



# The effects of threshold inspiratory muscle training in patients with obstructive sleep apnea: a randomized experimental study

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## Abstract

**Objectives** Patients with obstructive sleep apnea (OSA) (an obstructed airway and intermittent hypoxia) negatively affect their respiratory muscles. We evaluated the effects of a 12-week threshold inspiratory muscle training (TIMIT) program on OSA severity, daytime sleepiness, and pulmonary function in newly diagnosed OSA.

**Methods** Sixteen patients with moderate-to-severe OSA were randomly assigned to a TIMIT group and 6 to a control group. The home-based TIMIT program was 30–45 min/day, 5 days/week, for 12 weeks using a TIMIT training device. Their apnea-hypopnea index (AHI), Epworth sleepiness scale (ESS), and forced vital capacity (FVC) scores were evaluated pre- and post-treatment. Polysomnographic (PSG) analysis showed that 9 TIMIT-group patients had positively responded (TIMIT-responder group: post-treatment AHI < pre-treatment) and that 7 had not (TIMIT non-responder group: post-treatment AHI > pre-treatment).

**Results** Post-treatment AHI and ESS scores were significantly (both  $P < 0.05$ ) lower 6% and 20.2%, respectively. A baseline AHI  $\leq 29.0/h$  predicted TIMIT-responder group patients (sensitivity 77.8%; specificity 85.7%). FVC was also significantly ( $P < 0.05$ ) higher 7.2%. Baseline AHI and FEV<sub>6.0</sub> were significant predictors of successful TIMIT-responder group intervention. OSA severity and daytime sleepiness were also significantly attenuated.

**Conclusions** Home-based TIMIT training is simple, efficacious, and cost-effective.

**Keywords** Obstructive sleep apnea · Threshold inspiratory muscle training · Apnea-hypopnea index · Forced vital capacity

## Abbreviations

AE	Aerobic exercise	ATS	American Thoracic Society
AHI	Apnea-hypopnea index	BMI	Body mass index
AHI-NREM	Apnea-hypopnea index during non-rapid eye movement (NREM) sleep	EEG	Electroencephalography
AHI-REM	Apnea-hypopnea index during rapid eye movement (REM) sleep	ESS	Epworth sleepiness scale
		FEV <sub>1.0</sub>	Forced expiratory volume in 1 s
		FEV <sub>6.0</sub>	Forced expiratory volume in 6 s
		FVC	Forced vital capacity

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IMT	Inspiratory muscle training
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PFT	Pulmonary function test
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
PT	Physical therapist
REM	Rapid eye movement
RM	Repetition maximum
ROC	Receiver operating characteristic
RPE	Rating of perceived exertion
TIMT	Threshold inspiratory muscle training program

## Introduction

The prevalence of obstructive sleep apnea (OSA), which affects 34% of men and 17% of women, has recently reached alarming levels [1]. An obstructed airway and the subsequent asphyxia will lead to increased inspiratory effort and chronic overload of inspiratory muscles [2]. In a complete upper airway occlusion (e.g., no airflow, backward-falling tongue blocks airflow) in OSA patients, the activities of the inspiratory thoracic pump muscles continue to function. The airway may be triggered to open by a protective reflex originating in the inspiratory muscles upon reaching a certain degree of contraction [3]. However, repetitive efforts against an obstructed airway and intermittent hypoxia will negatively affect the inspiratory muscles of OSA patients: they become significantly weaker and have significantly less endurance.

Two studies [2, 4] that used aerobic and aerobic plus resistance exercise for 1–1.5 h three times/week for 12 weeks with OSA patients reported that exercise had a significantly positive effect on the apnea-hypopnea index (AHI), which seems not to be dependent upon changes in body mass index (BMI). The exact mechanisms of these effects are unclear, and many different hypotheses have been proposed. A dog study [5] reported greater tone in the genioglossus (extrinsic tongue) muscle after the gastrocnemius (lower leg) muscle and sciatic nerve had been stimulated. Two later studies in humans [6, 7] raised some interest in a possible association between the strength of respiratory muscles and physical exercise in OSA patients. One viable treatment called inspiratory muscle training (IMT) is a regimen of breathing exercises aimed at increasing the strength and endurance of inspiratory muscles in people with and without chronic obstructive pulmonary disease (COPD). It tests the hypothesis that greater respiratory muscle capacity will mitigate the severity of breathlessness and augment the COPD patients' tolerance of physical activity during their activities of daily living. Treatment duration at 30% of maximal inspiratory pressure (MIP) ranged from 8 to 10 weeks, and treatment frequency was 6 or 7 days/week for

15–30 min/session. One study [8] of OSA patients with chronic cervical cord injury reported that IMT increased inspiratory muscle strength and ameliorated the severity of AHI. However, another study [9] said that IMT treatment for OSA patients led to rapid improvement of blood pressure, plasma norepinephrine level, and reported sleep quality, it did not affect AHI.

Threshold IMT (TIMT) uses a resistive loading device to increase inspiratory muscle endurance and strength; it includes (i) a flow-independent one-way valve to ensure consistent resistance and (ii) an adjustable specific pressure setting (in  $\text{cmH}_2\text{O}$ ) set by a healthcare professional. TIMT's efficacy for improving maximum inspiratory pressure and the baseline dyspnea index in COPD patients has been confirmed [10]; however, how TIMT will affect OSA patients is unclear.

We therefore investigated the effects of 12 weeks of TIMT training on OSA severity, daytime sleepiness, and pulmonary function and assessed the possible predictors associated with the responsiveness of TIMT.

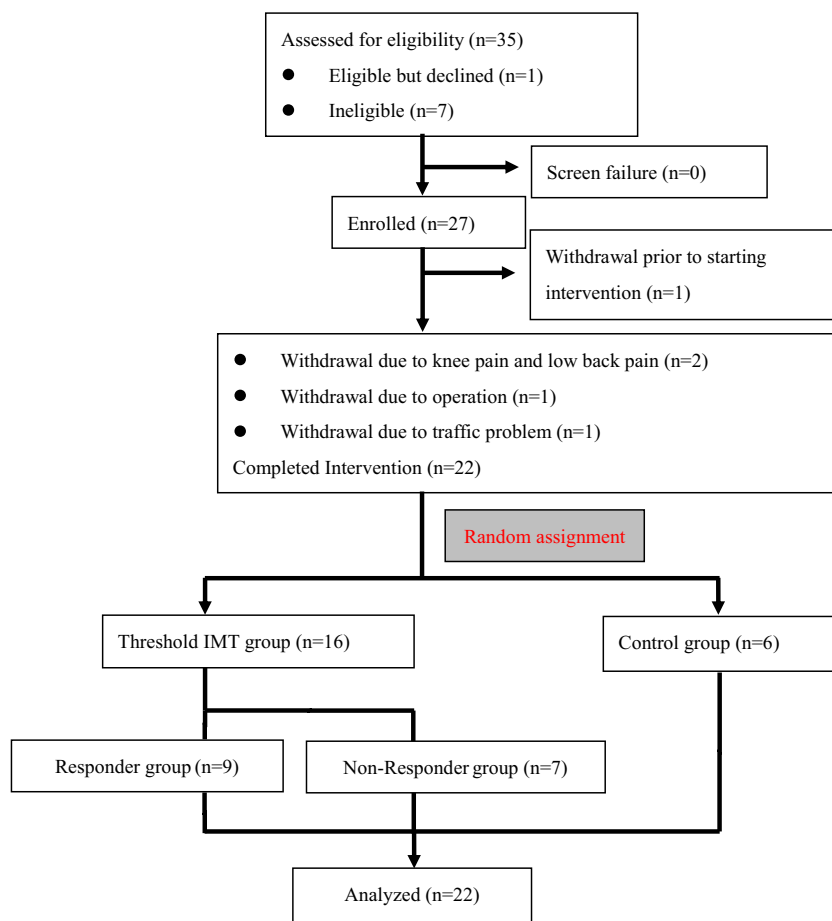
## Material and methods

### Study participants

We invited 35 adult patients with newly diagnosed moderate-to-severe OSA ( $\text{AHI} \geq 15/\text{h}$ ) to the Department of Otolaryngology, Tainan Hospital, Ministry of Health and Welfare, Taiwan. Exclusion criteria were inability to exercise and exercise-induced myocardial ischemia, chronic heart failure, myocardial infarction, unstable angina, respiratory or neuromuscular disease, morbid obesity, psychiatric disorder (e.g., bipolar disorder, schizophrenia), and uncontrolled chronic medical conditions (e.g., diabetes mellitus, hypertension, renal insufficiency, and hyperthyroidism). We excluded eight invitees from the study, and five withdrew for various reasons. The remaining 22 (18 men) satisfactorily completed the whole study (Fig. 1). The protocol of this study was approved by the Ethics Committee of the Human Research Committee at the National Cheng Kung University Hospital (NCKUH IRB No: A-ER-103-168) (Clinical Trials Register Number: NCT02278094). All the tests and the training program began only after the eligible participants had provided their written informed consent.

### Study procedure

Before the study, the participants underwent structured interviews, sleep-related questionnaires, overnight polysomnography (PSG), and a pulmonary function test (PFT). After the baseline data had been collected, patients were randomly assigned to the TIMT group or to the control group (Fig. 1). All participants were sex-, age-, and BMI-

**Fig. 1** The flow diagram of participant enrollment

matched (Table 1). TIMT group members were given medical treatment, routine care, and TIMT; control group members were given only medical treatment and routine care, but no TIMT (Table 2). Patients started TIMT at a threshold pressure between 11 and 21 cmH<sub>2</sub>O; the pressure increased once a week as tolerated (average weekly pressure increase was 5%; combined rating of perceived exertion (RPE) was between 13 and 15 (Table 3)). At the end of the study, assessments identical to those before baseline were done again. Patients subjectively evaluated differences between their pre- and post-TIMT OSA.

## Clinical measurements

### Questionnaires

A structured questionnaire was used to record demographic characteristics, health habits (drinking alcohol and smoking), medical conditions, and medication use (Table 1). Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [11]. A PSQI total score > 5 indicated poor sleep quality. Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) [12]. An ESS total score > 10 indicated significant daytime sleepiness (Table 2).

## Overnight polysomnography

All patients underwent standard overnight hospital PSG (Somté recorder; Compumedics, Abbotsford, Victoria, Australia). AHI was calculated as the number of apnea and hypopnea events per hour of sleep. AHI during rapid eye movement (REM) sleep (AHI-REM) = the number of apnea-hypopnea events per hour of REM sleep; AHI during non-REM (NREM) sleep = AHI-NREM [13, 14]. Our PSG reader was our sleep technician (Grace Lin), who was blinded to patients' assigned groups and to their pre-TIMT AHI levels. PSG data were interpreted by a sleep physician (C.Y. Lin) based on established criteria (Table 2).

## Pulmonary function test

Pulmonary function was assessed using standard spirometry and included forced vital capacity (FVC), forced expiratory volume in 1.0 s (FEV<sub>1.0</sub>), FEV<sub>1.0</sub>/FVC, and FEV in 6.0 s (FEV<sub>6.0</sub>) based on the guidelines of the American Thoracic Society (ATS). For the adult population 40–80 years old, the mean FVC was 3.517 ± 0.662 L in females and 3.913 ± 0.773 L in males; the mean FEV<sub>1.0</sub> was 2.856 ± 0.534 L in females and 4.922 ± 0.941 L in males [15]. The calculation of

**Table 1** Characteristics in our study ( $n = 22$ )

Quantitative variable	Threshold IMT <sup>a</sup> ( $n = 16$ )						Control ( $n = 6$ )		<i>P</i> value <sup>c</sup>	<i>P</i> value <sup>d</sup>
	Responders+non-responders		Responders ( $n = 9$ )		Non-responders ( $n = 7$ )		Mean	(S.D.)		
	Mean	(S.D.) <sup>b</sup>	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)		
Age (years)	47.9	(12.2)	50.1	(11.1)	45.0	(13.8)	56.2	(11.5)	0.165	0.380
Baseline body mass index (kg/m <sup>2</sup> )	26.2	(3.3)	27.2	(2.1)	25.0	(3.8)	27.3	(3.6)	0.516	0.309
Baseline neck circumference (cm)	38.3	(2.8)	39.3	(4.0)	36.9	(1.8)	38.5	(2.9)	0.537	0.176
Percent change after intervention (%)										
Body mass index (kg/m <sup>2</sup> )	-1.6	(4.5)	-2.1	(3.7)	-1.0	(1.2)	0.0	(0.2)	0.523	0.749
Neck circumference (cm)	-1.5	(2.7)	-2.1	(2.4)	-0.7	(0.4)	-0.3	(3.5)	0.377	0.556
Categorical variable										
	Number	(%)	Number	(%)	Number	(%)	Number	(%)		
Gender (male)	13	(81.3)	7	(78.0)	6	(86.0)	5	(83.0)	0.708	0.914
Drinking alcohol										
Yes	6	(37.5)	5	(55.6)	1	(14.3)	4	(67.0)	0.353	0.122
No	10	(62.5)	4	(44.4)	6	(85.7)	2	(33.0)		
Smoking tobacco										
Yes	1	(6.3)	0	(0.0)	1	(14.3)	0	(0.0)	0.762	0.325
No	15	(93.7)	9	(100)	6	(85.7)	6	(100.0)		

<sup>a</sup> IMT inspiratory muscle training

<sup>b</sup> S.D. standard deviation

<sup>c</sup> *P* value comparison between threshold IMT (overall) and control groups

<sup>d</sup> *P* value comparison among responders and non-responders of threshold IMT and control groups

FEV<sub>1.0</sub>/FVC allows us to identify ventilation obstructions and restrictions. In healthy adults, the value of FEV<sub>1.0</sub>/FVC is usually approximately 70–85% (declining with age). An FEV<sub>1.0</sub>/FVC < 70% indicates a ventilation obstruction (Table 2).

## TIMT

TIMT was scheduled once per week in the hospital and 4 days per week at home. Before each hospital TIMT session, PFT, inspiratory muscle function test, and RPE [16] scores were obtained (Table 3). According to the finding of inspiratory muscle function test, we set the target threshold for the TIMT device (Healthscan Products, Cedar Grove, NJ, USA). The target threshold of TIMT was adjusted every week to maintain the threshold to reach 30% of each patient's MIP. The initial setting range of target threshold was between 11 and 21 (14 ± 6) cmH<sub>2</sub>O, which was 10 repetitions maximum (RM) [2], and the combined RPE was between 13 and 15 as the standard TIMT intensity (Table 3). PT taught patients the diaphragm breathing exercise and combined it with TIMT device training in the hospital. Patients spent 30–45 min each day 5 days/week for 12 weeks doing these exercises [17]. During training, patients were instructed to maintain diaphragmatic breathing between 15 and 20 breaths/min. Therefore, the training intensity (range: from moderate to high) was

adjusted case by case for initially 60–70% of maximal workload. The final training intensity ranged from 19 to 29 (24 ± 3) cmH<sub>2</sub>O (Table 3). All TIMT assessments and training sessions were supervised by the PT, who, using weekly telephone calls, monitored patients' progress in and adherence to the program. All patients recorded this information in diary notes that were given to the PT at the end of the program and then evaluated by the sleep technician.

## Statistical analysis

The Mann-Whitney *U* test and the Pearson  $\chi^2$  test were used to compare differences in the basic characteristics and outcome measurements of the TIMT (overall) and control groups. The Mann-Whitney *U* test was also used to evaluate the percentage changes in the PSG, questionnaire, and PFT scores of the participants' pre- and post-TIMT. Pearson correlation analysis was used to determine the correlations the PSG, questionnaire, and PFT scores of the participants. The Kruskal-Wallis test was used for continuous variables, and Fisher's exact test was used for categorical variables in the TIMT-responder group, TIMT non-responder group, and control groups. The Wilcoxon signed-rank test was used to compare pre- and post-TIMT parameters. In addition, a multivariate linear regression analysis was used to assess correlations

**Table 2** Findings of polysomnography, questionnaire, and pulmonary function tests in our study

	Threshold IMT <sup>a</sup>						Control		P value <sup>c</sup>	P value <sup>d</sup>
	Responders <sup>+</sup> non-responders		Responders (n = 9)		Non-responders (n = 7)					
	Mean	(S.D.) <sup>b</sup>	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)		
PSG <sup>e</sup>										
Baseline AHI <sup>f</sup> (/hr)	29.0	(2.8)	33.8	(21.9)	22.8	(2.8)	37.5	(14.1)	0.106	0.003
Baseline AI (/hr)	7.0	(2.9)	8.6	(8.3)	5.0	(2.9)	15.0	(11.1)	0.004	0.022
Baseline AHI-REM <sup>g</sup> / AHI-NREM <sup>h</sup>	2.1	(0.0)	1.8	(2.1)	2.5	(0.0)	1.5	(0.5)	0.519	0.981
Baseline Lowest SpO <sub>2</sub> (%)	76.5	(5.7)	74.9	(24.0)	78.6	(5.7)	75.6	(7.2)	0.863	0.871
Percent change after intervention (%)										
AHI (/hr)	-6.0	(21.8)	-32.8*	(27.9)	26.8	(21.8)	-4.5	(30.1)	0.852	0.002
AI (/hr)	-18.2	(13.1)	-51.0*	(18.1)	23.8	(13.1)	12.8	(15.9)	0.631	0.133
AHI-REM/ AHI-NREM(%)	4.7	(3.7)	-0.9	(43.0)	36.9	(3.1)	0.5	(18.7)	0.552	0.200
Lowest SpO <sub>2</sub> (%)	2.7	(6.9)	5.0	(7.2)	-0.4	(6.9)	4.2	(18.4)	0.152	0.332
Questionnaire										
Baseline ESS <sup>i</sup> score (0–24)	10.5	(5.7)	10.4	(0.7)	10.6	(5.7)	13.0	(2.6)	0.516	0.457
Baseline PSQI <sup>j</sup> score (0–21)	8.2	(4.9)	7.3	(0.7)	9.3	(4.9)	8.6	(2.1)	0.936	0.675
Percent change after intervention (%)										
ESS score	-20.2	(2.2)	-19.8*	(42.4)	-20.8*	(2.2)	9.0	(21.2)	0.032	0.048
PSQI score	-14.5	(4.7)	-20.8	(48.6)	-9.0	(4.7)	4.4	(19.0)	0.090	0.279
Pulmonary function test										
Baseline FVC <sup>k</sup> (L)	3.5	(0.5)	3.4	(0.8)	3.6	(0.59)	3.4	(0.9)	0.842	0.974
Baseline FEV <sub>1.0</sub> / FVC <sup>l</sup> (%)	0.8	(0.1)	0.8	(0.1)	0.8	(0.1)	0.8	(0.1)	0.346	0.932
Baseline FEV <sub>6.0</sub> <sup>m</sup> (L)	3.5	(0.7)	3.5	(0.8)	3.7	(1.2)	3.4	(0.4)	0.745	0.932
Percent change after intervention (%)										
FVC (L)	7.2	(11.2)	7.5*	(0.7)	6.9*	(11.2)	-7.1*	(8.6)	0.066	0.018
FEV <sub>1.0</sub> / FVC (%)	-1.5	(6.1)	-0.7	(1.7)	-2.5	(6.1)	-1.2	(3.5)	0.419	0.597
FEV <sub>6.0</sub> (L)	9.1	(16.7)	8.5*	(0.7)	9.7*	(16.7)	-7.3*	(8.4)	0.034	0.003

<sup>a</sup> IMT inspiratory muscle training<sup>b</sup> S.D. standard deviation<sup>c</sup> P value comparison between threshold IMT (overall) and control groups<sup>d</sup> P value comparison among responders and non-responders of threshold IMT and control groups<sup>e</sup> PSG polysomnography<sup>f</sup> AHI apnea-hypopnea index<sup>g</sup> AHI-REM apnea-hypopnea index during rapid eye movement (REM) sleep<sup>h</sup> AHI-NREM apnea-hypopnea index during non-rapid eye movement (NREM) sleep<sup>i</sup> ESS Epworth sleepiness scale<sup>j</sup> PSQI Pittsburgh sleep quality index<sup>k</sup> FVC forced vital capacity<sup>l</sup> FEV<sub>1.0</sub> / FVC ratio of forced expiratory volume in 1 s and forced vital capacity<sup>m</sup> FEV<sub>6.0</sub> forced expiratory volume in 6 s

\*compared with baseline (P &lt; 0.05)

between different variables and AHI percentage changes post-intervention in the TIMT group. The area under the receiver operating characteristic curve (AUC) was estimated for the possible predictor of responsiveness to TIMT. Youden's index was calculated, and an optimal

cutoff point was determined for the predictor. Multivariate logistic regressions were used to calculate the odds ratios (ORs) and confidence intervals (CIs) of variables after confounders had been adjusted for. STATA 11 (STATA Corp., College Station, TX, USA)

**Table 3** Subjects' treatment pressure setting and total frequency (adherence) to prescribed TIMT program ( $n = 16$ )

TIMT intervention group												
Subject	Age	Sex	BMI	AHI <sup>a</sup>		Pressure setting (cmH <sub>2</sub> O)				Total frequency <sup>b</sup> (days)		
				Baseline	Percent change after intervention	Baseline	1st month	2nd month	3rd month	1st month	2nd month	3rd month
1	60	1	19.70	23.60	4.66	14	18	21	24	21	15	19
2	21	1	30.10	18.10	55.8	21	21	23	23	16	31	26
3	52	1	25.00	22.00	13.64	15	19	23	25	14	14	9
4	47	2	31.90	19.30	-0.52	11	15	17	19	29	26	25
5	69	2	24.20	31.60	-6.96	11	13	17	23	20	16	18
6	38	1	23.40	21.60	9.26	17	18	19	19	7	10	9
7	40	1	23.70	30.40	43.65	13	19	19	21	8	11	10
8	54	1	28.00	32.10	25.35	13	17	23	23	7	11	10
9	60	1	22.70	32.30	-50.00	13	17	19	21	16	10	11
10	42	2	29.80	14.20	-30.84	13	21	23	25	7	11	10
11	43	1	27.80	22.20	-40.54	15	21	25	29	22	25	28
12	59	1	26.30	41.90	-28.88	13	19	23	25	25	29	21
13	61	1	24.90	36.80	-63.04	15	19	23	27	27	26	25
14	39	1	28.70	39.30	-32.32	13	17	23	25	9	20	15
15	39	1	29.00	50.30	-30.42	13	19	19	21	17	34	30
16	42	1	23.40	27.60	35.51	13	21	25	27	28	39	39

<sup>a</sup>AHI apnea-hypopnea index

<sup>b</sup>Total frequency: summation of frequency (days) at the hospital and the subject's home

was used for all analyses. Data are expressed as mean  $\pm$  standard deviation (SD). Significance was set at  $P < 0.05$ .

## Results

### Demographics and baseline data

There were nine patients in the TIMT-responder group, seven in the TIMT non-responder group, and six in the control group (Fig. 1). Their mean age was  $50.1 \pm 12.3$  years, and mean BMI was  $26.5 \pm 3.3$ . There were no significant differences in age, BMI, or neck circumference at baseline. The post-intervention change in BMI was not significantly different (Table 1).

### Polysomnography, questionnaire, and pulmonary function tests

The baseline AHI score in the control group was significantly ( $P = 0.003$ ) higher than that in the TIMT group (Table 2). However, in the TIMT group, the baseline AHI score was not significantly different between responder group and non-responder group patients. After the 12-week intervention, the mean reductions in AHI scores were a nonsignificant  $3.50 \pm 6.2$  h and  $6.0 \pm 21.8\%$  in the TIMT group. However, the reduction in the responder group was significantly greater than

that in the control group ( $P = 0.002$ ). Similarly, the increase in ESS scores was significant in the TIMT group  $20.2 \pm 2.2\%$ . The AHI and ESS improvements in the TIMT-responder group were significant ( $P < 0.05$ ) 32.8% and 19.8%, respectively. PFT assessments showed significantly higher post-intervention scores for TIMT-group patients 7.2% and 9.1%, respectively (Table 2).

### TIMT

The average hospital TIMT training frequency was  $11.6 \pm 2.0$  days within 3 months, and the average home-based training was  $45.0 \pm 14.0$  days within 3 months (Table 3). The mean of the hospital TIMT training days were  $11.3 \pm 6.0$  days in the TIMT non-responder group within 3 months and 12.0 (SD 0.1) in the TIMT-responder group within 3 months. The mean of the home TIMT training was  $13.5 \pm 8.1$  days within 3 months in the TIMT non-responder group and  $16.1 \pm 7.8$  in the TIMT-responder group within 3 months.

### TIMT and AHI

A multivariate linear regression analysis of the TIMT group showed that baseline AHI (ORs 3.857; 95% CIs 1.095–13.586; AUC 0.825;  $P = 0.012$ ) and FEV<sub>6,0</sub> (ORs: 1.800; 95% CIs: 1.003–3.229;  $P = 0.042$ ) were significant predictors

of AHI post-intervention percent change (Table 4). The baseline AHI had a high Youden's index value that was used to predict the responsiveness of TIMT (optimal cutoff point 29.0/h; sensitivity 77.8%; specificity 85.7%).

## Discussion

We found that TIMT-group patients with moderate-to-severe OSA had less daytime sleepiness and had better AHI and pulmonary function scores and that TIMT group patients with moderate OSA had significantly better AHI scores than did TIMT-group patients with severe OSA. Other studies [2, 4, 6, 18] have also reported reductions in AHI scores after 12 weeks of physical training, and one [9] reported no improvement in nighttime AHI after 6 weeks of training. We hypothesize that at least 12 weeks of TIMT is sufficient to reduce the AHI score.

One study [19] said that a 16-week respiratory muscle training program using the didgeridoo significantly reduced daytime sleepiness, but that it did not significantly mitigate sleep apnea. Another [20] claimed that 5 weeks of expiratory muscle strength training reduced the AHI scores of patients with moderate OSA more than it did for patients with mild OSA, but it did not ameliorate their ESS scores. A clinical trial [21] reported that, after 12 weeks of oropharyngeal muscle exercises, AHI, daytime sleepiness, and OSA severity was significantly lower in their patients with moderate OAS. Changes in neck circumference correlated inversely with changes in the AHI. Another study [22] reported that 10 weeks of neuromuscular stimulation (NMS)—lingual and suprahyoid muscle strengthening—significantly reduced AHI scores in most patients with mild-to-severe OSA. Lower

baseline AHI scores were associated with larger reductions in AHI. Similarly, our TIMT study found that a 12-week TIMT program significantly reduced the AHI and ESS scores of patients with moderate-to-severe OSA. Baseline AHI was significantly negatively correlated with the percentage change post-intervention. Furthermore, OSA patients with AHI scores < 29.0/h predictably responded positively to TIMT. These therapeutic effects might be attributable to the various degrees of OSA severity among our patients and to the 12-week (long) duration of the intervention. However, the reduction in AHI was only temporary. The sustained effects of IMT on OAS severity are still not known, and additional studies are warranted.

Many studies have clinically important effects in inspiratory muscle strength and endurance after IMT, especially in cohorts diagnosed with chronic heart failure and COPD [9, 23, 24]. The intrathoracic pressures generated during IMT resemble pressures generated during OSA. IMT differs from OSA in that the former's stimulus occurs when one is awake and well-oxygenated. However, the latter's intrathoracic pressure swings, which are the typical characteristics of OSA, occur when one is asleep, and they result in hypoxemia during sleep [9]. The inspiratory muscles of OSA patients are subjected to large loads with every breath for prolonged periods during sleep and have little opportunity to rest [25]. Thus, it seems likely that the inspiratory muscles are the muscles most prone to fatigue [26]. One study reported that OSA patients were unable to increase motor unit recruitment of inspiratory muscles during incremental exercise [27]. For most OSA patients, the diaphragm appeared to be the primary inspiratory muscle during apnea. Patients with vigorous diaphragmatic and abdominal muscle responses during apnea tended to have

**Table 4** Association of percent change after intervention in apnea-hypopnea index with different variables in the threshold IMT<sup>a</sup> group ( $n = 16$ )

	Percent change after intervention in AHI <sup>b</sup> (%)			
	$\beta$	ORs <sup>c</sup>	CI <sup>s</sup> <sup>d</sup>	<i>P</i> value
Age (years)	− 0.291	1.125	0.893–1.417	0.362
Body mass index (kg/m <sup>2</sup> )	− 0.176	1.714	0.557–5.279	0.341
Baseline AHI (/hr)	− 0.483	3.857	1.095–13.586	0.012
Percent change after intervention (%)				
ESS <sup>e</sup> score	0.302	1.286	0.096–17.136	0.849
FVC <sup>f</sup> (L)	− 0.694	1.929	0.875–4.252	0.091
FEV <sub>6,0</sub> <sup>g</sup> (L)	1.033	1.800	1.003–3.229	0.042

<sup>a</sup> IMT inspiratory muscle training

<sup>b</sup> AHI apnea-hypopnea index

<sup>c</sup> ORs odds ratio

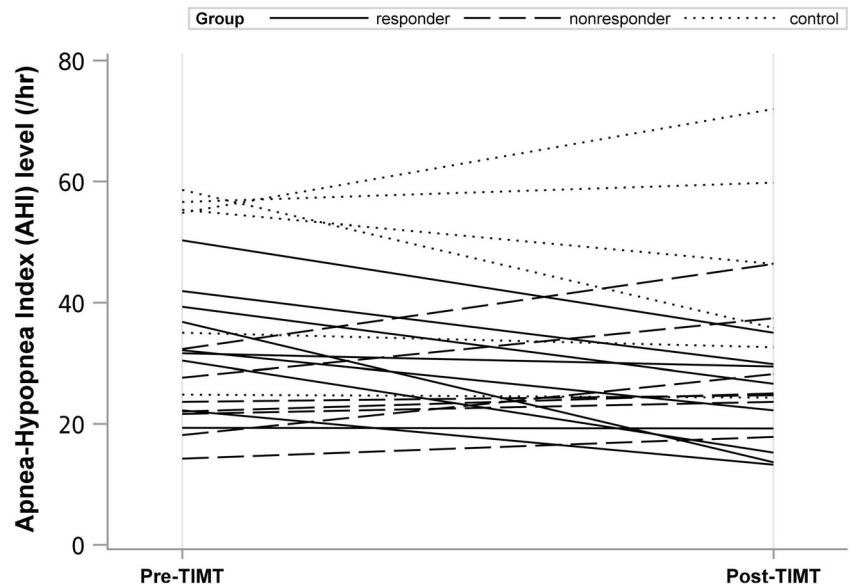
<sup>d</sup> CI<sup>s</sup> confidence interval

<sup>e</sup> ESS Epworth sleepiness scale

<sup>f</sup> FVC forced vital capacity

<sup>g</sup> FEV<sub>6,0</sub> forced expiratory volume in 6 s

**Fig. 2** Apnea-hypopnea index (AHI) level before and after receiving threshold inspiratory muscle training (TIMT), based on responders (solid line) and non-responders (dashed line) in 12-week home-based training, individually. The AHI changes of controls were also presented (dotted line). A total of 22 subjects were showed, including responders ( $n = 9$ ), non-responders ( $n = 7$ ), and controls ( $n = 6$ )



less severe OSA [28], and one study [29] reported that inspiratory pressure threshold loading (IPTL) during TIMT was the predominant activator of the diaphragm [29]. In our study, the significant changes in FVC and FEV<sub>6.0</sub> after 12 weeks of TIMT intervention might be because of increased diaphragm activity and more air entering the lungs. Therefore, the effects of TIMT might be more analogous to traditional forms of aerobic exercise than to TIMT [9].

### Strengths and limitations

The strengths of our study included the 12-week (long) duration of the training and its effects. Moreover, our patients had a greater range of OSA severity (moderate 10 cases; severe 12 cases) than did patients in other studies we reviewed, which provided extensive estimates of the treatment effects of TIMT. However, our study had some limitations. First, we did not measure respiratory muscle strength; therefore, we could not explore the mechanisms of TIMT with respiratory muscle function. Second, overall AHI in the TIMT-group was 6.0% lower than at baseline than was AHI in the control group, which was only 4.5% lower. In both groups, AHI fell in some patients but rose in others. This is probably attributable to unpredictable nightly variability. However, the individual post-intervention changes in AHI in TIMT-responder group patients were larger than that of nightly variability [30]. Third, we identified TIMT-group members who responded to intervention with a decrease in AHI (“TIMT responders”) and then compared them with control group members after our study had ended (Fig. 2). This might lead to a selection bias in the intervention group. Confounding factors were no more equally distributed between the two groups (“TIMT responders” and controls). Nevertheless, post hoc analysis showed that a subset of patients (with a lower baseline AHI score  $\leq 29.0/h$ ) might have a positive response to

TIMT intervention. Additional studies are needed to confirm this finding. Fourth, our findings cannot be generalized to dissimilar cohorts. Exclusion criteria included cardiac and pulmonary comorbidities. Moreover, the mean BMI in the intervention group was 26.2 kg/m<sup>2</sup>. This group constituted the minority of OSA patients in other countries such as the USA. Fifth, control group patients did not undergo placebo training, but their ESS scores were 9.0% lower at the end of the study. Moreover, because the ESS score was significantly better in the TIMT group, the placebo effect might partially explain this finding. Finally, our sample was small ( $n = 22$ ) and the dropout rate was high. Further, subgrouping the participants resulted in smaller samples (TIMT-responder group 9; TIMT non-responder group 7; control 6) (Fig. 1). Therefore, it is not possible to analyze the influence of sex and age on the TIMT effect. Larger clinical trials with longer follow-ups are needed to confirm our preliminary findings.

### Conclusions

TIMT is a simple, home-based therapy and is thus cost-effective respiratory training. The severity of OSA and daytime sleepiness was significantly ameliorated after TIMT. This effect indicated the potential therapeutic benefits of TIMT for OSA. It is promising as an adjunct treatment for OSA patients who are unwilling or unable to tolerate nightly CPAP.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were approved by the Institutional Review Board of National Cheng Kung University (IRB No. A-ER-103-168).

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