EFFICACY OF A NOVEL METHOD FOR INSPIRATORY MUSCLE TRAINING IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Running Head: A Novel Method for IMT in COPD

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1 **Abstract**

2 ***Background:*** Most inspiratory muscle training (IMT) interventions in patients with COPD have

3 been implemented as fully supervised daily training for 30 minutes with controlled training

4 loads using mechanical threshold loading (MTL) devices. Recently, an electronic tapered flow

5 resistive loading (TFRL) device was introduced that has a different loading profile and stores

6 training data during IMT sessions.

7 ***Objective:*** We aimed to compare the effectiveness of a brief, largely unsupervised IMT

8 protocol, conducted using either traditional MTL or TFRL on inspiratory muscle function in

9 patients with COPD.

10 ***Design:*** Twenty clinically stable patients with inspiratory muscle weakness, participating in a

11 pulmonary rehabilitation program, were randomly allocated to perform eight weeks of either

12 MTL- or TFRL-IMT.

13 ***Methods:*** Patients performed two daily home-based IMT sessions of 30 breaths (3-5 minutes

14 per session) at the highest tolerable intensity, supported by twice weekly supervised sessions.

15 Compliance, progression of training intensity, increases in maximal inspiratory mouth pressure

16 (Pi,max) and endurance capacity of inspiratory muscles (T,lim) were evaluated.

17 ***Results:*** More than 90% of IMT sessions were completed in both groups. The TFRL group

18 tolerated higher loads during the final three weeks of the IMT program (all $p<0.05$) with similar

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effort scores on a Borg CR-10 scale, and achieved larger improvements in Pi,max (p=0.02), and T,lim (p=0.02) than the MTL-group.

Limitation: Absence of a study arm involving a sham-IMT intervention.

Conclusion: The short and largely home-based IMT protocol was effective in both groups and is an alternative to traditional IMT protocols in this population. Patients in the TFRL-group tolerated higher training loads and achieved larger improvements in inspiratory muscle function than patients in the MTL group.

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1 **Introduction**

2 Inspiratory muscle training (IMT) has frequently been applied in patients with COPD to improve

3 inspiratory muscle function, exertional dyspnea, and exercise tolerance. Results of the latest

4 meta-analysis indicate that IMT as a standalone treatment yields clinically meaningful

5 improvements in inspiratory muscle strength and endurance, functional exercise capacity,

6 dyspnea, and quality of life.[1] Studies included in the meta-analysis implemented fully

7 supervised training protocols with controlled training loads, and mostly consisted of daily

8 training with mechanical threshold loading (MTL) devices for about 30 minutes.[1] To our

9 knowledge only a single shorter (42 minutes of weekly training in comparison to 150-210

10 minutes), but still fully supervised IMT protocol has previously been studied in patients with

11 COPD.[2;3] This shorter IMT protocol resulted in improvements in inspiratory muscle function that

12 were comparable to longer programs.[4-6] There is currently a scarcity of research relating to the

13 efficacy of short and largely unsupervised (home-based) IMT programs in patients with COPD.

14 **The latest systematic review[1] was further accompanied by an editorial that questioned the**

15 **role for inspiratory muscle training in the comprehensive rehabilitative treatment for patients**

16 **with COPD with the main argument that time spent supervising patients during IMT sessions**

17 **should rather be spent offering them general exercise training since this is would be more**

18 **beneficial for patients.[7]**

19 Recently, an electronic IMT device was introduced (POWERbreathe® KH1, HaB International

20 Ltd, Southam, UK), that applies a dynamically controlled tapered flow resistive loading (TFRL).[8]

Another novel feature of the electronic IMT device is that flow and pressure data are stored continuously during IMT sessions, permitting objective monitoring of home-based IMT programs from a distance. We hypothesized that this feature would reduce the amount of supervision needed for a short IMT program to be effective. **Large differences that have been observed in response to previous training interventions that were not performed fully supervised might have partly been due to insufficient compliance to the training intervention. This could however so far not be reliably assessed. This is why we believed that an intervention that has the potential to reduce weekly training time and time spent supervising patients (by electronically controlling training compliance) would be worthy of further exploration.**

We further hypothesized that TFRL would enable higher intensities of IMT to be tolerated than MTL. Gradual reduction of the *absolute* load during inhalation against the TFRL accommodates the pressure-volume relationship of the inspiratory muscles and thereby helps to maintain resistance at the same *relative* intensity throughout inhalation. This theoretically should enable patients to tolerate higher training intensities (see methods section for more detail).

The aims of the current study were therefore 1) **to assess the effectiveness of a short and largely home-based IMT program**; and 2) to find out whether performing and monitoring this program with an electronic TFRL device would enable patients to reach higher training intensities and achieve larger improvements in inspiratory muscle function than after training with a MTL device.

Methods

The study was approved by the University Hospital Leuven's Institutional Review Board (Approval Number ML7489). Interventions started after patients gave written informed consent and outcomes were evaluated after 8 weeks. Clinically stable COPD patients with inspiratory muscle weakness (maximal inspiratory mouth pressure (Pi,max) <100% of the predicted normal value) who were participating in a multidisciplinary pulmonary rehabilitation program were eligible for participation in the study. **Patients were eligible to participate in the rehabilitation program if they 1) were younger than 75 years of age; 2) had a forced expiratory volume in 1 second (FEV_1) that was less than 65% of the predicted value; and 3) if their clinical condition was stable at inclusion, with no infection or COPD exacerbation in the previous 4 weeks. Exclusion criteria consisted of 1) diagnosed psychiatric or cognitive disorders; 2) progressive neurological or neuromuscular disorders; 3) severe orthopaedic problems having a major impact on daily activities; 4) previous inclusion in rehabilitation program (<1 year); and 5) severely reduced maximal inspiratory mouth pressures (Pi,max<60cmH$_2$O). The latter group of patients with severe weakness was not eligible since they were included into an ongoing multicenter-trial.[9] Allocation concealment was ensured by using a previously described method to assign patients** randomly to either MTL or TFRL-IMT, using sequentially numbered, opaque sealed envelopes.[10]

Training method. In analogy to training protocols that have frequently and successfully been applied in healthy subjects,[11] patients performed two daily sessions of 30 breaths of MTL-IMT

1 (Threshold®, Philips Respironics, Brussels, Belgium **or POWERbreathe® Medic, HaB**

2 **International Ltd., Southam, UK)** or TFRL-IMT (POWERbreathe® KH1, HaB International Ltd.,

3 Southam, UK) at the highest tolerable intensity. **Since the highest resistance that the**

4 **Threshold® trainer can provide is 41 cmH$_2$O, the POWERbreathe® Medic device (maximal**

5 **resistance of up to 90cmH$_2$O) was used in patients who were able to tolerate higher training**

6 **intensities.** An example of a supervised TFRL-IMT session is provided in a supplemental video

7 clip. Differences in the characteristics of the applied inspiratory resistances between devices

8 are summarized in Figure 1. Methods used to obtain these data from both the MTL and the

9 TFRL device using continuous registrations of flow and pressure with external, laboratory

10 measurement equipment have previously been reported.[8] Figure 1 illustrates a comparison

11 between a single inhalation undertaken by the same patient during either mechanical pressure

12 threshold loading (MTL - left panel) or tapered flow resistive loading (TFRL - right panel). The

13 TFRL device applies a tapered resistance provided by an electronically controlled, dynamically

14 adjusted valve, which contrasts to the constant load applied by the MTL device. After flow-

15 independently overcoming an initial threshold load (in this case 50 cmH$_2$O corresponding to

16 60% of subjects Pi,max on both devices) pressure remains constant during MTL (left panel),

17 whereas during TFRL, pressure is volume-dependently tapered during inhalation (right panel).

18 This reduction of the *absolute* load during inhalation against the TFRL accommodates the

19 pressure-volume relationship of the inspiratory muscles and thereby helps to maintain

20 resistance at the same *relative* intensity throughout inhalation.[12] This application of a tapered

load allows end-inspiratory volume to approach total lung capacity, even at high training intensities. It is apparent from the example shown in Figure 1 that this patient with COPD, training at 60% of his $P_{i,max}$, was able to achieve an inspiratory volume during TFRL (right panel) that was twice that achieved during MTL (left panel). Furthermore, due to this higher inspiratory tidal volume, more external work was performed per breath (see Figure 1, AUC), despite of a lower mean inspiratory pressure during inhalation. These observations confirm limitations to the intensity of pressure threshold loading that were recently identified in healthy people.[13] In this study, the authors found that the amount of external mechanical work undertaken during loading >60% of $P_{i,max}$ decreased considerably due to impairment of tidal volume expansions and premature termination of inhalation.[13] In this way high intensity TFRL (in contrast to MTL) provides a training stimulus to the inspiratory muscles at shorter lengths which corresponds to operating lengths of these muscles during exercise (especially in patients with COPD who dynamically hyperinflate).

The tapered flow resistive loading (TFRL) approach is novel and developed specifically to overcome the limitations of previous inspiratory flow resistive loading (IFRL) techniques and devices (Pflex, DHD-IMT and TIRE).[14-16] The inherent limitation of traditional non-targeted IFRL devices is that inspiratory pressure (i.e. training load) varies with inspiratory flow (the slower the inspiratory flow, the smaller the resistive load) and not only with orifice size (the smaller the orifice, the greater the resistive load). Whilst this specific limitation is overcome by devices that provide biofeedback of load (TIRE) or flow (DHD-IMT), these devices have

their own limitations. The Test of Incremental Respiratory Endurance (TIRE; RT2 and Trainair)

overcomes the primary limitation of IFRL by setting inspiratory pressure relative to a

participant's Pi,max, and by providing biofeedback via a target template. However the

functional relevance of the approach is questionable, since each breath manoeuvre requires a

full inspiratory inhalation through a very small inspiratory orifice (comparable to the

inspiratory valve leak of a mouth pressure meter), resulting in unphysiological inspiratory

flow (inspiratory time can exceed 20 seconds); the method is also time consuming, and very

demanding for the patient. The main limitation of the target flow IMT (e.g. combining an

incentive spirometer with DHD-IMT) is that there is no monitoring or control of inspired

volume, which is a crucial determinant of inspiratory work.[13]

All of these limitations are overcome with the TFRL device. The valve in the TFRL device

adjusts dynamically (100 times per second), in real-time to accommodate within breath

changes in inspiratory flow rate. These adjustments maintain the pressure load that is

delivered to the inspiratory muscles at the same relative intensity (percentage of Pi,max)

across the vital capacity. It is a dynamic adjustment to a prescribed target, not the passive

decrease in pressure that occurs in response to decreasing inspired flow rate with IFRL.

Moreover, TFRL also incorporates an initial threshold load that must be overcome before the

flow dependent, dynamical adjustments to the resistive load come into play.

Perhaps more importantly, TFRL also facilitates simultaneous high pressure and high flow

training, across the full vital capacity (typical inspiratory times at resistances of ~50-55%

Pi,max are about 2 seconds; see also supplementary video, Table 2 and previously published data[8]). Tidal volume is unconstrained by functional weakening of the inspiratory muscles, because the load tapers during inhalation, thereby permitting full use of the inspiratory capacity, maintenance of maximal inspiratory flow rate, and maximized inspiratory muscle work and power. Patients with expiratory flow limitation (EFL) must overcome high elastic and resistive loads (due to EFL and acute-on-chronic dynamic hyperinflation) during exercise, whilst simultaneously being forced to generate high inspiratory flow rates (high inspiratory work and power) to meet their increasing ventilatory needs. Further functional weakening occurs by being forced to operate at shorter lengths due to increases in end-expiratory lung volume. The loading characteristics delivered by TFRL are optimized to these demands and it is hypothesized that the resulting training stimulus will prepare the inspiratory muscles better for these specific task requirements.

A further advantage of the TFRL device over previously used MTL devices (especially during unsupervised training programs) might be the ability to store parameters of up to 38 IMT sessions. Continuous registrations of pressure and flow (500Hz) provide data on the external work of breathing and allow control of both quantity and quality of unsupervised training sessions. The device reliably stores data on average mean pressure (cmH$_2$O), average mean power per breath (Watt), average peak flow per breath (L/s) and total external mechanical work of breathing (Joules) during training sessions of 30 breaths.[8]

1   Two weekly IMT sessions in both the TFRL- and the MTL- group were performed under

2   supervision of a physiotherapist and all other sessions were performed by the patients at home,

3   without supervision. **Patients had to wear nose clips during all IMT sessions. Both groups were**

4   **instructed to perform fast and forceful inspirations and were encouraged to achieve maximal**

5   **inhalation and exhalation with every breath** (start inhaling from residual volume and to finish

6   their breath as close to total lung capacity as possible). The main aim of this training method

7   was to increase inspiratory muscle power output by improving both strength and velocity of

8   contractions over the full range of motion. We aimed to initiate IMT at a minimum of 40% of

9   baseline Pi,max (assessed from residual volume). In both groups inspiratory load was increased

10   during each supervised session to the highest tolerable intensity at that moment. Intermediate

11   measurements of Pi,max were performed once weekly. The *a priori* aim in both groups was to

12   increase training loads during the program to equal at least 50% of the patients' actual Pi,max

13   in every week. Rates of perceived inspiratory effort on a modified CR-10 Borg Scale,[17] and

14   subjective impressions of physiotherapists during supervised sessions, were taken into account

15   to determine the highest tolerable load for each individual patient. **Respiratory effort scores**

16   **between 4 and 6 were aimed at to stimulate patients to train at the highest tolerable**

17   **intensity.** Compliance with the IMT protocol was assessed by a written training diary in the MTL

18   group and by analyzing objectively registered, and automatically stored training session

19   parameters (pressure, flow, power, and work) in the TFRL group. Physiotherapists compared

20   performance data from the TFRL-group during supervised sessions with results from home-

1 based sessions to elicit full effort during unsupervised IMT. This was not possible in the MTL

2 group.

3 **Measurements.** Primary (Pi,max and inspiratory muscle endurance) and secondary endpoints

4 (changes in breathing pattern during the inspiratory muscle endurance task) were assessed by

5 experienced investigators who were not involved with the IMT sessions and thereby blinded to

6 group allocation. **The physiotherapists who provided the IMT sessions to the patients in both**

7 **groups were not blinded to the intervention.**

8 *Inspiratory muscle strength.* Pi,max was recorded at the mouth as a surrogate of inspiratory

9 muscle force. Measurements were performed from residual volume using the technique

10 proposed by Black and Hyatt.[18] An electronic pressure transducer was used (MicroRPM;

11 Micromedical, Kent, UK). Assessments were performed on two separate days and were

12 repeated at least 5 times on each occasion until the three best measurements differed from

13 each other by less than 5cmH$_2$O. Reference values published by Rochester and Arora were used

14 to define normal respiratory muscle force.[19]

15 *Inspiratory muscle endurance.* Patients were asked to breathe against a sub maximal inspiratory

16 load provided by the TFRL device (POWERbreathe® KH1, HaB International Ltd., Southam, UK)

17 until task failure due to symptom limitation (T,lim). At baseline an inspiratory load was selected

18 that allowed patients to continue breathing for 3-7 minutes. After an initial familiarization trial

19 at 40% Pi,max the load was either increased or decreased for the next test based on the

20 performance of the patient during the trial. Up to two additional trials were performed on the

same day to determine a load that would allow patients to continue breathing for 3-7 minutes.

On a separate day the test was repeated at least once against the established load and the best

result was recorded as the baseline T,lim. Breathing instructions were the same as during the

training sessions. Number of breaths, average inspiratory time (Ti) as a fraction of the total

respiratory cycle duration (Ttot), average mean load, average mean power, and total external

inspiratory work were derived from continuous measurements of flow and pressure during the

test and recorded by the previously validated electronic loading device.[8] Simultaneous

continuous measurements of flow and pressure were also performed with external, laboratory

measurement equipment according to methods previously described.[8] After 8 weeks of IMT the

endurance test was repeated using an identical load. Improvements in T,lim and changes in

breathing parameters were recorded as main outcomes. A limit of 15 minutes was handled as

the maximum duration of the test performed after 8 weeks. In case patients were not symptom

limited at this time point the assessor stopped the test.

Pulmonary function. Spirometry and whole body plethysmography were performed according

to international guidelines for pulmonary function testing (Vmax Autobox, Sensor Medics,

Bilthoven, the Netherlands).[20;21]

Statistical Analysis. In the absence of an established minimal clinically important difference,

the sample size calculation was based on a Pi,max effect size of 1.41 that was reported in a

study by Belman and colleagues on the effects of high-intensity vs. low-intensity targeted

resistive IMT in COPD.[22] To detect this effect size with a degree of certainty (statistical power)

1   of 80% and risk for type I error (α) < 5% a sample size of 7 patients for each group was

2   calculated. Taking an expected drop-out rate of 30% into account we included 10 patients in

3   each group. Differences between the MTL and the TFRL group after the intervention were

4   compared, adjusting for baseline differences, in an analysis of covariance (ANCOVA).[23] **The idea**

5   **behind using analysis of covariance is that a correction is made for regression to the mean.[24]**

6   **Regression to the mean at follow-up is expected to occur when the mean baseline values of**

7   **the intervention and control group differ. Correction for regression to the mean using**

8   **analysis of covariance was achieved in our analysis by addition of the baseline value as a**

9   **covariate in an analysis in which the follow-up measurement was the outcome variable and**

10   **group allocation was the independent variable. Not correcting for baseline differences in this**

11   **way has been shown to lead to either over- or underestimation of the estimated intervention**

12   **effect.[25]**

13   **Two-Way ANOVA using post-hoc tests with Bonferroni corrections on a group x time**

14   **interaction were performed to compare tolerated training intensities between groups. This**

15   **was done to investigate whether the group (TFRL or MTL) had the same influence on training**

16   **intensity at all time points.**

17

1 **Results**

2 Twenty patients were selected and randomized between January and December 2012 (10

3 patients in the TFRL group and 10 patients in the MTL group). **A diagram summarizing the flow**

4 **through the study is presented in Figure 2. All patients who were recruited for this study were**

5 **categorized in spirometric GOLD stages II and III.** After 8 weeks of IMT outcomes from 10

6 patients in the TFRL and 9 patients in the MTL group were analyzed. One patient from the MTL

7 group dropped out of the study during the final week of the intervention after a hospitalization

8 due to an acute exacerbation. Baseline characteristics of participants are presented in Table 1.

9 Groups were well matched for gender, age, inspiratory muscle function and pulmonary

10 function. **Patients in the TFRL group had a normal average weight, whereas patients from the**

11 **MTL group were on average overweight.** Patients in both groups had comparable impairment

12 of baseline Pi,max. T,lim and relative intensity (%Pi,max) of the endurance breathing task were

13 also comparable between groups (Table 1).

14 *Training Progression.* In the TFRL group 95±7% of sessions (based on data stored by the

15 electronic device) and 93±6% of the sessions in the MTL group (based on data from written

16 patient diaries) were completed. Duration of the supervised training sessions ranged from 3 to

17 5 minutes corresponding to a daily training duration for both groups ranging from 6 to 10

18 minutes. Progression of training intensity in both groups is illustrated in Figure 3. Patients in the

19 TFRL group increased their training load from 45±8% of their baseline Pi,max, in the first week

20 of training, to 84±16% in week 8 (p<0.001). Patients in the MTL group increased their training

1 load from 38±11% of their baseline Pi,max value, to 61±19% ($p<0.001$). Patients in the TFRL

2 group tolerated a significantly higher training load during the final three weeks of the training

3 protocol (all p <0.05; Figure 2). Despite the differing training intensities, average Borg CR-10

4 scores at the end of the supervised training sessions were similar for the TFRL group and MTL

5 group for perceived inspiratory effort (3.0±1.6 vs. 3.6±1.1, respectively; p=0.35) and perceived

6 dyspnea (2.3±0.6 vs. 2.0±0.2, respectively; p=0.70).

7 *Pulmonary function.* **There were no significant improvements in pulmonary function in either**

8 **of the two groups (both within group p>0.05) and also no differences in improvements**

9 **between groups (FEV$_1$*%pred*: 3±7 vs. 4±9, p=0.662; FVC*%pred*: 4±9 vs. 9±16, p=0.495; and**

10 **FRC*%pred*: -14±22 vs. -10±20, p=0.714).**

11 *Inspiratory Muscle Strength.* Both groups exhibited significant improvements in Pi,max (both

12 within group p<0.01), but patients in the TFRL group showed a significantly larger increase

13 (TFRL 31±4 cmH$_2$O, **67±17 to 99±16 cmH$_2$O** vs. MTL 18±6 cmH$_2$O, **70±14 to 89±26 cmH$_2$O**;

14 p=0.02).

15 *Inspiratory Muscle Endurance.* Changes in breathing parameters during the endurance

16 breathing task are summarized in Table 2. Increases in T,lim, number of breaths and total work

17 were significantly higher in the TFRL group. Patients in this group were also able to achieve

18 larger increases in their peak inspiratory flow during the loaded breathing task, indicating

19 enhanced velocity of shortening of the inspiratory muscles under load. This resulted in larger,

20 statistically significant improvements in inspiratory muscle power output and a shortening of

16

1   the duty cycle in the TFRL group. Increases in average inspiratory volume and average work

2   performed per breath were only significantly different from baseline in the TFRL group (Table

3   2).

4

Discussion

We studied the effects of a short and largely home-based IMT program in patients with COPD. Patients were compliant with the IMT protocol and achieved significant improvements in inspiratory muscle strength and endurance. Patients in the TFRL group tolerated significantly higher training loads, as well as achieving significantly larger and more comprehensive improvements in inspiratory muscle function (i.e. strength, power, shortening velocity, and endurance) than patients in the MTL group.

Effectiveness of the novel training method in comparison with previous IMT protocols. The average improvements in Pi,max of 18cmH$_2$O (MTL) and 31cmH$_2$O (TFRL) after 8 weeks of IMT in the current study both exceeded the average increase in Pi,max of 13cmH$_2$O that was reported in the latest meta-analysis of randomised controlled trials of standalone IMT.[1] Furthermore, the average increase in breathing endurance time reported in this meta-analysis (261 seconds) was exceeded in the TFRL group (532 seconds) and was approached in the MTL group (187 seconds).[1] These data are encouraging, since all RCTs included in the meta-analysis implemented fully supervised training protocols with daily training durations of 30 minutes.[1] Our IMT protocol was largely home-based and consisted of only two daily sessions of 30 breaths (~6-10 minutes) of daily training. Despite of this short daily training duration the program resulted not only in improved strength but also improved endurance capacity of the inspiratory muscles. Improvements in Pi,max of 25% (MTL) and 45% (TFRL) after this home-based program are also similar to findings from a fully supervised IMT protocol that used

18

1 shorter training durations (29% to 32% increases in Pi,max with 42 minutes of weekly

2 training).[2;3] This short protocol also resulted in improved endurance capacity.[26] These short IMT

3 protocols are similar to those that have been applied successfully in healthy subjects.[11] The

4 current findings support the feasibility and efficacy of a brief, intense, and largely home-based

5 IMT protocol in patients with COPD and demonstrate that this protocol seems to be most

6 effective when carried out and supervised with an electronic TFRL device. Reductions in time

7 investment in comparison to previous protocols might help to improve both adherence of

8 patients and to increase motivation of health care providers to prescribe and provide the

9 intervention.

10 ***Comparing effects of MTL- and TFRL-IMT.*** One factor that might have contributed to better

11 outcomes in the TFRL group during this home-based IMT program was the ability to objectively

12 monitor unsupervised training sessions. In contrast to the TFRL group, monitoring of the MTL

13 group completely relied on self-reported data of completed IMT sessions, which did not allow

14 us to control the quality of the unsupervised sessions and may also have over-estimated

15 training compliance. Another explanation for the larger improvements of inspiratory muscle

16 function in the TFRL group might have been related to the differences in the applied loads (see

17 methods). Inspiratory effort reported by patients at the end of supervised IMT sessions was

18 comparable between the MTL and the TFRL group, which confirms that both groups were

19 encouraged equally to perform IMT at the highest tolerable intensity.

Changes in breathing pattern characteristics during loaded breathing. We observed

significantly larger increases in inspiratory flow during the loaded breathing task in the TFRL

group, which resulted in larger increases in inspiratory power output and reductions in

inspiratory time. Significant enhancement in the velocity of inspiratory muscle shortening

during resistive breathing tasks, and increases in the size of type 2 muscle fibers following MTL-

IMT have been observed previously in patients with COPD.[6;27] These improvements might be of

clinical relevance to patients since they should prepare them for the requirements that

increasing ventilatory needs impose on their inspiratory muscles during physical activity. During

exercise in COPD functional weakening of inspiratory muscles occurs when they are forced to

contract at shorter lengths (high lung volumes) and higher velocities (shortened time for

inspiration). At the same time these muscles face increasingly higher elastic loads during

exercise due to progressive dynamic hyperinflation. This results in an increase in motor drive to

the inspiratory muscles that is associated with an increased sense of respiratory effort and

dyspnea.[28;29] Further studies are warranted to explore whether the improvements in inspiratory

muscle power characteristics with TFRL-IMT can help to reduce efferent drive to these muscles

and improve the perception of respiratory effort and dyspnea during exercise.

Limitations. A valid concern is that we were assessing the efficacy of our interventions against

the background of improvements due to simultaneous exercise training. A limitation of this

study is therefore the absence of a control group performing a pulmonary rehabilitation

program without IMT.[30] On the other hand the average improvements in Pi,max observed after

1 both of our interventions exceed improvements in Pi,max of 11cmH$_2$O that were reported

2 previously after a similar, but longer, pulmonary rehabilitation program without additional

3 IMT.[31] We further focused exclusively on measurements of inspiratory muscle function and

4 found significantly larger improvements in the TFRL group, which is suggesting a true training

5 effect. Our study was not designed and sufficiently powered to investigate whether this

6 additional improvement in inspiratory muscle function yielded greater changes in exercise

7 capacity and quality of life. A large, adequately powered RCT examining the effects of IMT as an

8 adjunct to pulmonary rehabilitation on functional exercise capacity and quality of life is

9 currently addressing this question.[9] Another shortcoming is that improvements in Pi,max were

10 only assessed from residual volume, and not from FRC, or higher volumes that are more

11 representative of operating lung volumes during rest and exercise in these patients. Length

12 specificity of inspiratory muscle training has been demonstrated previously,[32] and it might be

13 that TFRL has a larger effect on pressure generating capacities of inspiratory muscles at shorter

14 muscle lengths (i.e. higher lung volumes) than MTL-IMT which should be further studied.

15 Finally, the endurance breathing task was only performed against TFRL and not against MTL.

16 Larger improvements in endurance capacity and more pronounced changes in breathing

17 pattern in the TFRL group might therefore have been related to the higher task specificity of the

18 test. **Based on the current data it is unclear whether the observed changes in breathing**

19 **pattern are restricted to the specific test that we performed or whether these will translate**

to less specific tasks such as breathing during exercise or breathing against a different type of inspiratory resistance. This should be investigated in future studies.

Conclusions

The presented IMT method required less time investment from both health care providers and patients and resulted in significant improvements in inspiratory muscle function in comparison with previously described fully supervised IMT interventions in patients with COPD. The largely home-based program was most efficient when performed and supervised with an electronic TFRL device. Patients in the TFRL group tolerated higher training intensities and achieved significantly larger improvements in inspiratory muscle function than patients using conventional MTL devices for the same perceived effort. **Costs and effectiveness of the different approaches need to be weighed against each other when implementing the intervention in clinical practice.** Further research should be directed towards assessing the effects of this novel IMT method on inspiratory muscle function and dyspnea perception during whole body exercise in patients with COPD.

8   **Competing interests**

9   AKM acknowledges a beneficial interest in the POWERbreathe® inspiratory muscle trainers in

10   the form of a share of royalty income to the University of Birmingham and potential income to

11   Brunel University. She has also provided consultancy services to POWERbreathe International

12   Ltd., but has not done so since October 2013.

13

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Tables

Table 1: Baseline characteristics.

	TFRL (n=10)	MTL (n=10)
Sex (F/M)	5/5	5/5
Age (years)	64±5	67±8
BMI (Kg/m^2)	22.6±6.6	27.7±6.0
Pi,max (cmH$_2$O)	67±17	70±19
Pi,max (%pred.)	67±10	71±15
T,lim (sec)	219±71	208±139
Intensity Endurance test	50±11	50±13
FEV$_1$ (%pred.)	60±17	54±15
FVC (%pred.)	91±16	79±22
FRC (%pred.)	**132±35**	**138±36**

Table 1 Legend: TFRL = tapered flow resistive loading; MTL = mechanical threshold loading; F = female; M = male; BMI = Body Mass Index; Pi,max = maximal inspiratory pressure; T,lim = time that patients could sustain the endurance breathing task until symptom limitation; FEV$_1$ = forced expiratory volume in one second; FVC = forced vital capacity; FRC = functional residual capacity. Values are expressed as mean ± standard deviation.

Table 2: Changes in breathing characteristics during the inspiratory muscle endurance task.

	TFRL (n=10)			MTL (n=9)			p-value[#]
	Pre	**Post**	Changes	**Pre**	**Post**	Changes	
Δ tlim *sec*	**219±71**	**751±168**	+532±204*	**193±124**	**361±309**	+187±233*	0.02
Δ Breaths *n*	**32±12**	**95±34**	+64±27*	**32±18**	**52±33**	+21±33*	0.03
Δ Total Work *J*	**132±73**	**539±235**	+407±230*	**157±188**	**331±466**	+193±245*	0.03
Δ Avg. Inspiratory Time (ti) *sec*	**2.7±1.3**	**1.6±0.6**	-1.1±0.8*	**2.3±1.1**	**2.0±0.8**	-0.2±0.3	0.02
Δ Ti/Ttot (duty cycle) *%*	**37±6**	**21±8**	-16±6*	**37±7**	**33±11**	-5±5*	0.02
Δ Avg. Peak Inspiratory Flow *L/sec*	**2.1±0.5**	**3.4±0.7**	+1.4±0.6*	**1.9±0.5**	**1.9±0.8**	+0.1±0.3	0.001
Δ Avg. Mean Power per Breath *Watt*	**1.9±0.6**	**4.2±1.5**	+2.3±1.0*	**2.0±0.9**	**2.5±1.7**	+0.5±1.2	0.004
Δ Avg. Inspiratory Volume *L*	**1.8±0.7**	**2.2±0.6**	+0.4±0.2*	**1.6±0.7**	**1.7±1**	+0.1±0.1	0.25
Δ Avg. Work per Breath *J*	**4.7±3.5**	**6.4±3.9**	+1.7±1.0*	**4.6±3.7**	**5.3±5.2**	+0.7±1.1	0.27

Table 2 Legend: TFRL = tapered flow resistive loading; MTL = mechanical threshold loading; tlim = time that patients could sustain the endurance breathing task; Ti = inspiratory time; Ttot = time of a complete respiratory cycle; * indicates a statistically significant increase from baseline to 8-weeks within groups (p<0.05). Changes are expressed as differences (Δ) between pre and post values and presented as means ± standard deviate ons. [#]P-values are reported for between group comparisons (TFRL *vs* MTL) of post-intervention values with baseline values entered as covariates (ANCOVA).

Figure Legends

Figure 1: Comparison between two training devices during a typical inhalation against a resistance corresponding to 60% of baseline Pi,max (50cmH$_2$O). AUC = Area under the curve for total external inspiratory work as integrated from mouth pressure (cmH$_2$O) and volume (L) signals over time.

Figure 2: **A diagram summarizing the flow of patients through the study.**

Figure 3: Progression of training intensity expressed as a percentage of baseline Pi,max. TFRL = tapered flow resistive loading; MTL = mechanical threshold loading. * = p<0.05 between groups. Dotted lines represent the highest average training intensities reached in the TFRL and the MTL group, respectively.
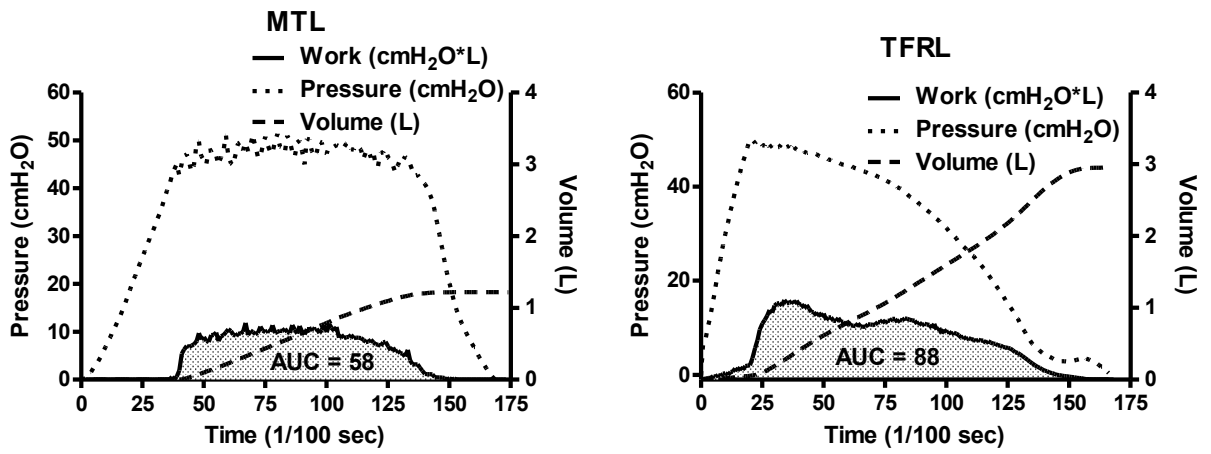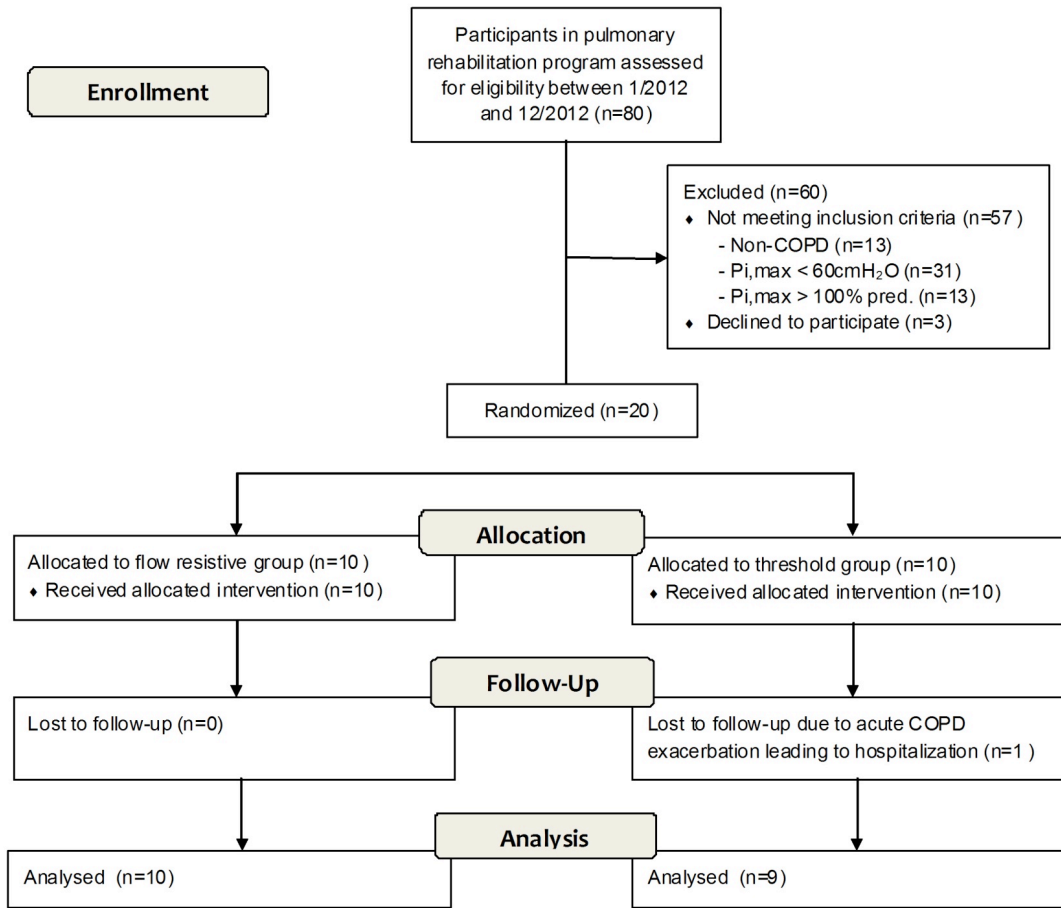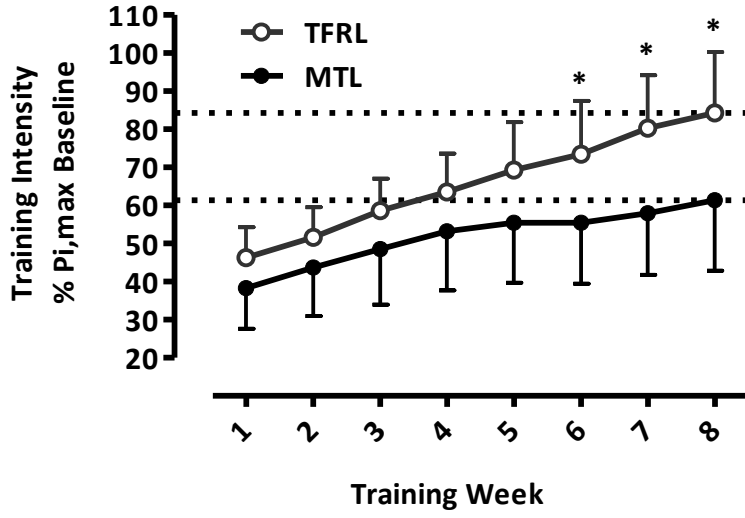
Figures

Figure 1:

Figure 2:

Enrollment

Participants in pulmonary rehabilitation program assessed for eligibility between 1/2012 and 12/2012 (n=80)

Excluded (n=60)
- ♦ Not meeting inclusion criteria (n=57)
  - Non-COPD (n=13)
  - Pi,max < 60cmH$_2$O (n=31)
  - Pi,max > 100% pred. (n=13)
- ♦ Declined to participate (n=3)

Randomized (n=20)

Allocation

Allocated to flow resistive group (n=10)
- ♦ Received allocated intervention (n=10)

Allocated to threshold group (n=10)
- ♦ Received allocated intervention (n=10)

Follow-Up

Lost to follow-up (n=0)

Lost to follow-up due to acute COPD exacerbation leading to hospitalization (n=1)

Analysis

Analysed (n=10)

Analysed (n=9)

Figure 3:

Video Legends

Video 1 Legend: Example of a supervised inspiratory muscle training session performed with the tapered flow resistive loading device illustrating 1) the selection of an appropriate training load; 2) administration of BORG CR-10 scores for dyspnea and inspiratory effort before and after the training session; and 3) registration of training session data (pressure, flow, power, and work) that are stored by the handheld training device in a personalized training diary.