Effects of a new respiratory muscle training device in community-dwelling elderly men: an open-label, randomized, non-inferiority trial

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Abstract

Background: Respiratory muscle training (RMT) has various clinical benefits in older adults, but the low adherence to training remains a difficult issue to resolve. The present study aimed to confirm the efficacy of a new device compared to the Threshold IMT device (Philips Respironics Inc) and to determine whether home-based training was different from rehabilitation center training.

Methods: This four-arm, multicenter, prospective, parallel, non-inferiority trial randomized 80 active community-dwelling elderly males (mean age = 72.9 years) to center-based groups (new IMT/PEP device or Threshold IMT device; 16 supervised sessions) or home-based groups (new IMT/PEPdevice or Threshold IMT device; 2 supervised sessions and individual sessions). Participants in all groups performed RMT twice a day for eight weeks. Assessments were performed at baseline and post-training. The primary outcomes were maximum inspiratory pressure and maximal expiratory pressure. The secondary outcomes included forced vital capacity and forced expiratory volume in the first second, peak cough flow, diaphragm thickness, VO_2 peak, the International Physical Activity Questionnaire score, electromyographic activities of the sternocleidomastoid muscle, and skeletal muscle mass and phase angle measured by bioimpedance analysis. In addition, adherence rates to each protocol were also compared.

Results: The maximal inspiratory pressure improved among all groups post-training. Furthermore, the non-inferiority of the IMT/PEP device was validated. However, the maximal expiratory pressure showed improvement only in the IMT/PEP groups. A statistically significant improvement in diaphragm thickness was found. However, no consistent improvement was shown in other secondary outcomes. No significant difference in training adherence rate between protocols was observed (mean adherence rate of 91%–99%).

Conclusion: Compared to the Threshold IMT, using the new IMT/PEP device showed no significant difference in maximal inspiratory pressure but improved maximal expiratory pressure in the elderly. The IMT/PEP devices reduced training time and improved usability, associated with exercise adherence, provided distinct advantages in this cohort. If preceded by proper education, home-based RMT alone is expected to provide sufficient effect in the elderly.

Trial registration: This trial was registered in the database cris.nih.go.kr with the number KCT0003901 on 10/05/2019.

Introduction

Globally, the proportion of the population that is elderly is increasing. With the progression of aging, lean body mass is decreased, and the fat ratio is increased [1]. These changes in metabolism result in a loss of muscle mass, and lower muscle strength, endurance, and functional status leading to various diseases. Physiological pulmonary function changes in older individuals are characterized by reductions in the elasticity of the lungs, respiratory muscle strength, and chest wall compliance [2]. A recent study also reported that respiratory muscle strength could be used as an indicator of sarcopenia [3]. Various clinical effects of respiratory muscle training (RMT) have been reported, such as a strengthened diaphragm and improved aerobic capacity and coughing ability in the elderly [4,5]. RMT uses the principles of either flow-dependent resistance or working against a pressure threshold. Although there is no significant difference in the effect of the two types of RMT, a superior effect was obtained when both inspiration and expiration training were performed together [6]. However, low adherence to pulmonary rehabilitation exercise, including RMT, remains a difficult issue to resolve [7]. Thus, we have designed a new device that combines inspiratory muscle training (IMT) and a positive expiratory pressure (PEP) threshold. The new device allows a two-way simultaneous threshold RMT (IMT/PEP, GH INNOTEK, Busan, South Korea; Supplemental Figure 1). The aim of this present study was to confirm the efficacy of this new device and to determine whether home-based training was better than rehabilitaion center training for improving training adherence rate and effect.

Therefore, the questions for this randomized clinical trial were:

1. Is RMT using the new combined IMT/PEP device non-inferior to that using the existing Threshold IMT (Philips Respironics Inc., Murrysville, PA, USA) device?

2. Does a home-based RMT program have a non-inferior effect compared to center-based RMT?

Methods

Study design

This study was a four-group, multicenter, prospective, randomized, parallel, non-inferiority trial with concealed allocation and assessor blinding. All participants provided written informed consent. Ethics approval was obtained from the Institutional Review Boards (IRB) of Pusan National University Hospital (IRB No. 1903-028-076) and Pusan National University Yangsan Hospital (IRB No. 03-2019-006). Written informed consent was obtained from all participants. All procedures of the study were performed in accordance with the amended Declaration of Helsinki. This study was registered at Clinical Research Information Service (No. KCT0003901).

Recruitment

Participants were recruited through the research recruitment flyer at elderly welfare centers in Busan, South Korea, from April 2019 to August 2020. Community-dwelling men over 60 years of age who were able to walk without a mobility aid were included. Exclusion criteria were: known cardiopulmonary disease causing chest pain or dyspnea during activity; uncontrolled musculoskeletal pain; participation in other clinical trials within the last four weeks; the presence of diseases, such as glaucoma, aneurysm, or pulmonary artery hypertension, which would prohibit the Valsalva maneuver [8]. The level of dyspnea during activity that was used to exclude participants was more than two points on the modified Medical Research Council dyspnea scale [9]. The sample size was determined by calculations performed from data collected from a previous study [4]. We used the G*power 3.1 statistical program, using a power (1–β) of 80%, and alpha of 5% for the maximum inspiratory pressure (MIP), based on the mean and standard deviation of the MIP of the training and control group after the intervention. The result indicated that 17 participants were needed in each group to identify significant differences. Assuming a dropout rate of about 15%, about 20 participants in each group were considered enough.

Randomization and interventions

Prior to randomization, all participants underwent screening and familiarization with the training protocol before the baseline outcomes were evaluated. A block randomization process was performed with a block size of 16 using a computer-generated random allocation in Excel 2016 (Microsoft, Redmond, WA, USA). Random allocation was generated by requesting a third party who did not participate in the study. The participants were randomly assigned in a 1:1:1:1 manner into the following groups, depending on the device allocated and the training site: IMT/PEP in the rehabilitation center (Group N-C), Threshold IMT in the rehabilitation center (Group I-C), IMT/PEP at home (Group N-H), and Threshold IMT at home (Group I-H). For all participants, several practice tests were performed to correct possible training and learning effects, before the tests were conducted. All evaluations and training were conducted by different blinded researchers. The new IMT/PEP device used in this study has a threshold IMT range of 10–40 cmH_2O and PEP of 5–20 cmH_2O with a resolution of 2 cmH_2O. A variable loading can be set on the IMT/PEP device, providing flow-independent resistance to inspiration or expiration, by using two spring-loaded one-way valves. The valves only open when the

pressure generated by the participant exceeds the set spring tension during inspiration and expiration. This concept is similar to that of the existing individual Threshold IMT and Threshold PEP devices (Philips Respironics Inc., Murrysville, PA, USA), but is designed in a way that allows simultaneous training of both in one breathing cycle. Groups N-C and I-C visited the rehabilitation center twice a week to undergo supervised training for eight weeks. They also performed self-training with the individualized intensity twice a day at home for eight weeks. Groups N-H and I-H performed the same RMT twice a day at home for eight weeks, with only two supervised training sessions. For all participants, one self-training session was omitted on the day of supervised training. A telephone interview was conducted four weeks after enrollment to confirm whether there were any problems with the training or device for the participants in Groups N-H and I-H.

The inspiratory threshold for each device was set to 40% of the initial MIP of the each participant, and the maximum threshold of the device was 40 cmH_2O. Considering that the average maximal expiratory pressure (MEP) is above 100 cmH_2O for those over sixty years of age [10], the expiratory threshold was set to 20 cmH_2O, the maximum load of the device, for groups using the combined IMT/PEP (Groups N-C and N-H). All participants were instructed to inspire, from residual volume, at a constant intensity and strength to exceed the threshold pressure. When they reached vital capacity, they held their breath for several seconds and then exhaled at a constant intensity for as long as possible. Each set of RMT consisted of ten deep and forceful breaths against the threshold pressure of the device. Twice a day, ten sets were performed with two minutes of rest after each set. During the first training, two sets of training were practiced at half the target threshold to allow the patient to adapt to the devices. All participants kept a home exercise diary, which was used to check the training adherence, and all training in the rehabilitation center was conducted under the supervision of an experienced physiotherapist.

Measurements

All participants were assessed on the date of their first visit and one week after the program by an assessor blinded to the group allocation. Clinical and demographic data were collected and the level of physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ), adapted to older individuals [13]. The primary outcomes in this study were MIP and MEP, and the secondary outcomes were forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1), peak cough flow (PCF), diaphragm thickness with ultrasound, predicted VO_2 peak, IPAQ, electromyography activities of the sternocleidomastoid muscle, and skeletal muscle mass and phase angle by bioimpedance analysis (BIA).

Primary outcomes

MIP, MEP, and pulmonary functions were evaluated in a standardized method using a desktop spirometer Pony FX (Cosmed, Rome, Italy) [10,14]. MIP and MEP, respectively, reflect inspiratory and expiratory muscle strength. Measurements were obtained with the participants in a sitting position utilizing a flange-type mouthpiece. The MIP was acquired from one maximal inspiration, starting from close to the residual volume. The MEP was obtained from the maximal expiration, starting from close to the vital capacity. At least five measurements were obtained, and the highest three measurements were recorded when reproducible measurements with a difference of less than 10% were obtained [15]. Prediction of MIP and MEP was calculated using the following reference equations [10]:

Male MIP reference = 120 – (0.41 * age)

Male MEP reference = 174 – (0.83 * age)

Secondary outcomes

The PCF was measured with the Micro Peak-flow meter (Micro Medical, CA, USA.) The result recorded was the maximum value obtained from three trials of a short and forceful expiration after amaximum inspiration. FVC and FEV_1 were measured from a maximum inspiration and expiration after three normal breaths, in accordance with the following reference equations [16].

FVC in male (liter) = -4.8434 - 0.00008633×Age^2 + 0.05292×Height (cm) + 0.01095×Weight (kg)

FEV1 in male (liter) = -3.4132 - 0.0002484×Age^2 + 0.04578×Height (cm)

Ultrasound (Z.ONE, ZONARE, Mountain View, CA, USA) was used to measure diaphragm thickness. This was measured between the 8th and 9th ribs of the anterior and mid-axillary lines using a linear probe of 12 MHz on B-mode [17]. Participants were instructed to breathe quietly and spontaneously in the lying position, and the right diaphragm thickness at the end of quiet expiration (Texp) and at the end of quiet inspiration (Tins) was measured in mm. A total of five measurements were obtained, and the three values recorded excluded the maximum and minimum values.

The Chester step test is an effective and simple evaluation method for assessing aerobic capacity [18]. As a submaximal test, steps with both feet can be performed at various heights according to a metronome rhythm. In this study, a 20 cm step box was used for participants over 60 years old. In stage 1, steps were performed at the speed of 60 beats per minute, and the speed was increased by 20 beats per minute every two minutes. Heart rate, oxygen saturation, and the Borg Category/Ratio-10 dyspnea Scale® were measured before and at the end of each stage. The predicted oxygen consumption based on the heart rate at each stage was calculated [19]. Phase angles and skeletal muscle mass were quantified in participants using a segmental multi-frequency BIA system (S10, InBody Co., Ltd, Seoul, South Korea). Touch-type electrodes were attached between the participants' ankles and on the middle finger and thumb of both hands. Participants rested in a supine position for several minutes before the BIA measurements. The phase angles of each segment of the body were automatically calculated at frequencies of 5, 50, and 250 kHz by the BIA system's software. Among the many variables, we analyzed 50 kHz whole body phase angle.

To measure muscle activity required for the target pressures, during the first and last supervised training for effective RMT, a surface electromyography (sEMG) device was also applied. and. The single-channel sEMG device (PSL-EMG-Tr1; PhysioLab Co., Ltd., Busan, South Korea) was set to a sampling rate of 30,000 Hz, and signals were amplified within a 3–2,000 Hz bandwidth [11]. Conductive adhesive hydrogel electrodes (Covidien, Minneapolis, MN, USA) were placed parallel to the left SCM fibers according to the recommendation [12]. Before the sEMG measurement, the participants sat upright on an adjustable height stool with neutral head posture, maintaining normal curvature of the spine. Afterward, they held the RMT training device with the right hand, and muscle activity was measured during RMT. As a result, the muscle activity of the SCM used in forceful inspiration was presented in real-time through the tablet screen, and feedback on the proper use of respiratory muscle during training was available. The root mean square (RMS) reflects the activities of the motor unit in muscle contraction [20]. The RMS values of the recorded sEMG obtained from the initial feedback training and follow-up test were used for analysis. To standardize the measurement , the mean RMS of the left SCM muscle obtained in the fifth set of training was calculated for all participants. The mean RMS obtained in the middle two seconds of each inspiration was analyzed.

Statistical analysis

A minimal clinically important significance (MCID) of 11 cmH_2O difference in the MIP of the Threshold IMT group was used to confirm non-inferiority [21]. The IMT/PEP groups were considered non-inferior to the Threshold IMT groups if the

MIP upper limit did not exceed the 95% confidence interval in the Threshold IMT group. In addition, variables were compared between the center-training and the home-training groups to identify differences in the training protocol when using the same device. The result of the baseline characteristics and analyzed outcomes are presented as mean ± standard deviation. We used an intention-to-treat approach for the primary analysis. The one-way analysis of variance was used to identify demographic differences among the four groups. Normality was verified through the Shapiro–Wilk's test. The comparison of values pre- and post-training in each group were performed via the paired t-test and the Wilcoxon signed-rank test. The independent t-test and Mann-Whitney test were used to compare values between groups. A *p*-value below 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows (version 22, Chicago, IL, USA).

Results

Eighty participants were randomized equally into four groups. Groups N-C and N-H used the IMT/PEP device and Groups I-C and I-H used the Threshold IMT (Figure 1). During the eight-week intervention, seven (17.5%) participants in the center-based groups and two (5%) in the home-based groups withdrew from the study. Reasons for the dropout included a loss to follow-up, loss of interest in training, or participants being too busy. Table 1 presents the demographics and baseline outcomes of each group. There were no significant statistical differences in demographic variables among the four groups. There was no significant difference in the training adherence rate between the home- and center-training groups. Adherence rates in each group ranged from 91% to 99%. In the pre- and post-assessment of the eight-week intervention, MIP and MEP were significantly improved in Groups N-C (*P* =0.001 and P=0.000, respectively) and N-H (*P* =0.000 and P=0.008, respectively), but in Groups I-C (*P* =0.001 and P=0.874) and I-H (*P* =0.000 and P=0.136), significant improvements were only identified in MIP (Table 2). In addition, significant increases in the right diaphragm thickness at end-tidal volume were identified in Groups N-C (*P* =0.026), N-H (*P* =0.018), and I-H (*P* =0.022). Groups N-H (*P* =0.010) and I-H (*P* =0.007) had significant improvements in PCF (Table 3). As illustrated in Figure 2, the lower limit of the 95% confidence interval was within the non-inferiority margin of the MIP between Groups N-C, I-C and N-H, I-H. Specifically for MIP, improvements by training were identified in all groups, and there were no statistical differences between devices and training protocols. In MEP, significant statistical differences were identified only between Groups N-C and I-C (*P* =.002) (Table 2, Supplemental Figure 2). No adverse events related to the intervention were reported during the clinical trial among the participants, except for one with a transient headache. Although this possible mild adverse event appeared at the end of the first training, the hemodynamic response was normal, and the symptom was relieved within a five-minute break. In this participant, the intensity of the RMT was initiated at 50% of the target and gradually increased, with no subsequent symptoms.

Discussion

MIP, MEP and Exercise adherence

This is the first randomized, non-inferiority trial to validate the effect of a newly developed IMT/PEP device for older men. In a previous study, RMT was usually proposed for about 30 minutes every day [30]. In this study, the session was consisted of performing 10 sets of 10 breaths in consideration of the subject's compliance and ease of calculation of the number of repetitions. Therefore, the protocol was trained for eight weeks, two sessions a day. The primary finding of this study demonstrated that inspiratory muscle strengthening via the new IMT/PEP device was not inferior to that using the Threshold IMT device after eight weeks of training. Furthermore, the IMT/PEP device resulted in significant improvements in MEP, which is related to the power of expiratory muscles, that were not identifiable in the Threshold IMT training groups. Of course, significant MEP improvements could have been expected if the additional conventional Threshold PEP device (Philips Respironics Inc., Murrysville, PA, USA) was also included for use by Groups I-C and I-H. However, the use of two separate devices, namely the Threshold IMT and Threshold PEP, can be expected to double the

training time and complicate the training procedure. Although multiple factors affect training adherence [22], a previous study has shown that shorter training time has a positive effect on training adherence [23]. From this perspective, we used only the Threshold IMT device in Groups I-C and I-H to standardize the time spent on training. We hypothesized that simultaneous inspiration and expiration training within a single breath would result in an additional benefit. However, there were no statistically significant differences in the mean MIP between groups before and after training, compared to the results when the conventional Threshold IMT device was used. Furthermore, there were no significant differences in the primary outcome between protocols, which indicates that home-based training is non-inferior to a center-based protocol.

The role of home-based respiratory rehabilitation has been highlighted in the era of the COVID-19 Pandemic [24,25]. Exercise adherence––one of the barriers to home-based training––was greater than 90% in all groups. Of course, the high adherence rate seen in those who completed the training may have some selection bias, but the adherence rates between protocols were comparable. In addition, patient withdrawal from home-based training groups was less than that of center-based training. This result suggests that the lack of information and motivation, one of the barriers to pulmonary rehabilitation, can be overcome by just one supervised home-based RMT.

Exercise performance

Several studies have reported an improved effect of RMT on exercise performance in healthy subjects [26,27]. The protocol of alternating inspiratory and expiratory muscle training showed a better effect on exercise performance than one type of RMT alone [6]. RMT also had a greater effect in the less fit participants, such as the elderly [28,29]. Although we expected an improvement in exercise performance because of the targeted population, the mean value of the predicted VO_2 peak showed no significant improvement. Two reasons were considered for this result. First, the RMT device used in this study has a low maximum threshold setting and thus could not be sufficiently raised with exercise intensity. Second, various tests, such as the incremental test, constant load test, and time trial, have been used in an attempt to assess the effect of RMT on exercise performance improvement, but significant improvement has been confirmed only with the constant load and time trial test [6]. In this study, it is thought that it was difficult to verify the effect of exercise tolerance because the incremental ramp protocol (the Chester step test) was selected to measure aerobic capacity due to the limitation of the research equipment.

Diaphragm thickness and muscle mass

Low muscle mass and age-related sarcopenia also affect respiratory muscle strength in the elderly, precipitating a vulnerability to disease and disability [31]. RMT strengthens and improves the thickness and movement of the diaphragm, the main inspiratory muscle [4]. In this study, significant improvements in diaphragm thickness were found in groups N-C, N-H, and I-H.

In BIA, the phase angle is presented as an alternative predictor of health in the aging process [32,33]. In this study, the initial phase angle was above the average value of 5.32 ± 0.62 in the community-dwelling elderly identified in a previous study [34]. In addition, the skeletal muscle index exceeded the 7.0 kg/m^2 presented by the Asian Working Group for Sarcopenia [35]. We observed no significant differences in muscle mass and phase angle in any group. It is presumed that the initial values were too superior, so the low intensity of RMT did not influence these results. In the future, it is necessary to evaluate these effects on frail elderly or patients.

Respiratory muscle activation during RMT

It is known that loaded breathing leads to greater activation of neck muscles [36]. Generally, it is necessary to use accessory respiratory muscles and the diaphragm for effective RMT. Therefore, single-channel sEMG on the left SCM was used in the first and final training sessions for visual feedback of accessory muscle activity and as an outcome measure. We expected that if the diaphragm was strengthened, activation of the accessory muscles to overcome the same threshold loading would be relatively reduced. However, no significant differences were identified in all groups. A study of Chronic Obstructive Pulmonary Disease (COPD) patients suggested that PEP training reduces the activity of SCM muscles during respiration, which means improved respiratory efficiency [37]. In the community-dwelling elderly with normal lung function, it was difficult to confirm the significant difference in RMS because there was little use of accessory muscles during quiet breathing, and the function of the diaphragm was enough to overcome the threshold. However, it can be expected that the combined IMT/PEP training will show a difference in SCM muscle activity in COPD patients.

Limitations

There are limitations in this study that should be considered. First, significant effects, such as increased activity or aerobic capacity, could not be identified due to the low maximum thresholds in the devices used. In the next study, we plan to verify the clinical impact of the IMT/PEP device on patients with chronic lung disease. Second, the small sample size of each group limited the analysis of some statistical significance. In addition, due to the limitation of the protocol, there was no re-evaluation within the eight-week intervention. Therefore, the readjustment of the threshold was not applied during the training period. As a result, it is expected that the load during training gradually decreased below 40% of the MIP as the respiratory effort became stronger.

Conclusion

We observed additional effects as well as non-inferiority compared to the verified Threshold IMT. The reduced training time and improved usability associated with exercise adherence provide further advantages. If preceded by proper education, a home-based RMT alone with the new IMT/PEP is expected to provide a sufficient effect in the elderly. In addition, through the results of this study, it is expected that the new RMT device can be used as an effective treatment strategy, even in patients with chronic lung diseases requiring pulmonary rehabilitation.

Abbreviations

RMT: Respiratory muscle training; IMT: Inspiratory muscle training; PEP: Positive expiratory pressure; MIP: Maximum inspiratory pressure; MEP: Maximal expiratory pressure; BMI: Body mass index; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in the first second; PCF: Peak cough flow; VO_2peak: Peak oxygen uptake; RMS: Root mean square; SMI: Skeletal muscle index; IPAQ: International Physical Activity Questionnaire; sEMG: Surface electromyography; MCID: Minimal clinically important significance; COPD: Chronic obstructive pulmonary disease

Declarations

Acknowledgments

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Authors' contributions:

SHK and SCH conceived and designed the trial. MJS designed the randomization procedure. JML and SHK collected data. SHK and YBS conceptualized the manuscript. SHK wrote the paper and MJS, SCH and YBS revised it critically. All authors have read and approved the final version of the manuscript.

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Availability of data and materials;

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

Ethics approvals were obtained from the Institutional Review Boards (IRB) of Pusan National University Hospital (IRB No. 1903-028-076) and Pusan National University Yangsan Hospital (IRB No. 03-2019-006).

Consent for publication:

Not applicable

Competing interests:

The authors declare that they have no competing interests.

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Tables

Table 1 Demographics and baseline characteristics of subjects

Parameters	Group N-C (n = 20)	Group I-C (n = 20)	Group N-H (n = 20)	Group I-H (n = 20)	*P* value
Age (years)	73.00 ± 5.36	73.86 ± 3.46	74.32 ± 4.82	71.95 ± 5.09	0.374
Weight (kg)	68.20 ± 8.94	67.55 ± 9.66	67.70 ± 10.44	71.91 ± 9.24	0.574
Height (m)	1.64 ± 0.04	1.63 ± 0.06	1.66 ± 0.06	1.67 ± 0.04	0.434
BMI (kg/m^2)	25.18 ± 3.08	24.94 ± 2.66	24.57 ± 2.75	25.78 ± 2.98	0.684
FVC (L)	3.22 ± 0.51	3.19 ± 0.57	3.04 ± 0.46	3.25 ± 0.58	0.403
FVC (% predicted)	99.23 ± 14.28	100.28 ± 16.20	94.15 ± 16.13	95.36 ± 13.89	0.583
FEV_1 (L)	2.48 ± 0.41	2.42 ± 0.59	2.31 ± 0.49	2.46 ± 0.59	0.653
FEV_1 (% predicted)	112.17 ± 16.71	110.35 ± 27.18	106.31 ± 24.73	105.84 ± 21.09	0.788
FEV_1/FVC (%)	76.17 ± 5.55	74.57 ± 9.61	75.57 ± 11.28	74.89 ± 9.71	0.734
PCF (L/min)	438.82 ± 74.57	414.28 ± 96.13	426.31 ± 87.63	424.21 ± 111.22	0.962
MIP (cmH_2O)	93.05 ± 23.81	78.35 ± 15.43	77.99 ± 18.01	85.33 ± 30.11	0.316
MIP (% predicted)	103.38 ± 26.78	87.42 ± 17.68	87.11 ± 20.23	94.13 ± 32.45	0.313
MEP (cmH_2O)	82.54 ± 24.11	96.07 ± 21.53	92.07 ± 18.03	99.00 ± 29.27	0.100
MEP (% predicted)	72.70 ± 20.61	85.26 ± 18.98	81.91 ± 15.42	86.55 ± 24.90	0.119
VO2 peak (ml/kg/min)	33.85 ± 5.55	29.01 ± 5.58	35.76 ± 9.45	34.52 ± 6.29	0.466
Adherence rate (% sessions completed)	91.94 ± 21.93	99.50 ± 1.87	92.37 ± 14.35	92.05 ± 20.30	0.491
RMS (uV)	49.69 ± 20.56	46.27 ± 19.86	55.79 ± 31.96	42.37 ± 22.27	0.416
Right diaphragm thickness at end inspiration (mm)	2.90 ± 0.82	3.24 ± 0.94	2.63 ± 0.77	2.88 ± 0.59	0.207
SMI (kg/m^2)	8.88 ± 0.89	8.90 ± 0.73	8.74 ± 0.72	9.13 ± 0.69	0.453
Bioimpedance-derived phase angle	5.84 ± 0.71	5.84 ± 0.55	5.90 ± 0.50	6.16 ± 0.51	0.178
IPAQ (MET-min/week)	2998.23 ± 3135.65	2365.92 ± 2286.87	3071.89 ± 2164.56	3672.10 ± 4046.08	0.455
IPAQ (activity level)	2.11 ± 0.48	2.21 ± 0.57	2.36 ± 0.49	2.10 ± 0.73	0.422

Notes: Continuous variables are reported as mean ± standard deviation

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; PCF, peak cough flow; MIP, maximal expiratory pressure; MEP, maximal expiratory pressure; VO_2peak, peak oxygen uptake; RMS, root mean square; SMI, skeletal muscle index; IPAQ, International Physical Activity Questionnaire

Table 2. Mean changes and mean differences of MIP and MEP after training within and between groups.

	Group N-C (n = 17)		Group I-C (n = 16)		Group N-H (n = 19)		Group I-H (n = 19)	
Outcomes	Change from baseline	*P* value	Change from baseline	*P* value	Change from baseline	*P* value	Change from baseline	*P* value
MIP (cmH_2O)	18.03 ± 17.87 (9.15 to 26.9)	0.001*	12.66 ± 12.76 (5.86 to 19.46)	0.001*	15.65 ± 15.96 (7.95 to 23.34)	0.000*	10.17 ± 9.85 (5.42 to 14.92)	0.000*
MIP (% predicted)	20.34 ± 20.35 (9.87 to 30.80)	0.001*	14.04 ± 14.06 (6.55 to 21.53	0.001*	17.42 ± 17.82 (8.83 to 26.01)	0.000*	11.20 ± 10.75 (4.54 to 6.01)	0.000*
MEP (cmH_2O)	25.96 ± 20.23 (15.89 to 36.02)	0.000*	0.87 ± 21.66 (-10.66 to 12.41)	0.874*	14.75 ± 21.58 (4.35 to 25.15)	0.008**	8.08 ± 22.57 (-2.79 to 18.97)	0.136*
MEP (% predicted)	23.00 ± 18.23 (13.63 to 32.38)	0.000*	0.95 ± 19.57 (-9.47 to 11.38)	0.848*	13.18 ± 19.00 (-4.02 to 22.34)	0.007**	6.96 ± 20.07 (-2.70 to 16.64)	0.148*
	Group N-C and I-C		Group N-C and N-H		Group N-H and I-H		Group I-C and I-H	
MIP (cmH_2O)	5.77 ± 5.53 (-5.52 to 17.05)	0.305†	2.78 ± 5.72 (-8.84 to 14.40)	0.630†	5.48 ± 4.30 (-3.31 to 14.27)	0.212†	2.49 ± 3.82 (-5.29 to 10.27)	0.519†
MIP (% predicted)	5.38 ± 9.04 (-13.19 to 23.96)	0.556†	2.92 ± 6.36 (-10.01 to 15.85)	0.649†	6.22 ± 4.76 (-3.54 to 15.98)	0.203†	3.75 ± 7.43 (-11.37 to 18.87)	0.617†
MEP (cmH_2O)	25.14 ± 7.40 (10.05 to 40.24)	0.002†	11.27 ± 7.09 (-3.15 to 25.68)	0.121††	6.66 ± 7.17 (-7.87 to 21.20)	0.359††	-7.22 ± 7.52 (-22.52 to 8.09)	0.344†
MEP (% predicted)	22.06 ± 6.58 (8.64 to 35.48)	0.002†	9.82 ± 6.22 (-2.83 to 22.48)	0.124††	6.22 ± 6.34 (-6.65 to 19.08)	0.334††	-6.02 ± 6.73 (-19.72 to 7.68)	0.378†

Notes: Continuous variables are reported as mean ± standard deviation (95% CI)

*Data was calculated by paired t-test. **Data was calculated by Wilcoxon signed-rank test. †Data was calculated by independent t-test. ††Data was calculated by the Mann-Whitney test. **Abbreviations:** MIP, maximal expiratory pressure; MEP, maximal expiratory pressure

Table 3 Mean changes in secondary outcomes after eight weeks of inspiratory muscle training

	Group N-C (n = 17)		Group I-C (n = 16)		Group N-H (n = 19)		Group I-H (n = 19)	
Outcomes	Change from baseline	*P* value	Change from baseline	*P* value	Change from baseline	*P* value	Change from baseline	*P* value
Right diaphragm thickness at end inspiration (mm)	0.70 ± 1.17 (0.09 to 1.30)	0.026*	0.20 ± 1.27 (-0.47 to 0.88)	0.527	0.50 ± 0.83 (0.09 to 0.90)	0.018*	0.62 ± 1.09 (0.10 to 1.15)	0.022*
BMI (kg/m^2)	-0.99 ± 2.85 (-2.46 to 0.47)	0.169	0.78 ± 1.40 (0.00 to 1.56)	0.048*	0.19 ± 0.85 (-0.21 to 0.60)	0.340	0.23 ± 1.00 (-0.24 to 0.71)	0.318
FVC (% predicted)	2.05 ± 4.09 (0.04 to 4.16)	0.055	3.18 ± 6.96 (-0.52 to 6.90)	0.087	-1.63 ± 19.24 (-10.90 to 7.64)	0.716	0.57 ± 8.00 (-3.28 to 4.43)	0.756
FEV1 (% predicted)	-1.00 ± 4.25 (-3.18 to 1.18)	0.347	2.25 ± 14.59 (-5.52 to 10.02)	0.547	4.10 ± 19.80 (-5.44 to 13.65)	0.378	3.31 ± 10.23 (-1.61 to 8.24)	0.175
PCF (L/min)	6.11 ± 55.00 (-21.24 to 31.46)	0.643	3.12 ± 34.19 (-15.09 to 21.34)	0.720	23.68 ± 35.77 (6.43 to 40.92)	0.010*	29.47 ± 42.48 (8.99 to 49.95)	0.007*
RMS (uV)	9.76 ± 78.75 (-5.02 to 24.54)	0.181	6.23 ± 22.36 (-5.68 to 18.15)	0.283	8.23 ± 21.45 (-2.10 to 18.57)	0.112	7.89 ± 29.96 (-6.54 to 22.34)	0.266
SMI	-0.06 ± 0.33 (-0.23 to 0.10)	0.711	0.03 ± 0.34 (-0.15 to 0.22)	0.711	0.10 ± 0.26 (-0.02 to 0.22)	0.114	0.03 ± 0.31 (-0.11 to 0.18)	0.663
Bioimpedance-derived phase angle	0.06 ± 0.32 (-0.10 to 0.23)	0.428	0.12 ± 0.32 (-0.05 to 0.30)	0.152	-0.08 ± 0.30 (-0.22 to 0.06)	0.240	0.06 ± 0.30 (-3.28 to 4.43)	0.756
IPAQ (MET-min/week)	-236.82 ± 2294.48 (-1416.53 to 942.88)	0.676	-229.06 ± 2018.41 (-1304.60 to 846.47)	0.656	-165.73 ± 1745.60 (-1007.09 to 675.61)	0.684	-277.84 ± 2939.75 (-1694.75 to 1139.07)	0.685
VO2 peak (ml/kg/min)	1.44 ± 5.88 (-1.48 to 4.36)	0.312	0.73 ± 5.26 (-2.06 to 3.54)	0.583	-1.64 ± 7.63 (-5.32 to 2.03)	0.361	-1.76 ± 7.38 (-5.32 to 1.79)	0.312

Notes: Continuous variables are reported as mean ± standard deviation (95% CI).

Abbreviations: BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; PCF, peak cough flow; RMS, root mean square; SMI, skeletal muscle index; IPAQ, International Physical Activity Questionnaire; VO_2peak, peak oxygen uptake

Figures

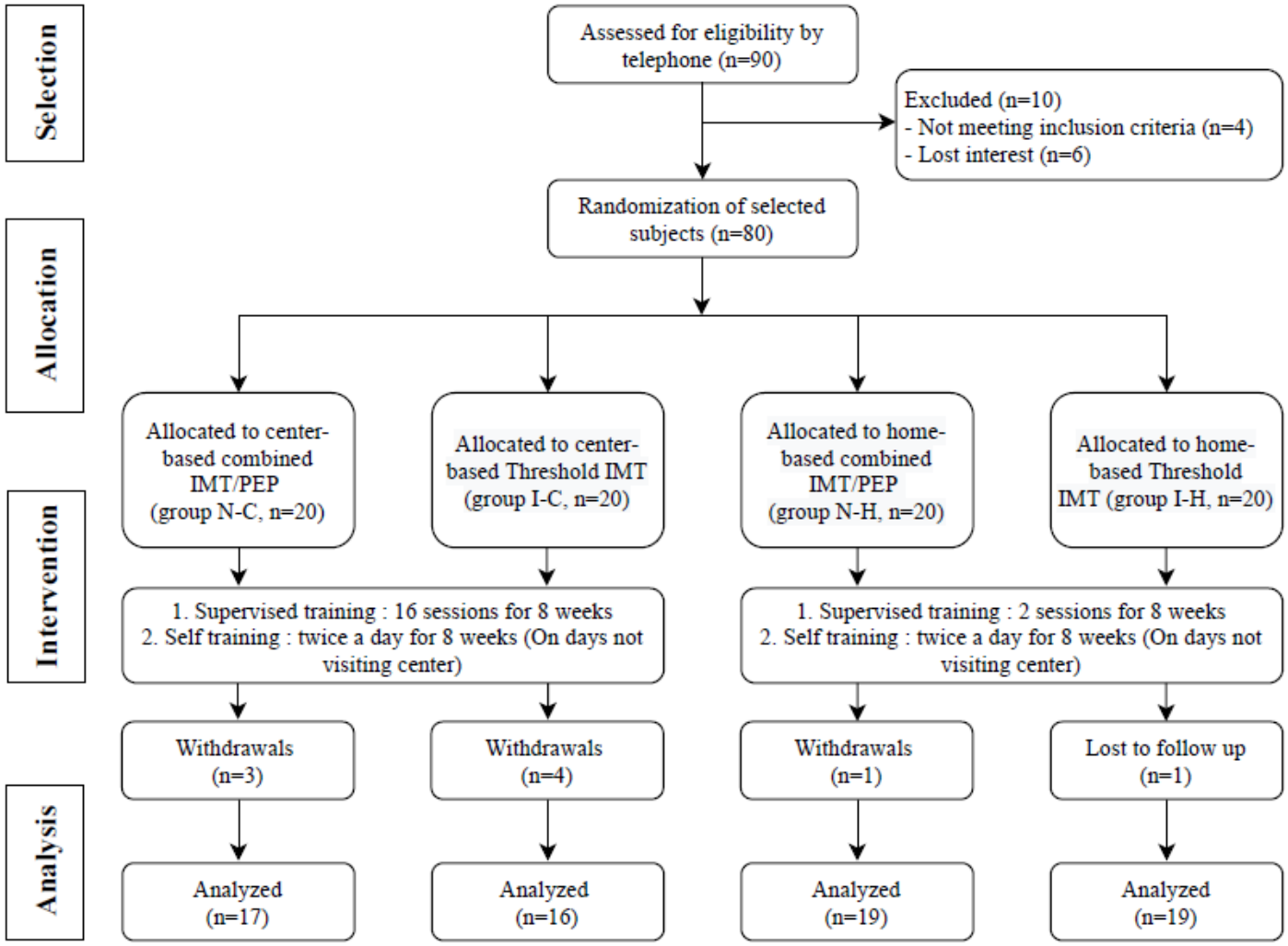

Figure 1

Flow diagram of the study subjects

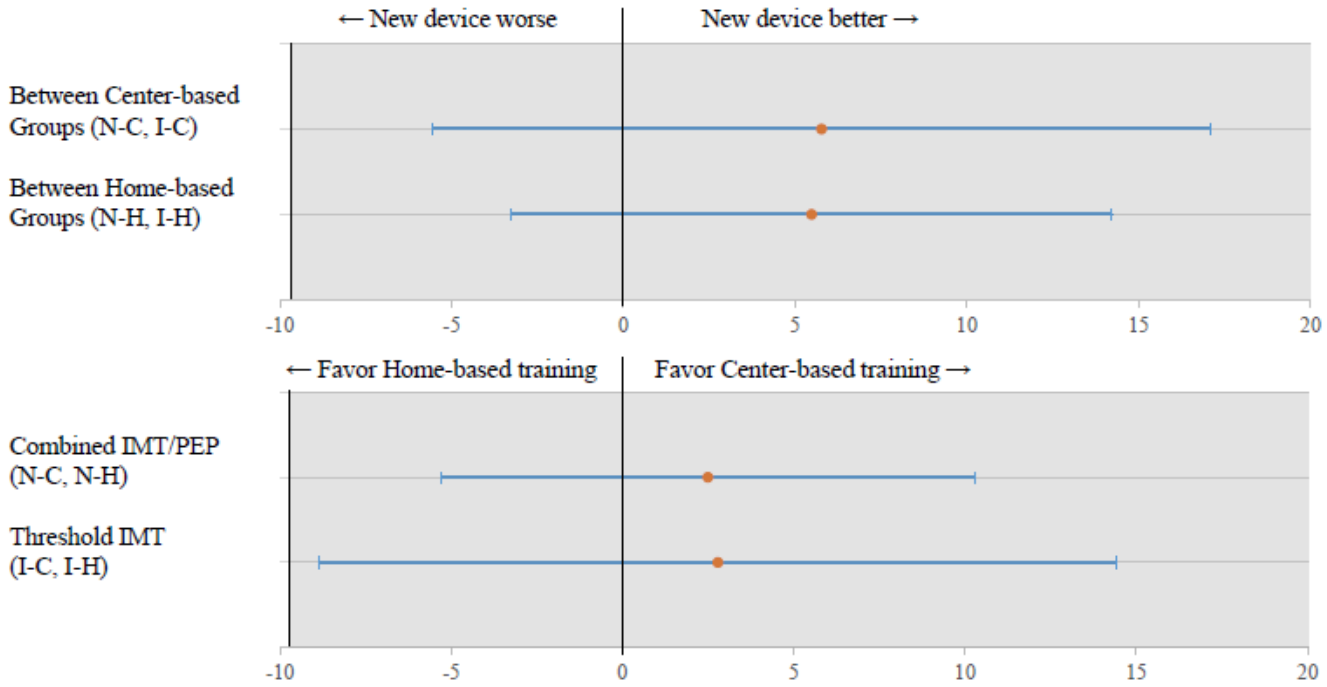

Figure 2

Non-inferiority plot of MIP. Difference between devices (above) and protocols (below) in the change of MIP from weeks 0 to 8. Error bars indicate the 95% confidence intervals, and the shaded area indicates the non-inferiority zone.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalFigure1.pdf
- SupplementalFigure2.pdf