# Inspiratory muscle training protocol for patients with chronic obstructive pulmonary disease (IMTCO-study): a multicentre randomised controlled trial

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-003101 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 22-Apr-2013 |
| Complete List of Authors: | Charususin, Noppawan; University of Leuven, Department of Rehabilitation Sciences; Thammasat University, Department of Physical Therapy<br>Gosselink, Rik; University of Leuven, Department of Rehabilitation Sciences; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division<br>Decramer, Marc; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division<br>McConnell, Alison; Brunel University, Centre for Sports Medicine and Human Performance<br>Saey, Didier; Laval University, Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec<br>Maltais, Francois; Laval University, Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec<br>Derom, Eric; University Hospital Ghent, Department of Pulmonology<br>Vermeersch, Stefanie; University Hospital Ghent, Department of Pulmonology<br>Helvoort, Hanneke; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Heijdra, Yvonne; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Klaassen, Mariska; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Glöckl, Rainer; Schön Klinik Berchtesgaden, Department of Respiratory Medicine & Sports Therapy<br>Kenn, Klaus; Schön Klinik Berchtesgaden, Department of Respiratory Medicine & Sports Therapy<br>Langer, Daniel; University of Leuven, Rehabilitation Sciences; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division |
| Primary Subject Heading: | Respiratory medicine |
| Secondary Subject Heading: | Rehabilitation medicine |
| Keywords: | Clinical trials < THERAPEUTICS, Chronic airways disease < THORACIC MEDICINE, Emphysema < THORACIC MEDICINE |
| | |

**Abstract:**

Introduction: Inspiratory muscle training (IMT) has been applied during pulmonary rehabilitation in COPD patients. However, it remains unclear if the addition of IMT to a general exercise training program leads to additional clinically relevant improvements in COPD patients. In this study, we will investigate whether the addition of IMT to a general exercise training program improves six-minute walking distance, health-related quality of life, daily physical activity, and inspiratory muscle function in COPD patients with inspiratory muscle weakness.

Methods and analysis: COPD patients (n=170) with inspiratory muscle weakness (Pimax < 60cmH2O or < 50%pred) will be recruited to a multicentre randomised placebo controlled trial of IMT and allocated into one of the two groups. Patients in both groups will follow a three month general exercise training programme, in combination with home based IMT. The IMT will be performed with a recently developed device (POWERbreathe® KH1). This device applies an inspiratory load that is provided by an electronically controlled valve (variable flow resistive load). The intervention group (n=85) will undertake an IMT program at a high intensity (≥ 50% of their PI,max) whereas the placebo group (n=85) will undertake IMT at a low training intensity (≤ 10% of PI,max). Total daily IMT time for both groups will be 21 minutes (six cycles of 30 breaths). Improvement in the six-minute walking distance will be the primary outcome. Inspiratory muscle function, health-related quality of life, and daily physical activity, will be assessed as secondary outcomes.

Ethics and dissemination: Ethics approval has been obtained from relevant centre committees and the study has been registered in a publicly accessible clinical trial database. The results will be easily interpretable and should immediately be communicated to health care providers, patients and the general public. Results can be incorporated into evidence based treatment recommendations for clinical

practice.

ClinicalTrials.gov: NCT01397396

## Article summary

### Article focus

- Inspiratory muscle dysfunction occurs in patients with COPD and is associated with dyspnea and decreased exercise capacity.
- What are the additional functional and health benefits of adding home-based IMT to a general exercise training program in COPD patients with inspiratory muscle weakness?

### Key messages

- This multicentre randomised controlled trial will investigate and report on the additional improvements in exercise tolerance after adding IMT to a 3-months general exercise training program. Inspiratory muscle function, health-related quality of life, and daily physical activity, will be assessed as secondary outcomes.
- The study will focus on COPD patients with inspiratory muscle weakness defined as Pimax < 60cm$H_2O$ or < 50%pred.
- The variable flow resistive training method applies a specific training stimulus and allows full monitoring of the compliance with the home based IMT.

### Strengths and limitations of this study

- In contrast to previous studies, we designed a large, adequately powered, multi-centre randomised controlled trial to investigate the effects of IMT in COPD patients with inspiratory muscle weakness. The results from this study will help to clarify whether adjunctive IMT leads to

greater functional improvements (exercise capacity, quality of life, participation in daily activity, and symptoms) than exercise training alone.

- The results will be focused on effects in COPD patients with inspiratory muscle weakness. The results of this study will therefore primarily be applicable in COPD patients with inspiratory muscle weakness.

## Background

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality worldwide.[1,2] COPD is characterized by persistent expiratory flow limitation that is usually progressive.[3] Dyspnea is the most prominent exercise-limiting symptom of the disease,[4] which leads to chronic avoidance of physical activities. Consequently, low physical activity levels contribute to skeletal muscle deconditioning and exercise capacity reduction, which impact negatively on health related quality of life.[5,6] Inspiratory muscle dysfunction is another extrapulmonary manifestation that is often present in patients with COPD.[7,8] It contributes to hypoxemia, hypercapnia, dyspnea and decreased exercise tolerance.[9-11] Pulmonary rehabilitation including exercise training, education, nutritional intervention, and psychosocial support is a standard care for COPD patients to counteract extrapulmonary disease manifestations.[6,12,13] Inspiratory muscle training (IMT) has also been applied frequently and is extensively studied in recent years in patients with COPD.[14] From meta-analyses of RCT's in patients with COPD it can been concluded that IMT as a standalone therapy improves inspiratory muscle function (strength and endurance), decreases symptoms of dyspnea, and improves exercise capacity.[14,15] The value of IMT as an add-on to a general exercise training program is however still under debate.[16-19] While IMT always results in significant improvements in inspiratory muscle function, its additional effects on more clinically relevant outcomes (e.g. functional exercise capacity and quality of life) are insufficiently supported by scientific evidence so far.[14] From subgroup

analyses in the most recent meta-analysis it was concluded that significant additional effects of IMT on more clinically relevant outcomes are more likely to be found in patients with inspiratory muscle weakness.[12] This was previously defined as a maximal inspiratory mouth pressure (Pi,max) of less than 60cm$H_2O$.[14] It has therefore been recommended that future studies in patients with COPD should focus specifically on patients with more pronounced inspiratory muscle weakness.[14,20] It was recently shown that adjunctive IMT led to significantly greater functional improvements in a well designed randomised controlled trial in patients with chronic heart failure selected for inspiratory muscle weakness.[21] Comparable RCTs in patients with COPD are so far lacking.[14] We are therefore carrying out a large, adequately powered, multi-centre randomised controlled trial on the effects of IMT as an adjunct therapy to a general exercise training program in COPD patients with inspiratory muscle weakness. Recommendations on the use of IMT as an adjunct to general exercise training in these patients in international guidelines are ambiguous.[12] The outcome of this study will therefore have a direct impact on clinical practice, as the results will clarify whether adjunctive IMT leads to superior clinically relevant improvements for COPD patients. Functional outcomes of relevance to patients (exercise capacity, quality of life, participation in daily physical activity, and symptoms) were therefore chosen as main outcomes.

One of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT should allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise.[22] In the present study we will use a recently developed IMT device that applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). In contrast to the traditionally applied threshold loading, this variable flow resistive load is specifically challenging the inspiratory muscles at higher lung volumes, and may lead to larger training effects in COPD patients who develop dynamic hyperinflation during exercise. Besides these potentially beneficial characteristics of the applied load another advantage of the device is the

ability to store home-based training data for up to 40 sessions. Continuous registrations of pressure and flow at 500 Hz provide data on the external work of breathing and enable the verification of both quantity and quality of unsupervised training sessions. The latter is of particular importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision.

## Aims

This study will examine the effects of adding a well controlled, high-intensity inspiratory muscle training (IMT) program to a 3-month general exercise training program, using a large, multi-centre, randomised controlled design, in COPD patients with inspiratory muscle weakness. Outcomes will be exercise capacity (primary outcome), inspiratory muscle function, health-related quality of life (HRQL), and participation in daily physical activity.

## Hypotheses

We hypothesize that the addition of IMT to a general exercise training program in patients with COPD and inspiratory muscle weakness will result in superior improvements exercise capacity, inspiratory muscle function, health-related quality of life (HRQL), and daily physical activity, compared with general exercise training alone.

## Methods

### Patients

All patients with spirometry-proven COPD who are referred for outpatient pulmonary rehabilitation will be screened for inclusion. Only patients with inspiratory muscle weakness ($P_{I,max}$ < 60cm$H_2O$ or <50% predicted) will be eligible to participate in the study. Exclusion criteria consist of (1) diagnosed psychiatric or cognitive disorders; (2) progressive neurological or neuromuscular disorders; (3) severe

orthopedic problems having a major impact on daily activities; (4) previous inclusion in rehabilitation program (<1 year).

## Study design

Patients will be informed about the study protocol prior to the start of the rehabilitation program. Informed consent will be obtained at that time. Patients will be randomised into an intervention and a placebo group. Group allocation will be performed by simple randomization using sealed opaque envelopes in random block sizes of 4 and 6 (order unknown to investigators).[23]

Both groups will follow a general exercise training program as described previously.[24] The intervention group will receive an additional inspiratory muscle training program described to patients as 'resistance training' at a high intensity (≥ 50% PI,max), whereas the placebo group will receive an inspiratory muscle training intervention described to patients as 'endurance training' at a low training intensity (≤ 10% PI,max).

Measurements of primary and secondary endpoints will be undertaken before and after 3 months of rehabilitation. All tests will be performed by experienced investigators who are blinded to group allocation. To ensure consistency between sites all assessments should be performed according to the instructions agreed upon and described in the manual and the video clip, even if they may differ slightly from usual local procedures.

To detect a minimally clinically important difference between groups of 26m in the 6-minute walking distance (6MWD),[25] assuming a standard deviation of the within group differences in the 6MWD at the end of the intervention period of 60m in both groups with a degree of certainty (statistical power) of

80% and a risk for a type I error (α) < 5%, a sample size for both groups of 85 patients is needed, given an anticipated dropout rate of 30%. This study will therefore be performed as a multi-centre randomised controlled trial to ensure inclusion of 170 patients within a time-frame of two years. Besides the lead centre at the University Hospital in Leuven, Belgium, patients will also be recruited in the University Hospital Gent, Belgium; Schön Klinik Berchtesgadener Land, Germany; University Hospital Nijmegen, The Netherlands; and Laval University Quebec, Canada. Each of the five centres is expected to include between 30 to 40 patients within the two year inclusion period.

## Interventions

### General exercise training

Patients in both groups will follow a three-month general exercise training program. Patients will perform cycling, treadmill walking, stair climbing, arm ergometry and resistance training of both arm and leg muscles.[26] Training frequency will be three sessions per week, resulting in a total of 36 training sessions. Duration of the training session will increase from 40-60 minutes at the start of the program to 60-90 minutes after 3 months. Patients will perform endurance training or interval training at moderate to high intensity (initially 60% to 70% of maximal workload). The overall training intensity will be increased gradually during the course of the program using a CR10 Borg scale rating of 4 to 6 on dyspnea sensation or leg effort as a means of maintaining training overload.[27] Physiotherapists providing this intervention will be blinded to group allocation of patients.

### Inspiratory muscle training program

Patients will receive either high intensity inspiratory muscle training (‘strength training’ = intervention group) or low intensity placebo IMT (‘endurance training’ = placebo group). Total daily training time for both groups will be 21 minutes, consisting of 6 cycles of 30 breaths (two cycles, three times daily in the

intervention group or three cycles, two times daily in the control group). There will be approximately 3.5 minutes of resistive breathing during every cycle, each followed by one minute of resting. Patients will train 7 days per week, for 12 weeks using the PowerBreathe KH1 device (POWERbreathe®KH1, HaB International Ltd., Southam, UK)). This handheld device applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). Loading is maintained at the same relative

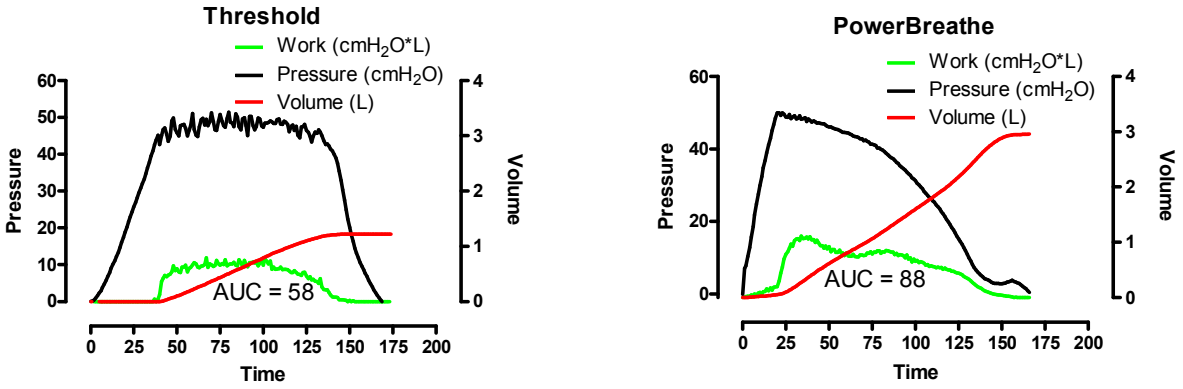



Figure 1: Comparison between constant threshold (Threshold) and variable resistive IMT (POWERbreathe® KH1).

AUC = Area Under Curve

intensity throughout the breath, by reducing the absolute load to accommodate the pressure-volume relationship of the inspiratory muscles. The application of a tapered load allows patients to get close to maximal inspiration, even at high training intensities (Figure 1).

Figure 1 illustrates a comparison of a single breath (training at an intensity of 60% Pi,max) using a conventional constant threshold loading device, with that of a variable flow resistive loading device (POWERBreathe® KH1) (unpublished data). It is apparent from this figure that, in contrast to the threshold loading, the variable flow resistive load overloads the inspiratory muscles at higher lung

volumes. Since one of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT may allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise,[22] we hypothesize that this variable flow resistive IMT should be better suited to reduce inspiratory effort (Pes/Pi,max) during whole body exercise. Besides these hypothetically beneficial characteristics of the applied load, a further advantage of the electronic leading device is the ability to store parameters of up to 40 IMT sessions. Continuous registrations of pressure and flow at 500Hz provide data on the external work of breathing and enable us to control both quantity and quality of unsupervised training sessions. This is of special importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision. The device stores data on average mean pressure ($cmH_2O$), average mean power per breath (Watt), average peak flow per breath (L/s) and total work of breathing during one session of 30 breaths (Joules). Patients will be instructed to perform fast and forceful inspirations and will be encouraged to achieve maximal inhalation and exhalation with every breath. This breathing pattern will be supported by acoustic signals from the loading device.

The intervention group will commence training at 40% of their initial Pi,max. Intermediate measurements of Pi,max will be performed every week. These Pi,max values will be used to calculate the training load to be implemented the following week. In other words, the training load in each week will be increased continuously over time by adjusting to at least 50% of the Pi,max value recorded in the previous week. Rates of perceived inspiratory effort on a modified CR 10 Borg-Scale (4-6 out of 10) will also be used to support decisions on training load increments. The control group will train at an inspiratory load of 10% of their initial Pi,max. This training intensity will not be changed during the study period. Each week, three training sessions will be performed under supervision at the outpatient clinic. During these supervised sessions the results of unsupervised sessions will be evaluated and patients will

receive instructions and feedback on their training efforts. Training intensity in the intervention group will be adapted during these supervised sessions.

## Outcome measures

Table 1 provides an overview of the outcome measures at different time points in the study.

**Table 1.** Outcome measurements

| | Start | 3 months |
|---|---|---|
| Screen | X | |
| Informed consent | X | |
| Respiratory muscle strength | X | X |
| Inspiratory muscle endurance | X | X |
| Maximal exercise capacity | X | X |
| Endurance exercise capacity | X | X |
| Six-minute walking distance | X | X |
| Daily physical activity (7 days): | X | X |
| Pulmonary function | X | X |
| Quadriceps force | X | X |
| Handgrip force | X | X |
| CRDQ[#] | X | X |
| HADS* | X | X |

[#]*CRDQ = Chronic Respiratory Disease Questionnaire (HRQL), *HADS = Hospital Anxiety and Depression Scale*

*Respiratory muscle force*

Maximal voluntary respiratory pressures will be registered at the mouth to assess respiratory muscle force. Measurements will be performed from total lung capacity for maximal expiratory pressure (Pe,max) or residual volume for maximal inspiratory pressure (Pi,max) using the technique proposed by Black and Hyatt.[28] An electronic pressure transducer will be used (MicroRPM; Micromedical, Kent, UK). Assessments will be repeated at least 5 times (30 seconds recovery between attempts), and should be continued until at least good reproducibility has been achieved from the three best measurements (within 10 $cmH_2O$ difference among measurements). Reference values published by Rochester and Arora will be used to define normal respiratory muscle force.[29]

*Inspiratory muscle endurance*

To measure inspiratory muscle endurance patients will be asked to breathe against a submaximal inspiratory load provided by the flow resistive loading device (POWERbreathe®KH1, HaB International Ltd., Southam, UK) until task failure. The inspiratory load that will be selected (typically between 50-60% of the Pi,max) will typically allow patients to continue breathing against the resistance for 3-7 minutes. Breathing instructions for patients will be the same as during the training sessions. Number of breaths, average duty cycle (inspiratory time as a fraction of the total respiratory cycle duration), average mean load, average mean power, and total external inspiratory work will be recorded during the test by the handheld loading device. We have recently performed a validation of the parameters that are recorded during this test and found excellent agreement between the handheld loading device and measurements performed with external, laboratory measurement equipment.[30] After 12 weeks of IMT the endurance test will be repeated using an identical load. Improvements in endurance time and breathing parameters will be recorded.

*Maximal exercise capacity (incremental exercise test)*

Maximal exercise capacity will be assessed by a maximal incremental cycle exercise test (Ergometrics 900, Ergoline, Bitz, Germany). After a two-minute resting period and three minutes of unloaded cycling, patients will start cycling at a load of 20 Watt. Load will then be increased by 10 Watt per minute and patients will cycle until symptom limitation. Oxygen uptake, carbon dioxide output and ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Heart rate and oxygen saturation will be recorded continuously. Maximal oxygen uptake will be compared with normal values.[31] The perception of dyspnea and leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified Borg scale.[27] Development of dynamic hyperinflation during the exercise test will be assessed by recording changes in end-expiratory lung volumes. Patients will be instructed to perform maximal inspiratory maneuvers after a normal expiration during resting breathing and at the end of each level of exercise. Assuming a constant total lung capacity a decrease in inspiratory capacity will indicate an increase in end expiratory lung volume, which indicates the degree of dynamic hyperinflation.[32] Tidal volume ($V_T$), inspiratory time ($T_I$), total time of the respiratory cycle ($T_{TOT}$) and respiratory frequency (fR) will be assessed. The $T_I/T_{TOT}$ (duty cycle) represents the proportion of the breath during which the inspiratory muscles are contracting.

*Endurance exercise capacity (constant work rate test)*

A constant power output cycle test until symptom limitation will be performed at 80% of the maximal power output (in Watts) that was reached during the initial incremental exercise test (Ergometrics 900, Ergoline, Bitz, Germany). Oxygen uptake, carbon dioxide output and minute ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Breathing pattern and dynamic hyperinflation will be monitored as described previously for the incremental cardiopulmonary exercise test. Heart rate and oxygen saturation will be monitored continuously. The perception of dyspnea and

leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified CR10 Borg scale.[27]

*6-minute walking distance (6MWD)*

Functional exercise performance will be measured using a six-minute walking test in a 50m corridor. Standardized encouragement will be provided.[33] The best of two tests separated by recovery time 30 minutes will be used and related to reference values.[34] Oxygen saturation, heart rate and symptoms of leg effort and dyspnea will be recorded before and after the test.

*Physical activity monitoring*

Measurements will be performed with an accelerometer-based activity monitor (DynaPort Minimod, McRoberts BV, The Hague, The Netherlands). The Minimod is a small (64x62x13mm) and lightweight device (68gram, including batteries) that contains a three-axial piezocapacitive sensor measuring at high time-resolution (100Hz). Analysis of raw data allows for classification of intensity, duration and frequency of movement. Different postures and walking are identified and energy expenditure is estimated. The Minimod has been validated in patients with COPD.[35] Assessments will be undertaken on seven consecutive days during waking hours.

*Pulmonary function*

Spirometry and whole body plethysmography will be performed according to the European Respiratory Society guidelines for pulmonary function testing (Vmax Autobox, Sensor Medics, Bilthoven, the Netherlands).[36] Diffusing capacity for carbon monoxide will be measured by the single breath method (Sensor Medics 6200, Bilthoven, the Netherlands).[37]

*Peripheral muscle force*

Isometric quadriceps force will be quantified using a Cybex Norm Dynamometer (Cybex® Norm, Enraf Nonius, Delft, the Netherlands). Peak extension torque will be measured at 60° of knee flexion. At least three measurements will be obtained and the highest reproducible value (within 11%) will be taken into analysis. Reference values have been developed in our laboratory.[38]

Isometric hand grip force will be measured using a hydraulic hand grip dynamometer (Jamar Preston, Jackson, MI). Peak force will be assessed with the elbow fixed to the rib cage and flexed 90° and with the wrist in neutral position. At least three measurements will be obtained and the highest reproducible value will be taken into analysis and related to reference values.[26]

*Health-related quality of life*

The Chronic Respiratory Disease Questionnaire (CRDQ) will be used to assess health-related quality of life.[39] This 20-item questionnaire scores quality of life in 4 domains (dyspnea, mastery, emotional functioning and fatigue) and has been validated in the Dutch, German and French language.[40-42] The total score can range from 20 to 140 with higher scores indicating better quality of life.

*Anxiety and depression*

The Hospital Anxiety and Depression Scale (HADS) will be used to assess emotional distress.[43] The HADS consists of 14 items and has separate scores for anxiety (7 items) and depression (7 items). A score of 11 or greater on either of the sub-scales suggests clinically significant symptoms of anxiety or depression.

## Statistical analysis

Differences in primary and secondary outcomes between groups after 3-months of intervention will be compared adjusting for baseline differences using analysis of covariance (ANCOVA).[44] Both an

'intention-to-treat' and a 'per-protocol' analysis will be carried out to compare outcomes between groups.

## Ethics and dissemination

Ethics approval has been obtained from relevant centre committees. The results from the randomised controlled trial of IMT will be submitted for publication.

## Discussion

This large, adequately powered, multi-centre randomised controlled trial will investigate effects of IMT as an adjunct to a general exercise training program. Outcomes will be exercise capacity (primary outcome), health related quality of life, and participation in daily physical activity in the selected COPD patients who have pronounced inspiratory muscle weakness. The IMT in this RCT will be performed using the variable flow resistive loading device described previously (POWERbreathe®KH1, HaB International Ltd., Southam, UK) and validated.[30] Besides the hypothetically beneficial characteristics of the applied load described above, a further advantage of this device is the ability to store training parameters of up to 40 sessions. Continuous recording of pressure and flow enable us to monitor both the quantity and quality of unsupervised training sessions. The latter is of special importance, since 85% of IMT sessions will be undertaken by patients in their homes, without supervision.

We anticipate that the outcomes of this study will be of direct relevance to clinical practice. The results of this study should therefore be incorporated immediately into evidence based treatment recommendations for clinical practice. During the communication of these recommendations it will be of special importance to stress that the results obtained in this RCT will limited to the selected group of patients with COPD, i.e. those with inspiratory muscle weakness.

**Funding**

None

**Competing Interests**

None

**Contributorship**

DL is the principal investigator and together with RG and NC designed and established the study. All authors are responsible for the selection of measures, recruitment and data collection. NC and DL are responsible for data analysis. All authors have read and approved the final manuscript.



## Reference List

1 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765-73.

2 Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532-55.

3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD*. available at: http://www.goldcopd.org/ . 2011.
Ref Type: Internet Communication

4 O'Donnell DE, Travers J, Webb KA, et al. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *Eur Respir J* 2009;**34**:866-74.

5 Hamilton N, Killian KJ, Summers E, et al. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;**152**:2021-31.

6 Lacasse Y, Goldstein R, Lasserson TJ, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;CD003793.

7 Decramer M, Demedts M, Rochette F, et al. Maximal transrespiratory pressures in obstructive lung disease. *Bull Eur Physiopathol Respir* 1980;**16**:479-90.

8 Polkey MI, Kyroussis D, Hamnegard CH, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1310-7.

9 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;**168**:10-48.

10 Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;**143**:905-12.

11 Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;**153**:976-80.

12 Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390-413.

13 Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007;**131**:4S-42S.

14 Gosselink R, De VJ, van den Heuvel SP, et al. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011;**37**:416-25.

15 Geddes EL, O'Brien K, Reid WD, et al. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med* 2008;**102**:1715-29.

16 Ambrosino N. The case for inspiratory muscle training in COPD. *Eur Respir J* 2011;**37**:233-5.

17 McConnell AK. CrossTalk opposing view: respiratory muscle training does improve exercise tolerance. *J Physiol* 2012;**590**:3397-8.

18 Patel MS, Hart N, Polkey MI. CrossTalk proposal: training the respiratory muscles does not improve exercise tolerance. *J Physiol* 2012;**590**:3393-5.

19 Polkey MI, Moxham J, Green M. The case against inspiratory muscle training in COPD. Against. *Eur Respir J* 2011;**37**:236-7.

20 Decramer M. Response of the respiratory muscles to rehabilitation in COPD. *J Appl Physiol* 2009;**107**:971-6.

21 Winkelmann ER, Chiappa GR, Lima CO, et al. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J* 2009;**158**:768-7.

22 Luo YM, Hopkinson NS, Polkey MI. Tough at the top: must end-expiratory lung volume make way for end-inspiratory lung volume? *Eur Respir J* 2012;**40**:283-5.

23 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;**20**:187-91.

24 Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000;**109**:207-12.

25 Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 2011;**37**:784-90.

26 Mathiowetz V, Dove M, Kashman N, et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985;**66**:69-72.

27 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377-81.

28 Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;**99**:696-702.

29 Rochester DF, Arora NS. Respiratory muscle failure. *Med Clin North Am* 1983;**67**:573-97.

30 Langer D, Jacome C, Charususin N, et al. Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med* 2013;**107**:633-5.

31 Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;**131**:700-8.

32 Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**:55-9.

33 Guyatt GH, Pugsley SO, Sullivan MJ, et al. Effect of encouragement on walking test performance. *Thorax* 1984;**39**:818-22.

34 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;**14**:270-4.

35 Langer D, Gosselink R, Sena R, et al. Validation of two activity monitors in patients with COPD. *Thorax* 2009;**64**:641-2.

36 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319-38.

37 MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;**26**:720-35.

38 Decramer M. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. 1994.

39 Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773-8.

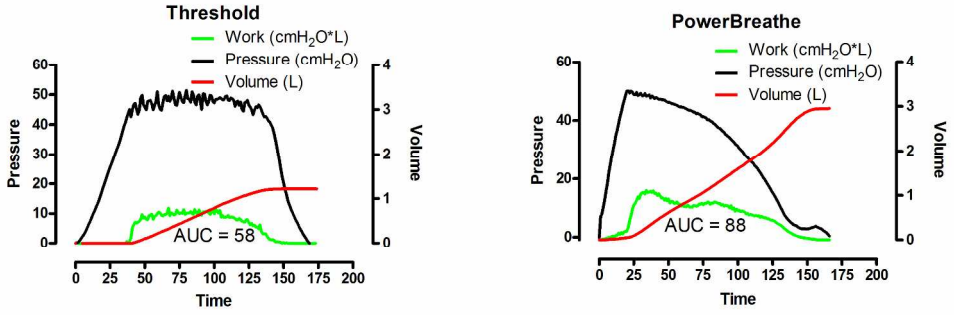
40 Puhan MA, Behnke M, Frey M, et al. Self-administration and interviewer-administration of the German Chronic Respiratory Questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004;**2**:1.

41 Bourbeau J, Maltais F, Rouleau M, et al. French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. *Can Respir J* 2004;**11**:480-6.

42 Wijkstra PJ, TenVergert EM, Van AR, et al. Reliability and validity of the chronic respiratory questionnaire (CRQ). *Thorax* 1994;**49**:465-7.

43 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-70.

44 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;**323**:1123-4.




(Figure 1)
250x91mm (300 x 300 DPI)

# Inspiratory muscle training protocol for patients with chronic obstructive pulmonary disease (IMTCO-study): a multicentre randomised controlled trial

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-003101.R1 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 05-Jul-2013 |
| Complete List of Authors: | Charususin, Noppawan; University of Leuven, Department of Rehabilitation Sciences; Thammasat University, Department of Physical Therapy<br>Gosselink, Rik; University of Leuven, Department of Rehabilitation Sciences; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division<br>Decramer, Marc; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division<br>McConnell, Alison; Brunel University, Centre for Sports Medicine and Human Performance<br>Saey, Didier; Laval University, Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec<br>Maltais, Francois; Laval University, Centre de recherche, Institut Universitaire de cardiologie et de pneumologie de Québec<br>Derom, Eric; University Hospital Ghent, Department of Pulmonology<br>Vermeersch, Stefanie; University Hospital Ghent, Department of Pulmonology<br>Helvoort, Hanneke; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Heijdra, Yvonne; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Klaassen, Mariska; Radboud University Nijmegen Medical Center, Department of Pulmonary Diseases<br>Glöckl, Rainer; Schön Klinik Berchtesgaden, Department of Respiratory Medicine & Sports Therapy<br>Kenn, Klaus; Schön Klinik Berchtesgaden, Department of Respiratory Medicine & Sports Therapy<br>Langer, Daniel; University of Leuven, Rehabilitation Sciences; UZ Gasthuisberg, Respiratory Rehabilitation and Respiratory Division |
| Primary Subject Heading: | Respiratory medicine |
| Secondary Subject Heading: | Rehabilitation medicine |
| Keywords: | Clinical trials < THERAPEUTICS, Chronic airways disease < THORACIC MEDICINE, Emphysema < THORACIC MEDICINE |
| | |

## Article summary

### Article focus

- Inspiratory muscle dysfunction occurs in patients with COPD and is associated with dyspnea and decreased exercise capacity.
- What are the additional functional and health benefits of adding home-based IMT to a general exercise training program in COPD patients with inspiratory muscle weakness?

### Key messages

- This multicentre randomised controlled trial will investigate and report on the additional improvements in exercise tolerance after adding IMT to a 3-months general exercise training program. Inspiratory muscle function, health-related quality of life, and daily physical activity, will be assessed as secondary outcomes.
- The study will focus on COPD patients with inspiratory muscle weakness defined as Pimax < 60cm$H_2O$ or < 50%pred.
- The variable flow resistive training method applies a specific training stimulus and allows full monitoring of the compliance with the home based IMT.

### Strengths and limitations of this study

- In contrast to previous studies, we designed a large, adequately powered, multi-centre randomised controlled trial to investigate the effects of IMT in COPD patients with inspiratory muscle weakness. The results from this study will help to clarify whether adjunctive IMT leads to greater functional improvements (exercise capacity, quality of life, participation in daily activity, and symptoms) than exercise training alone.

- The results will be focused on effects in COPD patients with inspiratory muscle weakness. The results of this study will therefore primarily be applicable in COPD patients with inspiratory muscle weakness.

## Background

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality worldwide.[1,2] COPD is characterized by persistent expiratory flow limitation that is usually progressive.[3] Dyspnea is the most prominent exercise-limiting symptom of the disease,[4] which leads to chronic avoidance of physical activities. Consequently, low physical activity levels contribute to skeletal muscle deconditioning and exercise capacity reduction, which impact negatively on health related quality of life.[5,6] Inspiratory muscle dysfunction is another extrapulmonary manifestation that is often present in patients with COPD.[7,8] It contributes to hypoxemia, hypercapnia, dyspnea and decreased exercise tolerance.[9-11] Pulmonary rehabilitation including exercise training, education, nutritional intervention, and psychosocial support is a standard care for COPD patients to counteract extrapulmonary disease manifestations.[6,12,13] Inspiratory muscle training (IMT) has also been applied frequently and is extensively studied in recent years in patients with COPD.[14] From meta-analyses of RCT's in patients with COPD it can been concluded that IMT as a standalone therapy improves inspiratory muscle function (strength and endurance), decreases symptoms of dyspnea, and improves exercise capacity.[14,15] The value of IMT as an add-on to a general exercise training program is however still under debate.[16-19] While IMT always results in significant improvements in inspiratory muscle function, its additional effects on more clinically relevant outcomes (e.g. functional exercise capacity and quality of life) are insufficiently supported by scientific evidence so far.[14] From subgroup analyses in the most recent meta-analysis it was concluded that significant additional effects of IMT on more clinically relevant outcomes are more likely to be found in patients with inspiratory muscle

weakness.[12] This was previously defined as a maximal inspiratory mouth pressure (Pi,max) of less than 60cm$H_2O$.[14] It has therefore been recommended that future studies in patients with COPD should focus specifically on patients with more pronounced inspiratory muscle weakness.[14,20] It was recently shown that adjunctive IMT led to significantly greater functional improvements in a well designed randomised controlled trial in patients with chronic heart failure selected for inspiratory muscle weakness.[21] Comparable RCTs in patients with COPD are so far lacking.[14] We are therefore carrying out a large, adequately powered, multi-centre randomised controlled trial on the effects of IMT as an adjunct therapy to a general exercise training program in COPD patients with inspiratory muscle weakness. Recommendations on the use of IMT as an adjunct to general exercise training in these patients in international guidelines are ambiguous.[12] The outcome of this study will therefore have a direct impact on clinical practice, as the results will clarify whether adjunctive IMT leads to superior clinically relevant improvements for COPD patients. Functional outcomes of relevance to patients (exercise capacity, quality of life, participation in daily physical activity, and symptoms) were therefore chosen as main outcomes.

One of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT should allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise.[22] In the present study we will use a recently developed IMT device that applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). In contrast to the traditionally applied threshold loading, this variable flow resistive load is specifically challenging the inspiratory muscles at higher lung volumes, and may lead to larger training effects in COPD patients who develop dynamic hyperinflation during exercise. Besides these potentially beneficial characteristics of the applied load another advantage of the device is the ability to store home-based training data for up to 40 sessions. Continuous registrations of pressure and flow at 500 Hz provide data on the external work of breathing and enable the verification of both

quantity and quality of unsupervised training sessions. The latter is of particular importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision.

## Aims

This study will examine the effects of adding a well-controlled, high-intensity inspiratory muscle training (IMT) program to a 3-month general exercise training program, using a large, multi-centre, randomised controlled design, in COPD patients with inspiratory muscle weakness. Outcomes will be exercise capacity (primary outcome), inspiratory muscle function, health-related quality of life (HRQL), and participation in daily physical activity.

## Hypotheses

We hypothesize that the addition of IMT to a general exercise training program in patients with COPD and inspiratory muscle weakness will result in superior improvements exercise capacity, inspiratory muscle function, health-related quality of life (HRQL), and daily physical activity, compared with general exercise training alone.

## Methods

### Patients

All patients with spirometry-proven COPD who are referred for outpatient pulmonary rehabilitation will be screened for inclusion. Only patients with inspiratory muscle weakness ($P_{I,max}$ < 60cm$H_2O$ or <50% predicted) will be eligible to participate in the study. Exclusion criteria consist of (1) diagnosed psychiatric or cognitive disorders; (2) progressive neurological or neuromuscular disorders; (3) severe orthopedic problems having a major impact on daily activities; (4) previous inclusion in rehabilitation program (<1 year).

## Study design

Patients will be informed about the study protocol prior to the start of the rehabilitation program. Informed consent will be obtained at that time. Patients will be randomised into an intervention and a placebo group. Group allocation will be performed by simple randomization using sealed opaque envelopes in random block sizes of 4 and 6 (order unknown to investigators).[23]

Both groups will follow a general exercise training program as described previously.[24] The intervention group will receive an additional inspiratory muscle training program described to patients as 'resistance training' at a high intensity (≥ 50% PI,max), whereas the placebo group will receive an inspiratory muscle training intervention described to patients as 'endurance training' at a low training intensity (≤ 10% PI,max).

Measurements of primary and secondary endpoints will be undertaken before and after 3 months of rehabilitation. All tests will be performed by experienced investigators who are blinded to group allocation. To ensure consistency between centres all assessments should be performed according to the instructions agreed upon and described in a manual of procedures and an instructional video, even if they may differ slightly from usual local procedures. To further improve the consistency, the five centres will regularly receive a newsletter to update them on the progress of the study and to share eventual technical problems between centers. Staff from all participating centres will be able to contact the coordinating center in Leuven by e-mail or telephone in case they should have any questions concerning the study.

To detect a minimally clinically important difference between groups of 26m in the 6-minute walking distance (6MWD),[25] assuming a standard deviation of the within group differences in the 6MWD at the end of the intervention period of 60m in both groups with a degree of certainty (statistical power) of

80% and a risk for a type I error (α) < 5%, a sample size for both groups of 85 patients is needed, given an anticipated dropout rate of 30%. This study will therefore be performed as a multi-centre randomised controlled trial to ensure inclusion of 170 patients within a time-frame of two years. Besides the lead centre at the University Hospital in Leuven, Belgium, patients will also be recruited in the University Hospital Gent, Belgium; Schön Klinik Berchtesgadener Land, Germany; University Hospital Nijmegen, The Netherlands; and Laval University Quebec, Canada. Each of the five centres is expected to include between 30 to 40 patients within the two year inclusion period.

In accordance with the Belgian law relating to experiments in humans dated May 7, 2004, KU/UZ Leuven shall assume, even without fault, the responsibility of any damages incurred by a Subject and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance program. All collaborating sites shall have and maintain in full force and effect during the term of this Agreement (and following termination of the Study to cover any claims arising from the Study) adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability, and (iii) other possible damages resulting from the Study at the Institution required by local law, each such insurance coverage in amounts appropriate to the conduct of the services of the Participating Site under this Agreement.

## Interventions

### General exercise training

Patients in both groups will follow a three-month general exercise training program. Patients will perform cycling, treadmill walking, stair climbing, arm ergometry and resistance training of both arm and leg muscles.[26] Training frequency will be three sessions per week, resulting in a total of 36 training sessions. Duration of the training session will increase from 40-60 minutes at the start of the program to 60-90 minutes after 3 months. Patients will perform endurance training or interval training at moderate

to high intensity (initially 60% to 70% of maximal workload). The overall training intensity will be increased gradually during the course of the program using a CR10 Borg scale rating of 4 to 6 on dyspnea sensation or leg effort as a means of maintaining training overload.[27] Physiotherapists providing this intervention will be blinded to group allocation of patients.

**Inspiratory muscle training program**

Patients will receive either high intensity inspiratory muscle training ('strength training' = intervention group) or low intensity placebo IMT ('endurance training' = placebo group). The training load in this study will be adjusted according to data from a previously performed pilot study about a home-based, high intensity IMT programs in COPD patients with inspiratory muscle weakness.[28] Total daily training time for both groups will be 21 minutes, consisting of 6 cycles of 30 breaths (two cycles, three times daily in the intervention group or three cycles, two times daily in the control group). There will be approximately 3.5 minutes of resistive breathing during every cycle, each followed by one minute of resting. Patients will train 7 days per week, for 12 weeks using the PowerBreathe KH1 device (POWERbreathe®KH1, HaB International Ltd., Southam, UK)). This handheld device applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). Loading is maintained at the same relative intensity throughout the breath, by reducing the absolute load to accommodate the pressure-volume relationship of the inspiratory muscles. The application of a tapered load allows patients to get close to maximal inspiration, even at high training intensities (Figure 1).

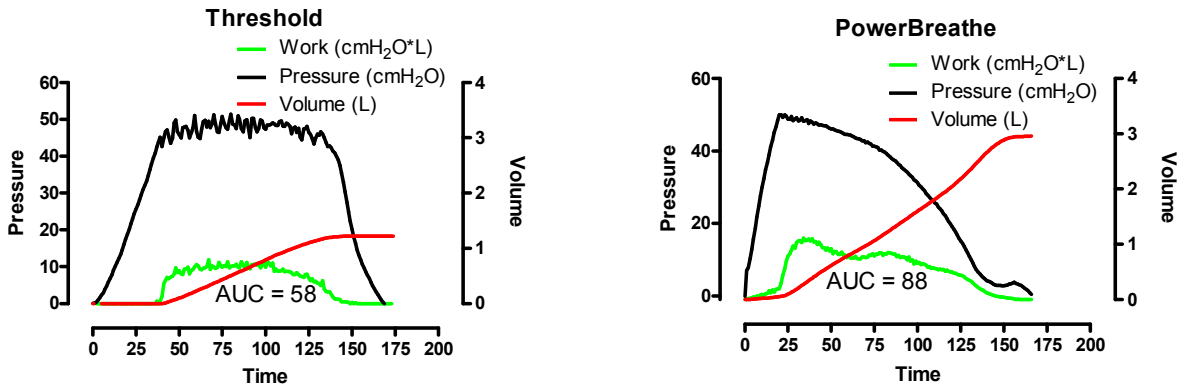



Figure 1: Comparison between constant threshold (Threshold) and variable resistive IMT (POWERbreathe® KH1).

AUC = Area Under Curve

Figure 1 illustrates a comparison of a single breath (training at an intensity of 60% Pi,max) using a conventional constant threshold loading device, with that of a variable flow resistive loading device (POWERBreathe® KH1).[28] It is apparent from this figure that, in contrast to the threshold loading, the variable flow resistive load overloads the inspiratory muscles at higher lung volumes. Since one of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT may allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise,[22] we hypothesize that this variable flow resistive IMT should be better suited to reduce inspiratory effort (Pes/Pi,max) during whole body exercise. Besides these hypothetically beneficial characteristics of the applied load, a further advantage of the electronic leading device is the ability to store parameters of up to 40 IMT sessions. Continuous registrations of pressure and flow at 500Hz provide data on the external work of breathing and enable us to control both quantity and quality of unsupervised training sessions. This is of special importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision. The device stores data on average mean pressure ($cmH_2O$), average mean power per breath (Watt), average peak flow per breath (L/s) and total work of breathing during one session of 30 breaths (Joules). Patients will be instructed to

perform fast and forceful inspirations and will be encouraged to achieve maximal inhalation and exhalation with every breath. This breathing pattern will be supported by acoustic signals from the loading device.

The intervention group will commence training at 40% of their initial Pi,max. Intermediate measurements of Pi,max will be performed every week. These Pi,max values will be used to calculate the training load to be implemented the following week. In other words, the training load in each week will be increased continuously over time by adjusting to at least 50% of the Pi,max value recorded in the previous week. Rates of perceived inspiratory effort on a modified CR 10 Borg-Scale (4-6 out of 10) will also be used to support decisions on training load increments. The control group will train at an inspiratory load of 10% of their initial Pi,max. This training intensity will not be changed during the study period. Each week, three training sessions will be performed under supervision at the outpatient clinic. During these supervised sessions the results of unsupervised sessions will be evaluated and patients will receive instructions and feedback on their training efforts. Resting periods will be given as needed as long as patients are able to complete the full volume of training that is prescribed. Training intensity in the intervention group will be adapted during these supervised sessions.

When patients experience acute exacerbations or respiratory infections, they will temporarily interrupt their participation in the rehabilitation and IMT program. Based on guidance from the treating pulmonologist they will however return to the program as quickly as possible. Periods of infections, exacerbations, and hospitalizations will be registered and their stay in the program will be prolonged in order to complete 12 weeks of IMT training program.

## Outcome measures

Table 1 provides an overview of the outcome measures at different time points in the study.

**Table 1.** Outcome measurements

| | Start | 3 months |
|---|---|---|
| Screen | X | |
| Informed consent | X | |
| Respiratory muscle strength | X | X |
| Inspiratory muscle endurance | X | X |
| Maximal exercise capacity | X | X |
| Endurance exercise capacity | X | X |
| Six-minute walking distance | X | X |
| Daily physical activity (7 days): | X | X |
| Pulmonary function | X | X |
| Quadriceps force | X | X |
| Handgrip force | X | X |
| CRDQ[#] | X | X |
| HADS* | X | X |

[#]*CRDQ = Chronic Respiratory Disease Questionnaire (HRQL), *HADS = Hospital Anxiety and Depression Scale*

*Respiratory muscle force*

Maximal voluntary respiratory pressures will be registered at the mouth to assess respiratory muscle force. Measurements will be performed from total lung capacity for maximal expiratory pressure (Pe,max) or residual volume for maximal inspiratory pressure (Pi,max) using the technique proposed by Black and Hyatt.[29] An electronic pressure transducer will be used (MicroRPM; Micromedical, Kent, UK). Assessments will be repeated at least 5 times (30 seconds recovery between attempts), and should be continued until at least good reproducibility has been achieved from the three best measurements

(within 10 $cmH_2O$ difference among measurements). Reference values published by Rochester and Arora will be used to define normal respiratory muscle force.[30]

*Inspiratory muscle endurance*

To measure inspiratory muscle endurance patients will be asked to breathe against a submaximal inspiratory load provided by the flow resistive loading device (POWERbreathe®KH1, HaB International Ltd., Southam, UK) until task failure. The inspiratory load that will be selected (typically between 50-60% of the Pi,max) will typically allow patients to continue breathing against the resistance for 3-7 minutes. Breathing instructions for patients will be the same as during the training sessions. Number of breaths, average duty cycle (inspiratory time as a fraction of the total respiratory cycle duration), average mean load, average mean power, and total external inspiratory work will be recorded during the test by the handheld loading device. We have recently performed a validation of the parameters that are recorded during this test and found excellent agreement between the handheld loading device and measurements performed with external, laboratory measurement equipment.[31] After 12 weeks of IMT the endurance test will be repeated using an identical load. Improvements in endurance time and breathing parameters will be recorded.

*Maximal exercise capacity (incremental exercise test)*

Maximal exercise capacity will be assessed by a maximal incremental cycle exercise test (Ergometrics 900, Ergoline, Bitz, Germany). After a two-minute resting period and three minutes of unloaded cycling, patients will start cycling at a load of 20 Watt. Load will then be increased by 10 Watt per minute and patients will cycle until symptom limitation. Oxygen uptake, carbon dioxide output and ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Heart rate and oxygen saturation will be recorded continuously. Maximal oxygen uptake will be compared with normal

values.[32] The perception of dyspnea and leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified Borg scale.[27] Development of dynamic hyperinflation during the exercise test will be assessed by recording changes in end-expiratory lung volumes. Patients will be instructed to perform maximal inspiratory maneuvers after a normal expiration during resting breathing and at the end of each level of exercise. Assuming a constant total lung capacity a decrease in inspiratory capacity will indicate an increase in end expiratory lung volume, which indicates the degree of dynamic hyperinflation.[33] Tidal volume ($V_T$), inspiratory time ($T_I$), total time of the respiratory cycle ($T_{TOT}$) and respiratory frequency (fR) will be assessed. The $T_I/T_{TOT}$ (duty cycle) represents the proportion of the breath during which the inspiratory muscles are contracting.

*Endurance exercise capacity (constant work rate test)*

A constant power output cycle test until symptom limitation will be performed at 80% of the maximal power output (in Watts) that was reached during the initial incremental exercise test (Ergometrics 900, Ergoline, Bitz, Germany). Oxygen uptake, carbon dioxide output and minute ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Breathing pattern and dynamic hyperinflation will be monitored as described previously for the incremental cardiopulmonary exercise test. Heart rate and oxygen saturation will be monitored continuously. The perception of dyspnea and leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified CR10 Borg scale.[27]

*6-minute walking distance (6MWD)*

Functional exercise performance will be measured using a six-minute walking test in a 50m corridor. Standardized encouragement will be provided.[34] The best of two tests separated by recovery time 30

minutes will be used and related to reference values.[35] Oxygen saturation, heart rate and symptoms of leg effort and dyspnea will be recorded before and after the test.

*Physical activity monitoring*

Measurements will be performed with an accelerometer-based activity monitor (DynaPort Minimod, McRoberts BV, The Hague, The Netherlands). The Minimod is a small (64x62x13mm) and lightweight device (68gram, including batteries) that contains a three-axial piezocapacitive sensor measuring at high time-resolution (100Hz). Analysis of raw data allows for classification of intensity, duration and frequency of movement. Different postures and walking are identified and energy expenditure is estimated. The Minimod has been validated in patients with COPD.[36] Assessments will be undertaken on seven consecutive days during waking hours.

*Pulmonary function*

Spirometry and whole body plethysmography will be performed according to the European Respiratory Society guidelines for pulmonary function testing (Vmax Autobox, Sensor Medics, Bilthoven, the Netherlands).[37] Diffusing capacity for carbon monoxide will be measured by the single breath method (Sensor Medics 6200, Bilthoven, the Netherlands).[38]

*Peripheral muscle force*

Isometric quadriceps force will be quantified using a Cybex Norm Dynamometer (Cybex® Norm, Enraf Nonius, Delft, the Netherlands). Peak extension torque will be measured at 60° of knee flexion. At least three measurements will be obtained and the highest reproducible value (within 11%) will be taken into analysis. Reference values have been developed in our laboratory.[39]

Isometric hand grip force will be measured using a hydraulic hand grip dynamometer (Jamar Preston, Jackson, MI). Peak force will be assessed with the elbow fixed to the rib cage and flexed 90° and with the wrist in neutral position. At least three measurements will be obtained and the highest reproducible value will be taken into analysis and related to reference values.[26]

*Health-related quality of life*

The Chronic Respiratory Disease Questionnaire (CRDQ) will be used to assess health-related quality of life.[40] This 20-item questionnaire scores quality of life in 4 domains (dyspnea, mastery, emotional functioning and fatigue) and has been validated in the Dutch, German and French language.[41-43] The total score can range from 20 to 140 with higher scores indicating better quality of life.

*Anxiety and depression*

The Hospital Anxiety and Depression Scale (HADS) will be used to assess emotional distress.[44] The HADS consists of 14 items and has separate scores for anxiety (7 items) and depression (7 items). A score of 11 or greater on either of the sub-scales suggests clinically significant symptoms of anxiety or depression.

## Statistical analysis

Differences in primary and secondary outcomes between groups after 3-months of intervention will be compared adjusting for baseline differences using analysis of covariance (ANCOVA).[45] Both an 'intention-to-treat' and a 'per-protocol' analysis will be carried out to compare outcomes between groups.

## Ethics and dissemination

Ethics approval has been obtained from relevant centre committees. The results from the randomised controlled trial of IMT will be submitted for publication.

## Discussion

This large, adequately powered, multi-centre randomised controlled trial will investigate effects of IMT as an adjunct to a general exercise training program. Outcomes will be exercise capacity (primary outcome), health related quality of life, and participation in daily physical activity in the selected COPD patients who have pronounced inspiratory muscle weakness. The IMT in this RCT will be performed using the variable flow resistive loading device described previously (POWERbreathe®KH1, HaB International Ltd., Southam, UK) and validated.[31] Besides the hypothetically beneficial characteristics of the applied load described above, a further advantage of this device is the ability to store training parameters of up to 40 sessions. Continuous recording of pressure and flow enable us to monitor both the quantity and quality of unsupervised training sessions. The latter is of special importance, since 85% of IMT sessions will be undertaken by patients in their homes, without supervision.

We anticipate that the outcomes of this study will be of direct relevance to clinical practice. The results of this study should therefore be incorporated immediately into evidence based treatment recommendations for clinical practice. During the communication of these recommendations it will be of special importance to stress that the results obtained in this RCT will limited to the selected group of patients with COPD, i.e. those with inspiratory muscle weakness.

## Reference List

1 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765-73.

2 Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532-55.

3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD*. available at: http://www.goldcopd.org/ . 2011.
Ref Type: Internet Communication

4 O'Donnell DE, Travers J, Webb KA, et al. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *Eur Respir J* 2009;**34**:866-74.

5 Hamilton N, Killian KJ, Summers E, et al. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;**152**:2021-31.

6 Lacasse Y, Goldstein R, Lasserson TJ, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;CD003793.

7 Decramer M, Demedts M, Rochette F, et al. Maximal transrespiratory pressures in obstructive lung disease. *Bull Eur Physiopathol Respir* 1980;**16**:479-90.

8 Polkey MI, Kyroussis D, Hamnegard CH, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1310-7.

9 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;**168**:10-48.

10 Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;**143**:905-12.

11 Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;**153**:976-80.

12 Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390-413.

13 Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007;**131**:4S-42S.

14 Gosselink R, De VJ, van den Heuvel SP, et al. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011;**37**:416-25.

15 Geddes EL, O'Brien K, Reid WD, et al. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med* 2008;**102**:1715-29.

16 Ambrosino N. The case for inspiratory muscle training in COPD. *Eur Respir J* 2011;**37**:233-5.

17 McConnell AK. CrossTalk opposing view: respiratory muscle training does improve exercise tolerance. *J Physiol* 2012;**590**:3397-8.

18 Patel MS, Hart N, Polkey MI. CrossTalk proposal: training the respiratory muscles does not improve exercise tolerance. *J Physiol* 2012;**590**:3393-5.

19 Polkey MI, Moxham J, Green M. The case against inspiratory muscle training in COPD. Against. *Eur Respir J* 2011;**37**:236-7.

20 Decramer M. Response of the respiratory muscles to rehabilitation in COPD. *J Appl Physiol* 2009;**107**:971-6.

21 Winkelmann ER, Chiappa GR, Lima CO, et al. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J* 2009;**158**:768-7.

22 Luo YM, Hopkinson NS, Polkey MI. Tough at the top: must end-expiratory lung volume make way for end-inspiratory lung volume? *Eur Respir J* 2012;**40**:283-5.

23 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;**20**:187-91.

24 Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000;**109**:207-12.

25 Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 2011;**37**:784-90.

26 Mathiowetz V, Dove M, Kashman N, et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985;**66**:69-72.

27 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377-81.

28 Langer D, Jacome C, Hoffman M, et al. Comparison of two high intensity inspiratory muscle training programs in patients with COPD: A randomized controlled trial. *Am J Respir Crit Care Med* **2013**; 187: A2566.

29 Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;**99**:696-702.

30 Rochester DF, Arora NS. Respiratory muscle failure. *Med Clin North Am* 1983;**67**:573-97.

31 Langer D, Jacome C, Charususin N, et al. Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med* 2013;**107**:633-5.

32 Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;**131**:700-8.

33 Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**:55-9.

34 Guyatt GH, Pugsley SO, Sullivan MJ, et al. Effect of encouragement on walking test performance. *Thorax* 1984;**39**:818-22.

35 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;**14**:270-4.

36 Langer D, Gosselink R, Sena R, et al. Validation of two activity monitors in patients with COPD. *Thorax* 2009;**64**:641-2.

37 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319-38.

38 MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;**26**:720-35.

39 Decramer M. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. 1994.

40 Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773-8.

41 Puhan MA, Behnke M, Frey M, et al. Self-administration and interviewer-administration of the German Chronic Respiratory Questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004;**2**:1.

42 Bourbeau J, Maltais F, Rouleau M, et al. French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. *Can Respir J* 2004;**11**:480-6.

43 Wijkstra PJ, TenVergert EM, Van AR, et al. Reliability and validity of the chronic respiratory questionnaire (CRQ). *Thorax* 1994;**49**:465-7.

44 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-70.

45 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;**323**:1123-4.

## Article summary

### Article focus

- Inspiratory muscle dysfunction occurs in patients with COPD and is associated with dyspnea and decreased exercise capacity.
- What are the additional functional and health benefits of adding home-based IMT to a general exercise training program in COPD patients with inspiratory muscle weakness?

### Key messages

- This multicentre randomised controlled trial will investigate and report on the additional improvements in exercise tolerance after adding IMT to a 3-months general exercise training program. Inspiratory muscle function, health-related quality of life, and daily physical activity, will be assessed as secondary outcomes.
- The study will focus on COPD patients with inspiratory muscle weakness defined as Pimax < 60cm$H_2O$ or < 50%pred.
- The variable flow resistive training method applies a specific training stimulus and allows full monitoring of the compliance with the home based IMT.

### Strengths and limitations of this study

- In contrast to previous studies, we designed a large, adequately powered, multi-centre randomised controlled trial to investigate the effects of IMT in COPD patients with inspiratory muscle weakness. The results from this study will help to clarify whether adjunctive IMT leads to greater functional improvements (exercise capacity, quality of life, participation in daily activity, and symptoms) than exercise training alone.

- The results will be focused on effects in COPD patients with inspiratory muscle weakness. The results of this study will therefore primarily be applicable in COPD patients with inspiratory muscle weakness.

## Background

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality worldwide.[1,2] COPD is characterized by persistent expiratory flow limitation that is usually progressive.[3] Dyspnea is the most prominent exercise-limiting symptom of the disease,[4] which leads to chronic avoidance of physical activities. Consequently, low physical activity levels contribute to skeletal muscle deconditioning and exercise capacity reduction, which impact negatively on health related quality of life.[5,6] Inspiratory muscle dysfunction is another extrapulmonary manifestation that is often present in patients with COPD.[7,8] It contributes to hypoxemia, hypercapnia, dyspnea and decreased exercise tolerance.[9-11] Pulmonary rehabilitation including exercise training, education, nutritional intervention, and psychosocial support is a standard care for COPD patients to counteract extrapulmonary disease manifestations.[6,12,13] Inspiratory muscle training (IMT) has also been applied frequently and is extensively studied in recent years in patients with COPD.[14] From meta-analyses of RCT's in patients with COPD it can been concluded that IMT as a standalone therapy improves inspiratory muscle function (strength and endurance), decreases symptoms of dyspnea, and improves exercise capacity.[14,15] The value of IMT as an add-on to a general exercise training program is however still under debate.[16-19] While IMT always results in significant improvements in inspiratory muscle function, its additional effects on more clinically relevant outcomes (e.g. functional exercise capacity and quality of life) are insufficiently supported by scientific evidence so far.[14] From subgroup analyses in the most recent meta-analysis it was concluded that significant additional effects of IMT on more clinically relevant outcomes are more likely to be found in patients with inspiratory muscle

weakness.[12] This was previously defined as a maximal inspiratory mouth pressure (Pi,max) of less than 60cm$H_2O$.[14] It has therefore been recommended that future studies in patients with COPD should focus specifically on patients with more pronounced inspiratory muscle weakness.[14,20] It was recently shown that adjunctive IMT led to significantly greater functional improvements in a well designed randomised controlled trial in patients with chronic heart failure selected for inspiratory muscle weakness.[21] Comparable RCTs in patients with COPD are so far lacking.[14] We are therefore carrying out a large, adequately powered, multi-centre randomised controlled trial on the effects of IMT as an adjunct therapy to a general exercise training program in COPD patients with inspiratory muscle weakness. Recommendations on the use of IMT as an adjunct to general exercise training in these patients in international guidelines are ambiguous.[12] The outcome of this study will therefore have a direct impact on clinical practice, as the results will clarify whether adjunctive IMT leads to superior clinically relevant improvements for COPD patients. Functional outcomes of relevance to patients (exercise capacity, quality of life, participation in daily physical activity, and symptoms) were therefore chosen as main outcomes.

One of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT should allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise.[22] In the present study we will use a recently developed IMT device that applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). In contrast to the traditionally applied threshold loading, this variable flow resistive load is specifically challenging the inspiratory muscles at higher lung volumes, and may lead to larger training effects in COPD patients who develop dynamic hyperinflation during exercise. Besides these potentially beneficial characteristics of the applied load another advantage of the device is the ability to store home-based training data for up to 40 sessions. Continuous registrations of pressure and flow at 500 Hz provide data on the external work of breathing and enable the verification of both

quantity and quality of unsupervised training sessions. The latter is of particular importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision.

## Aims

This study will examine the effects of adding a well-controlled, high-intensity inspiratory muscle training (IMT) program to a 3-month general exercise training program, using a large, multi-centre, randomised controlled design, in COPD patients with inspiratory muscle weakness. Outcomes will be exercise capacity (primary outcome), inspiratory muscle function, health-related quality of life (HRQL), and participation in daily physical activity.

## Hypotheses

We hypothesize that the addition of IMT to a general exercise training program in patients with COPD and inspiratory muscle weakness will result in superior improvements exercise capacity, inspiratory muscle function, health-related quality of life (HRQL), and daily physical activity, compared with general exercise training alone.

## Methods

### Patients

All patients with spirometry-proven COPD who are referred for outpatient pulmonary rehabilitation will be screened for inclusion. Only patients with inspiratory muscle weakness ($P_{I,max}$ < 60cm$H_2O$ or <50% predicted) will be eligible to participate in the study. Exclusion criteria consist of (1) diagnosed psychiatric or cognitive disorders; (2) progressive neurological or neuromuscular disorders; (3) severe orthopedic problems having a major impact on daily activities; (4) previous inclusion in rehabilitation program (<1 year).

## Study design

Patients will be informed about the study protocol prior to the start of the rehabilitation program. Informed consent will be obtained at that time. Patients will be randomised into an intervention and a placebo group. Group allocation will be performed by simple randomization using sealed opaque envelopes in random block sizes of 4 and 6 (order unknown to investigators).[23]

Both groups will follow a general exercise training program as described previously.[24] The intervention group will receive an additional inspiratory muscle training program described to patients as 'resistance training' at a high intensity (≥ 50% PI,max), whereas the placebo group will receive an inspiratory muscle training intervention described to patients as 'endurance training' at a low training intensity (≤ 10% PI,max).

Measurements of primary and secondary endpoints will be undertaken before and after 3 months of rehabilitation. All tests will be performed by experienced investigators who are blinded to group allocation. To ensure consistency between centres all assessments should be performed according to the instructions agreed upon and described in a manual of procedures and an instructional video, even if they may differ slightly from usual local procedures. To further improve the consistency, the five centres will regularly receive a newsletter to update them on the progress of the study and to share eventual technical problems between centers. Staff from all participating centres will be able to contact the coordinating center in Leuven by e-mail or telephone in case they should have any questions concerning the study.

To detect a minimally clinically important difference between groups of 26m in the 6-minute walking distance (6MWD),[25] assuming a standard deviation of the within group differences in the 6MWD at the end of the intervention period of 60m in both groups with a degree of certainty (statistical power) of

80% and a risk for a type I error (α) < 5%, a sample size for both groups of 85 patients is needed, given an anticipated dropout rate of 30%. This study will therefore be performed as a multi-centre randomised controlled trial to ensure inclusion of 170 patients within a time-frame of two years. Besides the lead centre at the University Hospital in Leuven, Belgium, patients will also be recruited in the University Hospital Gent, Belgium; Schön Klinik Berchtesgadener Land, Germany; University Hospital Nijmegen, The Netherlands; and Laval University Quebec, Canada. Each of the five centres is expected to include between 30 to 40 patients within the two year inclusion period.

In accordance with the Belgian law relating to experiments in humans dated May 7, 2004, KU/UZ Leuven shall assume, even without fault, the responsibility of any damages incurred by a Subject and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance program. All collaborating sites shall have and maintain in full force and effect during the term of this Agreement (and following termination of the Study to cover any claims arising from the Study) adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability, and (iii) other possible damages resulting from the Study at the Institution required by local law, each such insurance coverage in amounts appropriate to the conduct of the services of the Participating Site under this Agreement.

## Interventions

### General exercise training

Patients in both groups will follow a three-month general exercise training program. Patients will perform cycling, treadmill walking, stair climbing, arm ergometry and resistance training of both arm and leg muscles.[26] Training frequency will be three sessions per week, resulting in a total of 36 training sessions. Duration of the training session will increase from 40-60 minutes at the start of the program to 60-90 minutes after 3 months. Patients will perform endurance training or interval training at moderate

to high intensity (initially 60% to 70% of maximal workload). The overall training intensity will be increased gradually during the course of the program using a CR10 Borg scale rating of 4 to 6 on dyspnea sensation or leg effort as a means of maintaining training overload.[27] Physiotherapists providing this intervention will be blinded to group allocation of patients.

**Inspiratory muscle training program**

Patients will receive either high intensity inspiratory muscle training ('strength training' = intervention group) or low intensity placebo IMT ('endurance training' = placebo group). The training load in this study will be adjusted according to data from a previously performed pilot study about a home-based, high intensity IMT programs in COPD patients with inspiratory muscle weakness.[28] Total daily training time for both groups will be 21 minutes, consisting of 6 cycles of 30 breaths (two cycles, three times daily in the intervention group or three cycles, two times daily in the control group). There will be approximately 3.5 minutes of resistive breathing during every cycle, each followed by one minute of resting. Patients will train 7 days per week, for 12 weeks using the PowerBreathe KH1 device (POWERbreathe®KH1, HaB International Ltd., Southam, UK)). This handheld device applies a variable resistance provided by an electronically controlled valve (variable flow resistive load). Loading is maintained at the same relative intensity throughout the breath, by reducing the absolute load to accommodate the pressure-volume relationship of the inspiratory muscles. The application of a tapered load allows patients to get close to maximal inspiration, even at high training intensities (Figure 1).

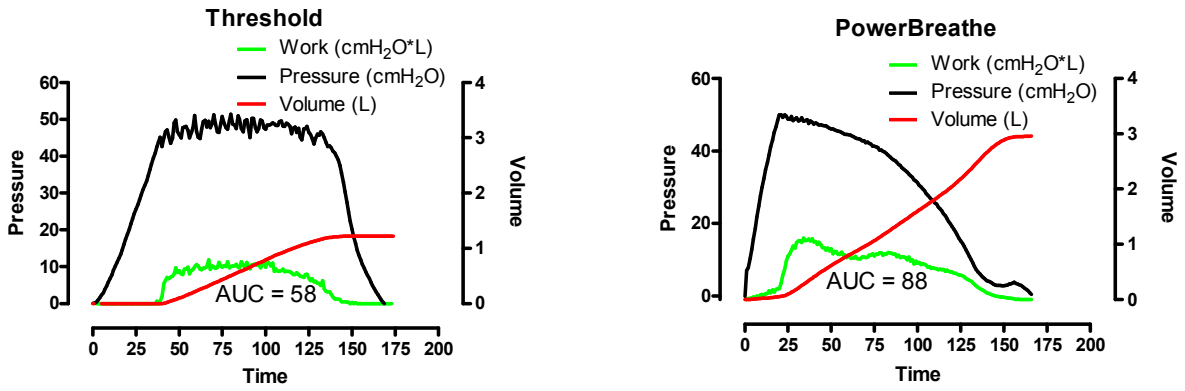



Figure 1: Comparison between constant threshold (Threshold) and variable resistive IMT (POWERbreathe® KH1).

AUC = Area Under Curve

Figure 1 illustrates a comparison of a single breath (training at an intensity of 60% Pi,max) using a conventional constant threshold loading device, with that of a variable flow resistive loading device (POWERBreathe® KH1).[28] It is apparent from this figure that, in contrast to the threshold loading, the variable flow resistive load overloads the inspiratory muscles at higher lung volumes. Since one of the hypotheses that links enhanced inspiratory muscle function to improvements in exercise capacity is that IMT may allow the respiratory system of patients with COPD to work more comfortably at high lung volumes during exercise,[22] we hypothesize that this variable flow resistive IMT should be better suited to reduce inspiratory effort (Pes/Pi,max) during whole body exercise. Besides these hypothetically beneficial characteristics of the applied load, a further advantage of the electronic leading device is the ability to store parameters of up to 40 IMT sessions. Continuous registrations of pressure and flow at 500Hz provide data on the external work of breathing and enable us to control both quantity and quality of unsupervised training sessions. This is of special importance since 85% of the training sessions during this RCT will be performed by patients at their homes without supervision. The device stores data on average mean pressure ($cmH_2O$), average mean power per breath (Watt), average peak flow per breath (L/s) and total work of breathing during one session of 30 breaths (Joules). Patients will be instructed to

perform fast and forceful inspirations and will be encouraged to achieve maximal inhalation and exhalation with every breath. This breathing pattern will be supported by acoustic signals from the loading device.

The intervention group will commence training at 40% of their initial Pi,max. Intermediate measurements of Pi,max will be performed every week. These Pi,max values will be used to calculate the training load to be implemented the following week. In other words, the training load in each week will be increased continuously over time by adjusting to at least 50% of the Pi,max value recorded in the previous week. Rates of perceived inspiratory effort on a modified CR 10 Borg-Scale (4-6 out of 10) will also be used to support decisions on training load increments. The control group will train at an inspiratory load of 10% of their initial Pi,max. This training intensity will not be changed during the study period. Each week, three training sessions will be performed under supervision at the outpatient clinic. During these supervised sessions the results of unsupervised sessions will be evaluated and patients will receive instructions and feedback on their training efforts. Resting periods will be given as needed as long as patients are able to complete the full volume of training that is prescribed. Training intensity in the intervention group will be adapted during these supervised sessions.

When patients experience acute exacerbations or respiratory infections, they will temporarily interrupt their participation in the rehabilitation and IMT program. Based on guidance from the treating pulmonologist they will however return to the program as quickly as possible. Periods of infections, exacerbations, and hospitalizations will be registered and their stay in the program will be prolonged in order to complete 12 weeks of IMT training program.

## Outcome measures

Table 1 provides an overview of the outcome measures at different time points in the study.

**Table 1.** Outcome measurements

| | Start | 3 months |
|---|---|---|
| Screen | X | |
| Informed consent | X | |
| Respiratory muscle strength | X | X |
| Inspiratory muscle endurance | X | X |
| Maximal exercise capacity | X | X |
| Endurance exercise capacity | X | X |
| Six-minute walking distance | X | X |
| Daily physical activity (7 days): | X | X |
| Pulmonary function | X | X |
| Quadriceps force | X | X |
| Handgrip force | X | X |
| CRDQ[#] | X | X |
| HADS* | X | X |

[#]*CRDQ = Chronic Respiratory Disease Questionnaire (HRQL), *HADS = Hospital Anxiety and Depression Scale*

*Respiratory muscle force*

Maximal voluntary respiratory pressures will be registered at the mouth to assess respiratory muscle force. Measurements will be performed from total lung capacity for maximal expiratory pressure (Pe,max) or residual volume for maximal inspiratory pressure (Pi,max) using the technique proposed by Black and Hyatt.[29] An electronic pressure transducer will be used (MicroRPM; Micromedical, Kent, UK). Assessments will be repeated at least 5 times (30 seconds recovery between attempts), and should be continued until at least good reproducibility has been achieved from the three best measurements

(within 10 $cmH_2O$ difference among measurements). Reference values published by Rochester and Arora will be used to define normal respiratory muscle force.[30]

*Inspiratory muscle endurance*

To measure inspiratory muscle endurance patients will be asked to breathe against a submaximal inspiratory load provided by the flow resistive loading device (POWERbreathe®KH1, HaB International Ltd., Southam, UK) until task failure. The inspiratory load that will be selected (typically between 50-60% of the Pi,max) will typically allow patients to continue breathing against the resistance for 3-7 minutes. Breathing instructions for patients will be the same as during the training sessions. Number of breaths, average duty cycle (inspiratory time as a fraction of the total respiratory cycle duration), average mean load, average mean power, and total external inspiratory work will be recorded during the test by the handheld loading device. We have recently performed a validation of the parameters that are recorded during this test and found excellent agreement between the handheld loading device and measurements performed with external, laboratory measurement equipment.[31] After 12 weeks of IMT the endurance test will be repeated using an identical load. Improvements in endurance time and breathing parameters will be recorded.

*Maximal exercise capacity (incremental exercise test)*

Maximal exercise capacity will be assessed by a maximal incremental cycle exercise test (Ergometrics 900, Ergoline, Bitz, Germany). After a two-minute resting period and three minutes of unloaded cycling, patients will start cycling at a load of 20 Watt. Load will then be increased by 10 Watt per minute and patients will cycle until symptom limitation. Oxygen uptake, carbon dioxide output and ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Heart rate and oxygen saturation will be recorded continuously. Maximal oxygen uptake will be compared with normal

values.[32] The perception of dyspnea and leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified Borg scale.[27] Development of dynamic hyperinflation during the exercise test will be assessed by recording changes in end-expiratory lung volumes. Patients will be instructed to perform maximal inspiratory maneuvers after a normal expiration during resting breathing and at the end of each level of exercise. Assuming a constant total lung capacity a decrease in inspiratory capacity will indicate an increase in end expiratory lung volume, which indicates the degree of dynamic hyperinflation.[33] Tidal volume ($V_T$), inspiratory time ($T_I$), total time of the respiratory cycle ($T_{TOT}$) and respiratory frequency (fR) will be assessed. The $T_I/T_{TOT}$ (duty cycle) represents the proportion of the breath during which the inspiratory muscles are contracting.

*Endurance exercise capacity (constant work rate test)*

A constant power output cycle test until symptom limitation will be performed at 80% of the maximal power output (in Watts) that was reached during the initial incremental exercise test (Ergometrics 900, Ergoline, Bitz, Germany). Oxygen uptake, carbon dioxide output and minute ventilation will be measured breath by breath (Vmax series, SensorMedics, Anaheim, CA). Breathing pattern and dynamic hyperinflation will be monitored as described previously for the incremental cardiopulmonary exercise test. Heart rate and oxygen saturation will be monitored continuously. The perception of dyspnea and leg effort will be quantified at two-minute intervals during exercise and at the end of the test using the modified CR10 Borg scale.[27]

*6-minute walking distance (6MWD)*

Functional exercise performance will be measured using a six-minute walking test in a 50m corridor. Standardized encouragement will be provided.[34] The best of two tests separated by recovery time 30

minutes will be used and related to reference values.[35] Oxygen saturation, heart rate and symptoms of leg effort and dyspnea will be recorded before and after the test.

*Physical activity monitoring*

Measurements will be performed with an accelerometer-based activity monitor (DynaPort Minimod, McRoberts BV, The Hague, The Netherlands). The Minimod is a small (64x62x13mm) and lightweight device (68gram, including batteries) that contains a three-axial piezocapacitive sensor measuring at high time-resolution (100Hz). Analysis of raw data allows for classification of intensity, duration and frequency of movement. Different postures and walking are identified and energy expenditure is estimated. The Minimod has been validated in patients with COPD.[36] Assessments will be undertaken on seven consecutive days during waking hours.

*Pulmonary function*

Spirometry and whole body plethysmography will be performed according to the European Respiratory Society guidelines for pulmonary function testing (Vmax Autobox, Sensor Medics, Bilthoven, the Netherlands).[37] Diffusing capacity for carbon monoxide will be measured by the single breath method (Sensor Medics 6200, Bilthoven, the Netherlands).[38]

*Peripheral muscle force*

Isometric quadriceps force will be quantified using a Cybex Norm Dynamometer (Cybex® Norm, Enraf Nonius, Delft, the Netherlands). Peak extension torque will be measured at 60° of knee flexion. At least three measurements will be obtained and the highest reproducible value (within 11%) will be taken into analysis. Reference values have been developed in our laboratory.[39]

Isometric hand grip force will be measured using a hydraulic hand grip dynamometer (Jamar Preston, Jackson, MI). Peak force will be assessed with the elbow fixed to the rib cage and flexed 90° and with the wrist in neutral position. At least three measurements will be obtained and the highest reproducible value will be taken into analysis and related to reference values.[26]

*Health-related quality of life*

The Chronic Respiratory Disease Questionnaire (CRDQ) will be used to assess health-related quality of life.[40] This 20-item questionnaire scores quality of life in 4 domains (dyspnea, mastery, emotional functioning and fatigue) and has been validated in the Dutch, German and French language.[41-43] The total score can range from 20 to 140 with higher scores indicating better quality of life.

*Anxiety and depression*

The Hospital Anxiety and Depression Scale (HADS) will be used to assess emotional distress.[44] The HADS consists of 14 items and has separate scores for anxiety (7 items) and depression (7 items). A score of 11 or greater on either of the sub-scales suggests clinically significant symptoms of anxiety or depression.

## Statistical analysis

Differences in primary and secondary outcomes between groups after 3-months of intervention will be compared adjusting for baseline differences using analysis of covariance (ANCOVA).[45] Both an 'intention-to-treat' and a 'per-protocol' analysis will be carried out to compare outcomes between groups.

## Ethics and dissemination

Ethics approval has been obtained from relevant centre committees. The results from the randomised controlled trial of IMT will be submitted for publication.

## Discussion

This large, adequately powered, multi-centre randomised controlled trial will investigate effects of IMT as an adjunct to a general exercise training program. Outcomes will be exercise capacity (primary outcome), health related quality of life, and participation in daily physical activity in the selected COPD patients who have pronounced inspiratory muscle weakness. The IMT in this RCT will be performed using the variable flow resistive loading device described previously (POWERbreathe®KH1, HaB International Ltd., Southam, UK) and validated.[31] Besides the hypothetically beneficial characteristics of the applied load described above, a further advantage of this device is the ability to store training parameters of up to 40 sessions. Continuous recording of pressure and flow enable us to monitor both the quantity and quality of unsupervised training sessions. The latter is of special importance, since 85% of IMT sessions will be undertaken by patients in their homes, without supervision.

We anticipate that the outcomes of this study will be of direct relevance to clinical practice. The results of this study should therefore be incorporated immediately into evidence based treatment recommendations for clinical practice. During the communication of these recommendations it will be of special importance to stress that the results obtained in this RCT will limited to the selected group of patients with COPD, i.e. those with inspiratory muscle weakness.

## Reference List

1 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765-73.

2 Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532-55.

3 Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD*. available at: http://www.goldcopd.org/ . 2011.
Ref Type: Internet Communication

4 O'Donnell DE, Travers J, Webb KA, et al. Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD. *Eur Respir J* 2009;**34**:866-74.

5 Hamilton N, Killian KJ, Summers E, et al. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;**152**:2021-31.

6 Lacasse Y, Goldstein R, Lasserson TJ, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006;CD003793.

7 Decramer M, Demedts M, Rochette F, et al. Maximal transrespiratory pressures in obstructive lung disease. *Bull Eur Physiopathol Respir* 1980;**16**:479-90.

8 Polkey MI, Kyroussis D, Hamnegard CH, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1310-7.

9 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;**168**:10-48.

10 Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;**143**:905-12.

11 Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;**153**:976-80.

12 Nici L, Donner C, Wouters E, et al. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 2006;**173**:1390-413.

13 Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007;**131**:4S-42S.

14 Gosselink R, De VJ, van den Heuvel SP, et al. Impact of inspiratory muscle training in patients with COPD: what is the evidence? *Eur Respir J* 2011;**37**:416-25.

15 Geddes EL, O'Brien K, Reid WD, et al. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respir Med* 2008;**102**:1715-29.

16 Ambrosino N. The case for inspiratory muscle training in COPD. *Eur Respir J* 2011;**37**:233-5.

17 McConnell AK. CrossTalk opposing view: respiratory muscle training does improve exercise tolerance. *J Physiol* 2012;**590**:3397-8.

18 Patel MS, Hart N, Polkey MI. CrossTalk proposal: training the respiratory muscles does not improve exercise tolerance. *J Physiol* 2012;**590**:3393-5.

19 Polkey MI, Moxham J, Green M. The case against inspiratory muscle training in COPD. Against. *Eur Respir J* 2011;**37**:236-7.

20 Decramer M. Response of the respiratory muscles to rehabilitation in COPD. *J Appl Physiol* 2009;**107**:971-6.

21 Winkelmann ER, Chiappa GR, Lima CO, et al. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J* 2009;**158**:768-7.

22 Luo YM, Hopkinson NS, Polkey MI. Tough at the top: must end-expiratory lung volume make way for end-inspiratory lung volume? *Eur Respir J* 2012;**40**:283-5.

23 Doig GS, Simpson F. Randomization and allocation concealment: a practical guide for researchers. *J Crit Care* 2005;**20**:187-91.

24 Troosters T, Gosselink R, Decramer M. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. *Am J Med* 2000;**109**:207-12.

25 Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. *Eur Respir J* 2011;**37**:784-90.

26 Mathiowetz V, Dove M, Kashman N, et al. Grip and pinch strength: normative data for adults. *Arch Phys Med Rehabil* 1985;**66**:69-72.

27 Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**:377-81.

28 Langer D, Jacome C, Hoffman M, et al. Comparison of two high intensity inspiratory muscle training programs in patients with COPD: A randomized controlled trial. *Am J Respir Crit Care Med* **2013**; 187: A2566.

29 Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 1969;**99**:696-702.

30 Rochester DF, Arora NS. Respiratory muscle failure. *Med Clin North Am* 1983;**67**:573-97.

31 Langer D, Jacome C, Charususin N, et al. Measurement validity of an electronic inspiratory loading device during a loaded breathing task in patients with COPD. *Respir Med* 2013;**107**:633-5.

32 Jones NL, Makrides L, Hitchcock C, et al. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis* 1985;**131**:700-8.

33 Yan S, Kaminski D, Sliwinski P. Reliability of inspiratory capacity for estimating end-expiratory lung volume changes during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;**156**:55-9.

34 Guyatt GH, Pugsley SO, Sullivan MJ, et al. Effect of encouragement on walking test performance. *Thorax* 1984;**39**:818-22.

35 Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. *Eur Respir J* 1999;**14**:270-4.

36 Langer D, Gosselink R, Sena R, et al. Validation of two activity monitors in patients with COPD. *Thorax* 2009;**64**:641-2.

37 Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319-38.

38 MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;**26**:720-35.

39 Decramer M. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. 1994.

40 Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773-8.

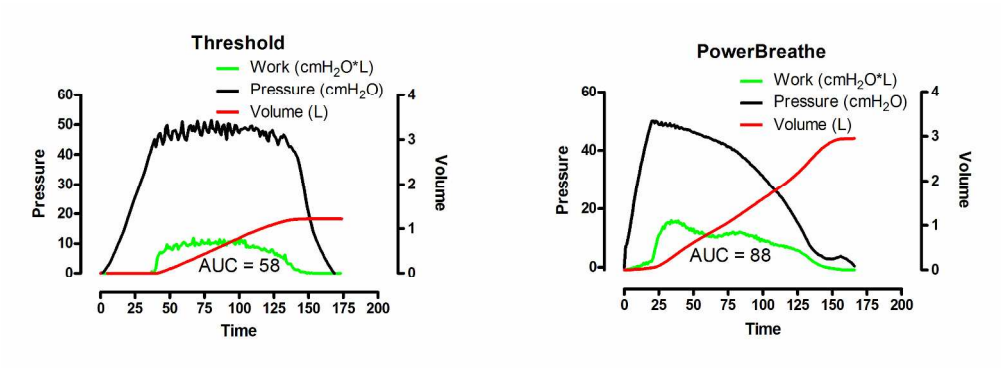
41 Puhan MA, Behnke M, Frey M, et al. Self-administration and interviewer-administration of the German Chronic Respiratory Questionnaire: instrument development and assessment of validity and reliability in two randomised studies. *Health Qual Life Outcomes* 2004;**2**:1.

42 Bourbeau J, Maltais F, Rouleau M, et al. French-Canadian version of the Chronic Respiratory and St George's Respiratory questionnaires: an assessment of their psychometric properties in patients with chronic obstructive pulmonary disease. *Can Respir J* 2004;**11**:480-6.

43 Wijkstra PJ, TenVergert EM, Van AR, et al. Reliability and validity of the chronic respiratory questionnaire (CRQ). *Thorax* 1994;**49**:465-7.

44 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;**67**:361-70.

45 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;**323**:1123-4.




(Figure 1)
250x91mm (300 x 300 DPI)