NYHA functional class, n (%)			
Class II	10 (83.3)	10 (83.3)	0.999[b]
Class III	2 (16.7)	2 (16.7)	
mPAP (mmHg)[a]	51.0 (36.50–60.0)	51.0 (40.0–69.0)	0.579[a]
BNP (pg/mL)[a]	201.0 (82.0–308.25)	85.0 (38.0–131.0)	0.205[a]
Cardiac output (L/dk)[a]	4.97 (3.18–6.85)	5.29 (3.97–7.39)	0.497[a]
Cardiac index (L/dk/m^2)[a]	2.89 (1.85–3.76)	2.90 (1.69–3.74)	0.790[a]
Pulmonary arterial wedge pressure (mmHg)[a]	12.0 (8.0–14.25)	12.0 (8.0–13.0)	0.805[a]
Pulmonary vascular resistance (Wood units)[a]	7.30 (5.0–9.0)	6.02 (3.20–10.53)	0.676[a]
TAPSE (mm)[a]	19.0 (16.0–23.0)	22.0 (18.0–24.75)	0.339[a]
Right atrial area (cm^2)[a]	26.5 (20.6–35.5)	26.0 (22.2–29.0)	0.618[a]

Data are median (interquartile range), unless otherwise stated.
BMI, body mass index; NYHA, New York Heart Association; mPAP, mean pulmonary arterial pressure; BNP, brain natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion.
[a] Mann-Whitney *U* test.
[b] Fisher's exact test.

Table 2
Comparisons of the baseline primary and secondary outcome measures.

	Intervention (n = 12)	Control (n = 12)	*p*
Knee extensors–right (kg)	14.65 (11.40–17.25)	13.15 (10.42–23.10)	0.795
Knee extensors–left (kg)	15.15 (12.42–17.32)	14.20 (10.35–20.77)	0.977
Shoulder flexors–right (kg)	12.25 (9.67–17.35)	12.50 (10.27–24.02)	0.564
Shoulder flexors–left (kg)	12.25 (10.42–18.47)	11.85 (9.60–21.77)	0.840
Shoulder abductors–right (kg)	11.55 (10.37–15.50)	11.75 (7.82–20.55)	0.686
Shoulder abductors–left (kg)	11.20 (9.70–16.17)	10.80 (8.0–18.32)	0.862
Quadriceps femoris muscle thickness–right (mm)	37.25 (34.60–41.62)	37.40 (29.35–38.97)	0.450
Quadriceps femoris muscle thickness–left (mm)	37.60 (36.50–39.80)	37.35 (31.85–38.50)	0.422
Rectus femoris cross-sectional area– right (cm^2)	6.86 (5.97–9.41)	7.15 (6.15–9.0)	0.824
Rectus femoris cross-sectional area– left (cm^2)	6.71 (5.40–9.0)	6.95 (5.98–8.82)	0.623
6MWD (m)	358.50 (206.25–435.0)	465.0 (420.0–532.50)	**0.006**[*]

Data are median (interquartile range). Mann-Whitney *U* test.
6MWD, six-minute walk distance.
[*] $p < 0.05$

Table 3
Changes in the study outcome measures of the intervention and control groups.

	Intervention Group (n = 11)				Control Group (n = 11)			
	Baseline	After	*p*	*d*	Baseline	After	*p*	*d*
Knee extensors–right (kg)	14.65 (11.40–17.25)	18.1 (15.1–21.7)	**0.003**[*]	3.194[b]	13.15 (10.42–23.10)	15.10 (10.60–21.30)	0.504	0.393
Knee extensors–left (kg)	15.15 (12.42–17.32)	17.40 (14.10–20.70)	**0.006**[*]	2.626[b]	14.20 (10.35–20.77)	16.90 (9.90–20.60)	0.533	0.366
Shoulder flexors–right (kg)	12.25 (9.67–17.35)	13.10 (12.70–20.90)	**0.003**[*]	3.213[b]	12.50 (10.27–24.02)	11.80 (10.10–24.70)	0.099	1.081[b]
Shoulder flexors–left (kg)	12.25 (10.42–18.47)	13.40 (12.90–19.90)	**0.003**[*]	3.194[b]	11.85 (9.60–21.77)	12.30 (9.90–23.80)	0.161	0.885[b]
Shoulder abductors–right (kg)	11.55 (10.37–15.50)	13.50 (10.40–17.60)	**0.008**[*]	2.417[b]	11.75 (7.82–20.55)	13.50 (8.0–22.80)	0.228	0.743
Shoulder abductors–left (kg)	11.20 (9.70–16.17)	12.80 (10.30–18.50)	**0.006**[*]	2.634[b]	10.80 (8.0–18.32)	11.20 (8.0–19.70)	0.305	0.620
Quadriceps femoris muscle thickness–right (mm)	37.25 (34.60–41.62)	40.60 (37.82–43.70)	**0.008**[*]	2.411[b]	37.40 (29.35–38.97)	38.20 (28.60–38.50)	0.866	0.098
Quadriceps femoris muscle thickness–left (mm)	37.60 (36.50–39.80)	39.0 (36.87–43.20)	**0.015**[*]	1.970[b]	37.35 (31.85–38.50)	37.20 (32.10–42.0)	0.866	0.098
Rectus femoris cross-sectional area– right (cm^2)	6.86 (5.97–9.41)	8.82 (6.62–10.04)	**0.011**[*]	2.170[b]	7.15 (6.15–9.0)	6.91 (5.79–9.0)	**0.028**[*]	1.641[b]
Rectus femoris cross-sectional area– left (cm^2)	6.71 (5.40–9.0)	8.56 (5.97–9.11)	**0.008**[*]	2.415[b]	6.95 (5.98–8.82)	6.47 (5.91–9.0)	0.293	0.637
6MWD (m)	358.50 (206.25–435.0)	420.0 (300.0–520.0)	**0.003**[*]	3.194[b]	465.0 (420.0–532.50)	460.0 (380.0–570.0)	0.439	0.458

6MWD, six-minute walk distance.
[*] $p < 0.05$.
[b] Large effect size.

functional mobility and balance, balance confidence, physical activity level, and quality of life in patients with PAH.

Skeletal muscle dysfunction is associated with deconditioning, systemic inflammation, low cardiac output, chronic acidosis, increased sympathetic activity, and deterioration of oxygen utilization in skeletal muscles in patients with PAH [23]. Changes in muscle fiber types are closely associated with clinical worsening, exercise intolerance, and reduced quality of life [2].

Table 4
Comparison of the difference between the baseline and post-intervention study outcome measures of the intervention and control groups.

	Intervention	Control	*p*
ΔKnee extensors–right (kg)	3.10 (2.30–6.50)	−0.2 (−0.6 to 0.4)	<**0.001***
ΔKnee extensors–left (kg)	2.80 (1.80–4.20)	0.10 (−0.3 to 1.0)	**0.001***
ΔShoulder flexors–right (kg)	2.10 (1.0–3.40)	−0.40 (−1.0 to 0.4)	<**0.001***
ΔShoulder flexors–left (kg)	1.90 (1.10–2.50)	0 (−0.70 to 0.20)	<**0.001***
ΔShoulder abductors–right (kg)	2.0 (0.80–2.40)	0.20 (−0.20 to 0.60)	**0.003***
ΔShoulder abductors–left (kg)	1.60 (0.90–2.20)	−0.30 (−0.70 to 0.40)	**0.001***
ΔQuadriceps femoris muscle thickness–right (mm)	3.50 (1.45–4.65)	−0.10 (−0.40 to 0.30)	**0.001***
ΔQuadriceps femoris muscle thickness–left (mm)	1.50 (1.0–4.95)	−0.10 (−0.30 to 1.0)	**0.050***
ΔRectus femoris cross-sectional area– right (cm^2)	0.47 (0.34–1.09)	−0.19 (−0.47 to −0.10)	**0.001***
ΔRectus femoris cross-sectional area– left (cm^2)	0.73 (0.19–0.96)	−0.01 (−0.60 to 0.01)	**0.002***
Δ6MWD (m)	75.0 (40.0–112.0)	−20.0 (−60.0 to 10.0)	**0.001***

Δ, After – Baseline.
6MWD, six-minute walk distance.
* $p < 0.05$.

A Cochrane review has suggested that NMES may be a safe and effective treatment for muscle weakness that can occur as a result of advanced diseases such as cancer, COPD, and chronic HF [24]. In this study, we found that 3.10 kg increase in isometric muscle strength of the dominant quadriceps femoris consistent with another study which found that 3.10 kg increase in patients with HF [25]. In a study, it was found that NMES was effective to improve both upper and lower extremity muscle strength in patients with COPD followed in an intensive care unit [26]. Consistent with the results obtained in COPD [6,10] and HF patients [27] after NMES intervention to the quadriceps femoris muscle, we observed an increase in quadriceps muscle CSA and strength. We also showed a significant increase in the rectus femoris and vastus medius thickness after eight-week NMES intervention. In the control group, the CSA of the right rectus femoris was reduced. Gruther et al. reported that ultrasound-measured quadriceps femoris muscle thickness (vastus intermedius and rectus femoris) increased as a result of 50 Hz NMES intervention to the quadriceps femoris muscle in critically ill patients in the NMES-treated group as long-term effects [13].

Although most of the studies have focused on lower extremities, recent studies reported reduced upper extremity muscle strength and its association with limitations in upper extremity-related activities in daily living, especially with the progression of the disease stage in patients with PAH [28,29]. In this study, the strength of shoulder flexor and abductor muscles was significantly increased after NMES intervention. Similarly, significant improvements in upper extremity muscle strength were reported in patients with COPD after NMES [26,30]. These gains of upper and lower extremity muscle strength are thought to be due to the positive effects of NMES on pro-inflammatory cytokine, oxidative enzyme activity, and protein anabolic and catabolic metabolism, which previously was shown in patients with HF [7]. Additionally, muscle strength might be increased due to increased muscle cross-sectional area and thickness after NMES. These findings suggest that the NMES intervention may be effective for increasing muscle strength in patients with PAH as well as for preserving muscular tissue and thus preventing muscle dysfunction.

The histopathology of PAH involves endothelial injury and proliferation, which can affect endothelial function and vascular wall flexibility. Pulmonary endothelial dysfunction is an important component of the underlying mechanism of PAH [1]. Pulmonary artery stiffness has been investigated in patients with PAH with PWV for many years, but peripheral arterial stiffness has received attention since it is understood that endothelial dysfunction affects systemic arteries [31,32]. It was reported that arterial stiffness was improved after both NMES intervention and aerobic exercise and there were significant changes in endothelial functions after NMES in patients with HF [33]. In our study, a significant decrease in PWV values after NMES was shown while there was no significant change in the control group. The NMES is thought to have effects on arterial stiffness by regulating the neurohormonal activity, such as aerobic exercise, and regulating disorders in the autonomic nervous system [33]. However, the evidence about the effects of NMES on arterial stiffness is limited.

Exercise capacity is one of the fundamental targets in a rehabilitation program for patients with PAH. Although the effects of aerobic exercise training alone or with strength training or respiratory exercises on functional exercise capacity have been well documented in patients with PAH [5,34], no evidence is available for the NMES. On the other hand, several studies reported significant improvements in functional exercise capacity in patients with COPD and HF [6,35]. In our study, 6MWD representing functional exercise capacity was significantly increased by 75 m after NMES, but there was no significant change in the control group. This result suggests that NMES can increase the 6MWD in PAH by more than 33 m, which is considered to be a minimal clinically important difference [36]. Baseline 6MWD of the control group was higher than the intervention group, but when the 6MWD changes and the pre- and post-assessment values of both groups are compared, it is suggested that the NMES is a method that can increase the exercise capacity in patients with PAH. We suggest that the improvements in exercise capacity after NMES intervention in this study could be related mostly to the improvements in muscle CSA and thickness, and strength.

Although the studies mentioned above investigated the exercise capacity related to lower extremities, to the best of our knowledge, upper extremity exercise capacity has not been investigated. Due to the importance of upper extremity function in patients with PAH, it is important to investigate the exercise capacity of the upper extremities. In this study, upper extremity exercise capacity was significantly improved in both groups, yet, the improvements were significantly higher in the NMES group.

There are several studies that examine the changes in functional outcome measures after NMES in patients with diseases other than PAH [37–39]. Similar to previous studies, we also observed significant improvements in functionality such as sit-to-stand, walking, balance, and balance confidence of patients with PAH. Underlying mechanisms are most probably related to the improvements in muscle strength and exercise capacity.

It was reported that 93% of patients with PH had fatigue [40]. Decreased type 1 fiber ratio, atrophy, increased anaerobic energy metabolism, and quadriceps femoris muscle weakness is associated with faster fatigue appearance in patients with PAH [2]. Our results suggest that NMES may be a suitable option in the management of fatigue in patients with PAH.

There is strong evidence that patients with PH have less physical activity compared to healthy controls, and more sedentary patients have lower survival time [3,28,41]. It has also been reported that less physical inactivity is related to muscle strength loss in PH [41]. In this study, physical activity significantly increased in the NMES group, but there was no significant difference in the control group. On the other hand, Maddocks et al. [6] showed insignificantly, yet, a greater increase in physical activity after NMES in COPD. The increase in the physical activity obtained after NMES could be attributed to the increase in muscle strength and exercise capacity and the decrease in fatigue.

Improving the quality of life is an important goal for researchers and clinicians working with PAH who are known as having a reduced health-related quality of life [3,40]. Several studies have reported that the NMES improved quality of life in patients with COPD and HF [7,25,30]. In this study, it was found that there were significant improvements in quality of life sub-domains including energy level, emotional reactions, and physical activity levels after NMES. There was no significant improvement in sleep sub-domain, but the large effect size was observed.

Our study has some limitations. First, there was no long-term follow-up. Second, we have not reached *a priori* sample size. However, *post-hoc* power analysis showed that the sample size was enough. Last, there was no placebo or sham control intervention group.

Conclusion

This pilot study has demonstrated that the NMES intervention improved peripheral muscle strength, muscle cross-sectional area and thickness, arterial stiffness, exercise capacity, functional mobility, balance, balance confidence, physical activity level, and quality of life in patients with PAH.

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Conflict of interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2019.12.013.

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