Respiratory Muscle Endurance Training in patients with Chronic Obstructive Pulmonary Disease

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The studies presented in this thesis were supported by the Netherlands Asthma Foundation (grant no 3.4.99.40)

Cover foto Helene Koppers-Høyset
Layout Twanny Jeijsman
Print PrintPartners Ipskamp B.V. Enschede

ISBN 90-9019941-1

Respiratory Muscle Endurance Training in patients with Chronic Obstructive Pulmonary Disease

Een wetenschappelijke proeve op het gebied

van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor

aan de Radboud Universiteit Nijmegen

op gezag van de Rector Magnificus prof.dr. C.W.P.M. Blom

volgens besluit van het College van Decanen

in het openbaar te verdedigen op dinsdag 1 november 2005

des namiddags om 1.30 uur precies

door

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geboren op 30 november 1967

te Venlo

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GENERAL INTRODUCTION

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is defined as a disorder that is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.[1]

The chronic airflow limitation is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation causes remodelling and narrowing of the small airways. Destruction of the lung parenchyma , also by inflammatory processes, leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil; in turn, these changes diminish the ability of the airways to remain open during expiration. The amount of airflow limitation is measured by spirometry. A simple classification, based on spirometric data is recommended by the Global Initiative for Chronic Obstructive Lung Disease: stage 0 to IV. (table 1)[1]

COPD is a major and growing global health problem. It ranks the fourth place in most common causes of death world wide. It is the only common cause of death which prevalence has increased over the past twenty years, and maybe even more important, it will increase in both death-ranking and cause of chronic disability until 2020. COPD primarily affects middle aged and older persons. Smoking is the most frequent cause of the development of COPD, accounting for more than 90% of cases in developed countries. However, COPD develops in only a minority of smokers (10

to 20 percent), indicating that there are differences in individual susceptibility to the effects of cigarette smoking.[2]

Table 1: Classification of COPD by severity (GOLD guidelines)[1]

stage	**characteristics**
0: at risk	-normal spirometry -chronic cough and sputum production
I: mild COPD	-FEV_1/FVC<70% -FEV_1≥80% predicted -with or without chronic symptoms; cough, sputum production
II:moderate COPD	-FEV_1/FVC<70% -50%≤ FEV_1<80% predicted -progression of symptoms, with shortness of breath typically developing on exertion.
III: severe COPD	-FEV_1/FVC<70% -30%≤ FEV_1<50% predicted -increased shortness of breath, and repeated exacerbations which have an impact on Quality of Life
IV: very severe COPD	-FEV_1/FVC<70% -FEV_1<30% predicted or presence of chronic respiratory failure

Respiratory complaints are variable and usually consist of cough, sputum production and recurrent exacerbations. These complaints usually progress with increasing disease severity. Most patients experience dyspnea on exertion, or even at rest when the disease progresses. COPD not only leads to respiratory problems, it also leads to systemic abnormalities. A lot of patients suffer from exercise intolerance. Maximal as well as endurance exercise capacity are often diminished. Furthermore, systemic inflammation can be found in COPD patients.[3] Peripheral muscle weakness is often

present in COPD patients, which also contributes to exercise limitation.[4-13] Weight loss and low fat free mass index is another important abnormality, which is associated with increased mortality and diminished exercise capacity.[14;15] (see table 1)

Respiratory muscles

The primary ventilatory muscle is the diaphragm. It is active throughout the entire life of an individual and to a certain extent represents the sole skeletal muscle that is essential for life. Other respiratory muscles are the scalenes and the external intercostals (inspiratory muscles) and abdominal muscles (rectus abdominis, external and internal obliques and transverses abdominis) and internal intercostals (expiratory muscles).[16;17] Respiratory muscles improve their function in response to training, like all skeletal muscles.

Dysfunction of the respiratory muscles frequently occurs in patients with COPD. Reduced respiratory muscle function is caused by either respiratory muscle weakness, relative inactivity due to dyspnea, increased work of breathing due to changes in the airways and lungs and inefficiency of the inspiratory muscles because of hyperinflation or a combination of these factors.[18] Respiratory muscle weakness may occur because of metabolic abnormalities such as malnutrition, abnormalities in arterial blood gases and electrolyte concentrations, infection and chronic systemic steroid administration. Airway obstruction due to mucus and/or inflammation of the airways, and loss of alveolar tissue, which all contribute to dynamic airway compression and hyperinflation, lead to increased work of breathing. Hyperinflation, leading to abnormally large lung volumes, causes the inspiratory muscles to operate at lengths shorter than normal. Because of the length-tension curve, this condition

places these muscles at a disadvantage for tension generation. The diaphragm, under quiet breathing conditions performing about 70-80% of the work of breathing, is affected to the greatest degree.[17]

This respiratory muscle dysfunction may contribute to sensations of dyspnea, limited exercise tolerance, reduced quality of life, and as the disease progresses, hypercapnic ventilatory failure.[18;19] The clinical importance is ambiguous: first of all there is the patient with her or his complaints and disabilities. Secondly an increased utilization of health care resources was observed in COPD patients with weakness of the respiratory muscles.[20]

As a consequence, treatment of respiratory muscle dysfunction has gained interest in the last three decades. Treatment modalities that were used include pharmacotherapy, nutritional repletion, and respiratory muscle training to improve strength and endurance. In this thesis we focus on respiratory muscle training.

Training principles

Training of the ventilatory muscles must follow the basic principles of training for any striated muscle with regard to the intensity and duration of the stimulus, the specificity of training and the reversibility of training. The basic principles are that for muscle fibres to change structure and function they must be stressed (loaded) above a critical threshold. This load may be applied by increasing the frequency of training, the duration of training, the intensity of the loading, or a combination of these factors. Secondly training is specific for the stimulus- that is, *strength training* will increase fibre size (muscle hypertrophy) whereas *endurance training* will increase oxidative enzymes and mitochondrial density, myoglobin content, and capillary density.

According to this principle, respiratory muscle training will improve respiratory muscle function during day to day activities when the type of recruitment pattern during training is most similar to the recruitment pattern required during those activities. Leith and Bradley showed that indeed ventilatory muscle strength or endurance can be specifically increased by appropriate ventilatory muscle training programs.[21] Furthermore training is reversible and the effects will be reduced (deconditioning) if the training ceases. As soon as the individual stops training, the structural and functional changes within the body related to training will begin to return to baseline. [18;22-24]

Concerning the respiratory muscles in patients with COPD, strength training, as well as endurance training has been performed, with different rates of success. Training of the respiratory muscles can also be achieved by both specific and non-specific conditioning programs. The obvious non-specific program is total body exercise. Specific training programs include inspiratory resistive training and threshold loading (strength training) and normocapnic hyperpnea (endurance training).

The effects of respiratory muscle training can be evaluated in several ways. First of all the performance of the muscles itself can be tested. Respiratory muscle strength can be tested by means of evaluation of maximal in- and expiratory pressures (Pimax and Pemax).[25;26] Endurance capacity can be tested by incremental threshold loading[27] and other endurance tests like maximal sustained ventilatory capacity. Determination of the tension-time index also provides information in this way.[28] Furthermore, the effects of respiratory muscle training can be evaluated in terms of functional and endurance exercise capacity, which are useful outcome measurements as was pointed out in a recent editorial by Polkey and Moxham.[29]

Respiratory muscle strength training: inspiratory resistive training and threshold loading

Respiratory muscle strength training can be described as performing (sub-)maximal inspiratory or expiratory manoeuvres against a resistance. The repetition rate is low (5-10 repetitions/minute). The primary goal of strength training is to improve force production of the respiratory muscles, thereby also improving, to some extent the endurance capacity of these muscles, and eventually improving the exercise capacity of the patient and reducing dyspnea.

Inspiratory resistive training (IRT) is a well known respiratory muscle *strength*-training technique, aimed at generating high inspiratory pressures. During IRT the patient inspires through a mouthpiece with a two-way valve with a resistance in the inspiratory line, usually at normal breathing frequencies. This method is highly dependent on the breathing strategy and subjects can adopt a non-fatiguing breathing pattern with low-flow rates.[30] Essentially, this type of training follows Ohm's law characteristics: P=VxR (P=driving pressure, V=inspiratory flow, R=resistance). When imposing only a resistance (R) the patient has two degrees of freedom to regulate breathing: pressure (P) and flow (V). Consequently, in this type of training, two parameters have to be imposed: P *and* R or V *and* R. Thus the breathing pattern is strictly defined and controlled.[31] Expiration is unimpeded.

Threshold loading is a method which imposes pressures independent of flow-rates. Subjects have to breathe through a device with an inspiratory valve (weighted plunger) or a spring loaded inspiratory valve. This inspiratory valve is opened when a

critical mouth pressure is reached.[32] It can also be performed for expiratory muscle training.

Most studies using these techniques showed that respiratory muscles can be trained.[31;33-40] Some studies also showed a reduction of dyspnea.[34-38] The effects of respiratory muscle strength training on general exercise capacity are however not unambiguous. Some investigators found a modestly increased exercise capacity after IRT[33-37;39;41-43], whereas other studies did not reveal such effects.[44;45] These differences may be due to the method and protocol of IRT that was used, due to patient selection, as well as the fact that the outcome parameters of these studies mostly were incremental maximal exercise tests.

Normocapnic hyperpnea: Respiratory Muscle Endurance Training (RMET)

Normocapnic hyperpnea is a mode of *endurance* training of the respiratory muscles. This Respiratory Muscle Endurance Training (RMET) has much wider potential clinical application than respiratory muscle strength training because the respiratory muscles must remain active continuously even when placed under added loads, for example during exercise, infection, or in case of severe COPD even during activities of daily life. Normocapnic hyperpnea is based on non-resistive hyperpnea, in which patients are inspiring or rebreathing CO_2 in order to maintain CO_2 homeostasis. RMET may be closer related to daily life situations of COPD patients. It has only been used for research purposes and not for routine clinical use, because of the complicated equipment needed, requiring a laboratory setting.[19;46]

Normocapnic hyperpnea requires the individual to sustain a period of hyperpnea for about 15 minutes. It is probably the best technique for improving endurance of the respiratory muscles at high speeds of muscle contraction, which occurs during hyperpnea and exercise.[18] An improvement of 268% in breathing endurance was found after isolated normocapnic hyperpnea in healthy sedentary subjects, whereas, in the same study, a sub-maximal exercise test increased with 50%.[47] Improvements in respiratory muscle function and exercise performance were described in trained athletes.[48] COPD-patients trained with RMET showed improvement of respiratory muscle function[49] and exercise performance.[50-52]

Home-based normocapnic hyperpnea requires special equipment to maintain arterial blood gases within a physiological range, because during a period of hyperpnea the partial pressure of arterial carbon dioxide ($paCO_2$) decreases. CO_2-homeostasis during normocapnic hyperpnea can be achieved by adding an external dead space to the respiratory system. Because of a lack of a home training device for normocapnic hyperpnea, this kind of training method has rarely been used as a training mode for patients with COPD. RMET was applied as a home-based training regimen in only two studies in patients with COPD.[51;52] The studies by Boutellier and Scherer,[47;48;52] that are mentioned above, were performed with a specially developed, electro-mechanical device, which is expensive and complicated. Enlargement of the respiratory dead space can also be done by breathing through a tube, which is much easier and less expensive. Therefore Respiratory Muscle Endurance Training (RMET) by means of tube breathing, might be a promising technique enabling a widespread use.

Exercise capacity

Maximal exercise tests are widely used to asses the factors that limit exercise tolerance, to quantify the extent of disability and to set up an exercise training program.

Exercise tolerance can be limited in several ways. The respiratory and cardio-circulatory systems are involved in the transport of oxygen from the atmosphere to the mitochondria of skeletal muscle.

Respiratory function can be diminished by impaired ventilatory capacity, impaired diffusion and ventilation-perfusion mismatch. CO_2 elimination is limited by alveolar ventilation, whereas O_2 uptake is most vulnerable at the diffusion through the alveolar membrane.

The cardio-circulatory transport of oxygen is dependent on cardiac output, peripheral vascularisation and the quantity of haemoglobin.

Exercise tolerance can furthermore be diminished because of peripheral muscle weakness, neurological problems and psychological factors such as dyspnea.

It is known that limited exercise capacity is frequently observed in patients with COPD. Diminished ventilatory efficiency and dyspnea can be one of the factors contributing to this impairment in exercise capacity. This diminished ventilatory efficiency results from either respiratory muscle weakness, increased work of breathing due to changes in the airways and lungs and inefficiency of the inspiratory muscles because of hyperinflation, or a combination of these factors.[18]

Patients with mild to moderate COPD (GOLD I and II) are, similarly to healthy subjects, limited during exercise by the cardio-circulatory system and on metabolic factors at the level of the peripheral muscles. During incremental exercise, these subjects may achieve their maximal, age-specific heart-rate and blood lactate may increase by more than 10 mmol/liter, reflected by a decrease in base-excess.[53] Dyspnea and perceived leg effort contribute to subjective exercise limitation.[54]

Patients with severe COPD (GOLD III) are usually limited by their ventilatory system: either by abnormal respiratory mechanics or by gas exchange disturbances. Failure of the respiratory pump function leads to hypercapnia and eventually hypoxemia because of insufficient alveolar ventilation. Respiratory muscle function, amongst others, is an important determinant of exercise capacity.[4] Maximal exercise capacity is substantially limited by dyspnea.[55] At the point of maximal exercise, maximal minute ventilation approaches or exceeds maximal voluntary ventilation, which as a consequence, results in a low or negative breathing reserve. Furthermore, dynamic hyperinflation during exercise may lead to an increased load on the respiratory muscles and increased exercise intolerance.[56] However, dyspnea may limit exercise before those mechanisms lead to a physiological limitation. As a consequence, age specific maximal heart rate will not be reached. Thus improvement of respiratory muscle function and improved alveolar ventilation, reduction of dyspnea, as well as bronchodilatation, may lead to improvement of exercise capacity.[33;35-37;57]

Although it was generally accepted that ventilation does not limit exercise performance in normal subjects without airway obstruction, literature from sports medicine suggests that respiratory muscle endurance training by means of

normocapnic hyperpnea in healthy volunteers leads to a substantial improvement of breathing endurance and endurance exercise capacity.[47;48;58] It is strikingly apparent that people with fully trained respiratory muscles have the lowest minute-ventilation possible, and their respiratory muscles fatigue later and metabolise more lactate, but the mechanism by which respiratory training improves overall physical performance is as yet unknown.[59]

It also seems important to take the different outcome parameters into account. Studies performed before 1990 mostly used maximal incremental exercise tests to determine exercise capacity,[41;42;45;60] whereas later studies also tested endurance capacity by means of constant load exercise testing.[47;48;52;57;58;61-65] Constant load exercise testing (CLET) can be used to measure endurance exercise capacity and to compare ventilatory and metabolic parameters at the same work-rate before and after intervention. The latter being an effort independent measurement of training effects. CLET has been proven to be a reproducible, reliable and valid method to assess endurance exercise capacity in patients with COPD.[66;67]

Considering the above-mentioned, training methods for respiratory muscles that improve *endurance* capacity may be more beneficial to patients with COPD, as in daily life maximal exercise is seldomly performed. Therefore outcome parameters should also focus on *endurance* capacity rather then maximal exercise.

Dyspnea

Dyspnea is an important symptom in patients with COPD. Dyspnea may be defined as the unpleasant awareness of the need to breathe. Dyspnea originates a.o. in the central nervous system because of an imbalance between motor neural output to the

respiratory muscles and the magnitude of ventilation resulting from it. In patients with COPD the sense of respiratory muscular effort is an important determinant of dyspnea.[68;69] The clinical rating of dyspnea as measured by the Baseline Dyspnea Index is significantly correlated with maximal inspiratory and expiratory pressure.[70] Several studies have shown that respiratory muscle strength-training, by means of resistive breathing or threshold loading, leads to an improvement of respiratory muscle function[31;33-39] and an improvement of dyspnea[33;35-38] in patients with COPD. Only one study, using endurance respiratory muscle training in COPD patients, looked at the effects of this training regimen on dyspnea. Scherer and co-workers showed an improvement of dyspnea after RMET.[52]

Other factors contributing to dyspnea are hypercapnia and hypoxia sensed by the chemo receptors. Proprio receptors in the respiratory muscles, especially the muscle spindles in the intercostals, are important contributors to dyspnea sensations. These spindles are essential in detecting a length-tension inappropriateness in every muscle. The tension/force, relative to the maximal force that a muscle can generate, is a major determinant of the sensation of load on a muscle. This type of sensations from intercostals muscles, is perceived as dyspnea. Furthermore different signals which originate in the parenchyma of the lung and in the airways contribute to dyspnea. It can be concluded that dyspnea is a multi-factorial problem. Interventions leading to improvement of respiratory muscle function or adaptation to signals from mechanoreceptors or chemo receptors thus may lead to a reduction of the unpleasant sensation of breathing/dyspnea.

Health related Quality of life

Survival and physiological parameters of airway narrowing do not represent the full impact of the disease for patients with COPD. It is also important to reduce the personal and social burden of the disease by improving symptoms and functional status.[71] Therefore health related quality of life has become an important outcome for treatment in studies with COPD patients. Measurement of health related quality of life, is a means of quantifying, in a standardised and objective manner, the impact of disease on a patient's daily life, health and wellbeing.[72] A number of instruments have been developed to measure (changes in) health status in COPD: The Chronic Respiratory Disease Questionnaire and the St George's Hospital Questionnaire have been validated and have proven to be responsive to (training induced) changes.[73;74] Only one study looked at the effects of RMET on quality of life in COPD. An improvement of the physical, but not the mental component of the SF-12 health questionnaire was found.[52] Since dyspnea is an important determinant of the health related quality of life in COPD it can be speculated that, once dyspnea improves as a result of respiratory muscle training, quality of life also may improve.

Pulmonary rehabilitation

Pulmonary rehabilitation is a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise physical and social performance and autonomy.[75] The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities.[1] To achieve these goals, smoking cessation must be encouraged and patients should be supported. Furthermore, medical therapy must be optimised and exercise training, physical therapy, breathing

retraining, nutrition counselling and education of the patient and family must be carried out.[1;76-79] The diagnosis must of course be accurate and an evaluation of the exercise limitation is preferable. COPD patients at all stages of disease benefit from exercise training programs. Specific pulmonary rehabilitation programs are recommended for GOLD stage II to IV.[1] There are no specific patient selection criteria, but patients must have symptomatic chronic lung disease. They must be stable with optimal standard medical therapy and experience functional limitation from their disease. Furthermore they must be motivated and there should be no interfering or unstable medical conditions.[75] The benefits of pulmonary rehabilitation in patients with COPD have been well established: improvement of exercise capacity, reduction in perceived breathlessness, improvement of quality of life, reduction in the number of hospitalisations and a reduction in anxiety and depression associated with COPD.[1;80-83] Guidelines for the assessment of candidates and goals of treatment have also been published in the Netherlands.[84]

Respiratory muscle training in pulmonary rehabilitation is a controversial issue.[76-79] Selection of patients, different training modalities and protocols and measurement of different outcome parameters may be the cause of this. However, the recent GOLD guidelines mention that respiratory muscle training is beneficial, especially when combined with general exercise training.[1]

OUTLINES AND AIMS OF THE STUDY

In the following studies we describe the applicability of home-based normocapnic hyperpnea by means of tube breathing and the effects of this respiratory muscle endurance training on CO2-homeostasis, endurance exercise capacity, dyspnea, quality of life and pulmonary rehabilitation.

The aim of *chapter 2* was to study the feasibility and safety of tube breathing as a new method of respiratory muscle endurance training (RMET) and its effects on CO2 homeostasis in healthy volunteers.

In *chapter 3* we describe the effects of tube breathing, on CO2 homeostasis in COPD patients.

Chapter 4 focuses on the results of home-based RMET, comparing normocapnic hyperpnea RMET with sham training, in patients with moderate to severe COPD, waiting for in-patient pulmonary rehabilitation. Outcome parameters were respiratory muscle performance, endurance and maximal exercise capacity and perception of dyspnea.

In *chapter 5*, which is closely related to chapter 4, we describe the effects of home-based RMET compared to sham training, with regard to quality of life and dyspnea in daily activities, in patients with moderate and severe COPD, before in-patient pulmonary rehabilitation.

The aim of *chapter 6* was to study the effects of optimising the respiratory muscles by means of RMET, on the outcome of a pulmonary rehabilitation program. We hypothesized that optimising the respiratory muscles *before* the rehab program would lead to a better outcome of this program in terms of respiratory muscle performance and endurance exercise capacity.

Chapter 7 gives a summary of the studies in this thesis. The general conclusions and implications for daily practice are discussed.

REFERENCES

1. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care 2001; 46(8):798-825.
2. Barnes PJ. Small airways in COPD. N Engl J Med 2004; 350(26):2635-2637.
3. Rabinovich RA, Figueras M, Ardite E, Carbo N, Troosters T, Filella X et al. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. Eur Respir J 2003; 21(5):789-794.
4. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 1996; 153(3):976-980.
5. Casaburi R. Skeletal muscle function in COPD. Chest 2000; 117(5 Suppl 1):267S-271S.
6. Debigare R, Cote CH, Maltais F. Peripheral Muscle Wasting in Chronic Obstructive Pulmonary Disease. Clinical relevance and mechanisms. Am J Respir Crit Care Med 2001; 164(9):1712-1717.
7. Maltais F, Leblanc P, Jobin J, Casaburi R. Peripheral muscle dysfunction in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):665-677.
8. Bernard S, Leblanc P, Whittom F, Carrier G, Jobin J, Belleau R et al. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 158(2):629-634.
9. Maltais F, Simard AA, Simard C, Jobin J, Desgagnes P, Leblanc P. Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am J Respir Crit Care Med 1996; 153(1):288-293.

10. Debigare R, Cote CH, Maltais F. Peripheral Muscle Wasting in Chronic Obstructive Pulmonary Disease. Clinical relevance and mechanisms. Am J Respir Crit Care Med 2001; 164(9):1712-1717.

11. Maltais F, Leblanc P, Jobin J, Casaburi R. Peripheral muscle dysfunction in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):665-677.

12. Reid MB. COPD as a muscle disease. Am J Respir Crit Care Med 2001; 164(7):1101-1102.

13. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 1999; 159:S1-40.

14. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J 2002; 20(3):539-544.

15. Agusti AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002; 166(4):485-489.

16. Poole DC, Sexton WL, Farkas GA, Powers SK, Reid MB. Diaphragm structure and function in health and disease. Med Sci Sports Exerc 1997; 29(6):738-754.

17. Reid WD, Dechman G. Considerations when testing and training the respiratory muscles. Phys Ther 1995; 75(11):971-982.

18. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther 1995; 75(11):996-1005.

19. Gosselink R, Decramer M. Inspiratory muscle training: where are we? Eur Respir J 1994; 7(12):2103-2105.

20. Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. Eur Respir J 1997; 10(2):417-423.

21. Leith DE, Bradley M. Ventilatory muscle strength and endurance training. J Appl Physiol 1976; 41(4):508-516.

22. Goldstein RS. Pulmonary rehabilitation in chronic respiratory insufficiency. 3. Ventilatory muscle training. Thorax 1993; 48(10):1025-1033.

23. NHLBI Workshop summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. Am Rev Respir Dis 1990; 142(2):474-480.

24. Casaburi R. Principles of exercise training. Chest 1992; 101:263S-267S.

25. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis 1969; 99(5):696-702.

26. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39(7):535-538.

27. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. Am Rev Respir Dis 1987; 135(4):919-923.

28. Hayot M, Perrigault PF, Gautier-Dechaud V, Capdevila X, Milic-Emili J, Prefaut C et al. Tension-time index of inspiratory muscles in COPD patients: role of airway obstruction. Respir Med 1998; 92(6):828-835.

29. Polkey MI, Moxham J. Improvement in volitional tests of muscle function alone may not be adequate evidence that inspiratory muscle training is effective. Eur Respir J 2004; 23:5-6.

30. Belman MJ, Thomas SG, Lewis MI. Resistive breathing training in patients with chronic obstructive pulmonary disease. Chest 1986; 90(5):662-669.

31. Belman MJ, Shadmehr R. Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease. J Appl Physiol 1988; 65(6):2726-2735.

32. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. J Appl Physiol 1982; 52(3):768-772.

33. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Specific expiratory muscle training in COPD. Chest 2003; 124(2):468-473.

34. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. Chest 2003; 124(4):1357-1364.

35. Sanchez RH, Montemayor RT, Ortega RF, Cejudo RP, Del Castillo OD, Elias HT et al. Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life. Chest 2001; 120(3):748-756.

36. Lisboa C, Munoz V, Beroiza T, Leiva A, Cruz E. Inspiratory muscle training in chronic airflow limitation: comparison of two different training loads with a threshold device. Eur Respir J 1994; 7(7):1266-1274.

37. Lisboa C, Villafranca C, Leiva A, Cruz E, Pertuze J, Borzone G. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. Eur Respir J 1997; 10(3):537-542.

38. Harver A, Mahler DA, Daubenspeck JA. Targeted inspiratory muscle training improves respiratory muscle function and reduces dyspnea in patients with chronic obstructive pulmonary disease. Ann Intern Med 1989; 111(2):117-124.

39. Larson JL, Kim MJ, Sharp JT, Larson DA. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988; 138(3):689-696.

40. Flynn MG, Barter CE, Nosworthy JC, Pretto JJ, Rochford PD, Pierce RJ. Threshold pressure training, breathing pattern, and exercise performance in chronic airflow obstruction. Chest 1989; 95(3):535-540.

41. Sonne LJ, Davis JA. Increased exercise performance in patients with severe COPD following inspiratory resistive training. Chest 1982; 81(4):436-439.

42. Wanke T, Formanek D, Lahrmann H, Brath H, Wild M, Wagner C et al. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD [see comments]. Eur Respir J 1994; 7(12):2205-2211.

43. Belman MJ, Kuei J. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1989; 139(3):851-852.

44. Andersen JB, Dragsted L, Kann T, Johansen SH, Nielsen KB, Karbo E et al. Resistive breathing training in severe chronic obstructive pulmonary disease. A pilot study. Scand J Respir Dis 1979; 60(3):151-156.

45. Chen H, Dukes R, Martin BJ. Inspiratory muscle training in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1985; 131(2):251-255.

46. Bourjeily G, Rochester CL. Exercise training in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):763-781.

47. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152.

48. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol 1992; 65(4):347-353.

49. Levine S, Weiser P, Gillen J. Evaluation of a ventilatory muscle endurance training program in the rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1986; 133(3):400-406.

50. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280.

51. Ries AL, Moser KM. Comparison of isocapnic hyperventilation and walking exercise training at home in pulmonary rehabilitation. Chest 1986; 90(2):285-289.

52. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000; 162(5):1709-1714.

53. Astrand PO, Rodahl R. Textbook of work physiology. New York, 1986: McGraw-Hill, 2004.

54. Hamilton AL, Killian KJ, Summers E, Jones NL. Symptom intensity and subjective limitation to exercise in patients with cardiorespiratory disorders. Chest 1996; 110(5):1255-1263.

55. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis 1992; 146(4):935-940.

56. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164(5):770-777.

57. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J 2004; 23(6):832-840.

58. Holm P, Sattler A, Fregosi RF. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. BMC Physiol 2004; 4(1):9.

59. Boutellier U. Respiratory muscle fitness and exercise endurance in healthy humans. Med Sci Sports Exerc 1998; 30(7):1169-1172.

60. Dekhuijzen PN, Folgering HT, van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. Chest 1991; 99(1):128-133.

61. Sonetti DA, Wetter TJ, Pegelow DF, Dempsey JA. Effects of respiratory muscle training versus placebo on endurance exercise performance. Respir Physiol 2001; 127(2-3):185-199.

62. Morgan DW, Kohrt WM, Bates BJ, Skinner JS. Effects of respiratory muscle endurance training on ventilatory and endurance performance of moderately trained cyclists. Int J Sports Med 1987; 8(2):88-93.

63. Markov G, Spengler CM, Knopfli-Lenzin C, Stuessi C, Boutellier U. Respiratory muscle training increases cycling endurance without affecting cardiovascular responses to exercise. Eur J Appl Physiol 2001; 85(3-4):233-239.

64. McMahon ME, Boutellier U, Smith RM, Spengler CM. Hyperpnea training attenuates peripheral chemosensitivity and improves cycling endurance. J Exp Biol 2002; 205(24):3937-3943.

65. Stuessi C, Spengler CM, Knopfli-Lenzin C, Markov G, Boutellier U. Respiratory muscle endurance training in humans increases cycling endurance without affecting blood gas concentrations. Eur J Appl Physiol 2001; 84(6):582-586.

66. van 't HA, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. J Cardiopulm Rehabil 2003; 23(2):143-150.

67. Covey MK, Larson JL, Wirtz S. Reliability of submaximal exercise tests in patients with COPD. Chronic obstructive pulmonary disease. Med Sci Sports Exerc 1999; 31(9):1257-1264.

68. Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med 1995; 333(23):1547-1553.

69. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1999; 159(1):321-340.

70. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3):580-586.

71. Curtis JR, Patrick DL. The assessment of health status among patients with COPD. Eur Respir J Suppl 2003; 41:36s-45s.:36s-45s.

72. Jones PW. Health status measurement in chronic obstructive pulmonary disease. Thorax 2001; 56(11):880-887.

73. Williams JE, Singh SJ, Sewell L, Morgan MD. Health status measurement: sensitivity of the self-reported Chronic Respiratory Questionnaire (CRQ-SR) in pulmonary rehabilitation. Thorax 2003; 58(6):515-518.

74. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987; 42(10):773-778.

75. Hodgkin J.E., Celli B.R., Connors G.L. Pulmonary Rehabilitation. third edition ed. Lippincott Williams & Wilkins, 2000.

76. Donner CF, Muir JF. Selection criteria and programmes for pulmonary rehabilitation in COPD patients. Rehabilitation and Chronic Care Scientific Group of the European Respiratory Society. Eur Respir J 1997; 10(3):744-757.

77. Pulmonary rehabilitation. Thorax 2001; 56(11):827-834.

78. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest 1997; 112(5):1363-1396.

79. Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview [see comments]. Chest 1997; 111(4):1077-1088.

80. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. Lancet 1996; 348:1115-1119.

81. Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH et al. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000; 117(4):976-983.

82. Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K et al. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000; 355(9201):362-368.

83. Goldstein RS, Gort EH, Stubbing D, Avendano MA, Guyatt GH. Randomised controlled trial of respiratory rehabilitation. Lancet 1994; 19;344(8934):1394-1397.

84. Longrevalidatie. Produktbeschrijving van de behandeling van volwassenen in het astmacentrum. 1996. Het Grafisch Huis Groningen.

2

Tube-breathing as a new potential method to perform respiratory muscle training: Safety and CO_2 homeostasis in healthy volunteers

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In Press: Respiratory Medicine

ABSTRACT

Normocapnic hyperpnea has been established as a method of respiratory muscle endurance training. This technique has not been applied on a large scale because complicated and expensive equipment is needed to maintain CO_2-homeostasis during hyperpnea. This CO_2-homeostasis can be preserved during hyperpnea by enlarging the dead space of the ventilatory system. One of the possibilities to enlarge dead space is breathing through a tube. If tube-breathing is safe and feasible, it may be a new and inexpensive method for respiratory muscle endurance training, enabling its widespread use.

The aim of this study was to evaluate the safety of tube-breathing and investigate the effect on CO_2-homeostasis in healthy subjects.

20 healthy volunteers performed 10 minutes of tube-breathing (dead space 60% of Vital Capacity). Oxygen-saturation, $PaCO_2$, respiratory muscle function, hypercapnic ventilatory response and dyspnea (Borg-score) were measured. Tube-breathing did not lead to severe complaints, adverse events or oxygen desaturations. 14 out of 20 subjects became hypercapnic ($PaCO_2$ >6,0 kpa) during tube-breathing. There were no significant correlations between $PaCO_2$ and respiratory muscle function or hypercapnic ventilatory responses. The normocapnic versus hypercapnic subjects showed no significant differences between decrease in oxygen saturation (–0,7% versus –0,2% respectively, p=0,6), Borg score (4,3 versus 4,7, p=0,9) , respiratory muscle function nor hypercapnic ventilatory responses.

Our results show that tube-breathing is well tolerated amongst healthy subjects. No complaints, nor desaturations occurred. Hypercapnia developed in a substantial number of subjects. When tube-breathing will be applied as respiratory muscle training modality, this potential development of hypercapnia must be considered.

INTRODUCTION

The function of respiratory muscles can improve in response to training. Normocapnic hyperpnea is probably the best technique for improving *endurance* respiratory muscle function, which is required during exercise.[1] During normocapnic hyperpnea the subject has to sustain a period of hyperpnea for about 10 to 15 minutes. Respiratory Muscle Endurance Training (RMET) is based on the principle of normocapnic hyperpnea. RMET, performed with a specially designed, expensive electromechanical device showed an improvement of 268% in breathing endurance in healthy sedentary subjects, and more-over, the endurance time of a sub-maximal exercise test increased with 50% in this study without placebo-training group.[2] RMET also led to improvements in respiratory muscle function and exercise performance in a study in trained athletes, also without a placebo group and in a randomised controlled trial in patients with Chronic Obstructive Pulmonary Disease (COPD).[3,4]

Despite these promising results, RMET is not applied on a large scale because of this complicated and expensive equipment that is needed to maintain O_2 and CO_2-homeostasis during hyperpnea. This CO_2-homeostasis can also be preserved during a period of hyperpnea by enlarging the dead space of the ventilatory system. One of the possibilities to do so is to breathe through a tube. Thus, RMET by means of tube-breathing might be a new, inexpensive method to perform respiratory muscle training, possibly even in a home-based setting. However, the safety and the effects of this kind of tube-breathing on CO_2-homeostasis have never been evaluated.

Therefore we investigated whether tube-breathing might be a safe and inexpensive technique to perform RMET, enabling widespread use.

The aim of this study was to study the safety and feasibility of tube-breathing in healthy subjects. We therefore evaluated oxygenation, perception of dyspnea and CO_2-homeostasis in 20 healthy volunteers during tube-breathing.

SUBJECTS AND METHODS

The study population consisted of twenty healthy subjects (13 females) (table 1). Exclusion criteria were: a pulmonary medical history, pulmonary complaints and current smoking. Subjects were recruited by means of an advertisement in a free local paper. The subjects were informed about the purpose of this study and gave informed consent. The study was approved by the Ethics Committee of the University Hospital Nijmegen.

Pulmonary function test

Pulmonary function tests at rest were measured according to ERS-criteria [5] with a Sensorloop spirometer (Sensormedics corporation, Bilthoven, the Netherlands): forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were recorded.

Hypercapnic ventilatory response

The steady state ventilatory response to CO_2 was measured. Subjects breathed in a closed spirometer circuit (Godart, Bilthoven, the Netherlands) in which the soda lime absorber could be partially bypassed with a three way valve. Oxygen was supplemented. End-tidal PCO_2 was monitored at the mouth (Drager, Typ 8290000). After at least 5 minutes, when the end-tidal PCO_2 value was stabilized, the soda lime absorber was partially bypassed. When the end-tidal PCO_2 increased by 1 kPa the

bypass around the soda lime absorber was readjusted to prevent the end-tidal PCO_2 from rising any further. After 5 minutes in this steady state the test was ended. Tidal volume and breathing frequency were obtained from the spirometer and were converted to minute volume of ventilation (V_E). The ventilatory response (S) to carbon dioxide is the slope of the relationship of ventilation versus end-tidal PCO_2 (l/min/kpa).[6,7]

PI_{max}/PE_{max}

Maximal static inspiratory and expiratory mouth pressures (PI_{max} and PE_{max}) were measured using a flanged mouthpiece connected to a rigid, plastic tube with a small air leak. Pressure was measured with a pressure transducer (Validyne, Northridge, California, USA) and recorded (Kipp & Zonen, Delft, the Netherlands). Plateau levels for PI_{max} were measured from residual volume, for PE_{max} from total lung capacity.[8]

Threshold loading

Inspiratory threshold loading was used to measure inspiratory muscle endurance. Subjects, wearing a nose clip, were connected with a mouthpiece to a threshold loading device.[9] They inspired against a loaded valve, starting with a load equal to 10% of Pimax, and 25 gram weights were added at 1.5 minute intervals.[10] Pressure was measured inside the mouthpiece with a pressure transducer (Validyne, Northridge, California, USA). Breathing was continued until inspiration could no longer be sustained. The pressure achieved during the heaviest load tolerated for at least 45 seconds was defined as the maximal sustainable inspiratory pressure (SIP_{max}).

Table 1. Variables for normocapnic versus hypercapnic group.

Variable	Normocapnic Mean (SD)	Hypercapnic Mean (SD)	P-value (between groups)
Female/male	4/2	9/5	
Age (yr)	21 (2)	29 (13)	0.9
Height (cm)	176 (15)	177 (11)	0.7
Weight (kg)	73 (13)	74 (12)	0.3
FEV_1 (litres)	4.0 (1.1)	3.9 (0.6)	0.9
FEV_1 (% predicted)	100 (12)	103 (10)	0.9
FVC (litres)	4.6 (1.4)	4.4 (0.6)	0.7
FVC (%predicted)	97 (10)	97 (14)	0.9
$PaCO_2$ rest (kPa)	5.1 (0.3) (38mmHg)	5.3 (0.4) (40 mm Hg)	0.9
$TBPaCO_2$ (kPa)	5.2 (0.7) (39 mm Hg)	6.6 (0.4) (50 mm Hg)	0.01
Delta $PaCO_2$ (tube-rest (kPa))	0.09 (0.60) (1 mm Hg)	1.29 (0.50) (10 mm Hg)	0.01
SaO_2 rest	98.5 (0.5)	96.2 (2.0)	0.02
SaO_2 tube	97.8 (2.0)	95.9 (1.0)	0.02
Delta SaO_2 (tube-rest (%))	-0.7 (1.9)	-0.2 (1.9)	0.6
Heart beats/min rest	74 (6)	70 (11)	0.5
Heart beats/min tube	81 (10)	81 (12)	0.7
Borg	4.3 (2.9)	4.7 (1.9)	0.9
S (l/min/kPa)	6.7 (4.7)	10.8 (7.2)	0.7
SIP_{max} (kPa)	3.6 (1.6)	4.5 (1.9)	0.2
PI_{max} (kPa)	7.1 (2.7)	8.7 (2.4)	0.2
PI_{max} % pred	82 (32)	99 (28)	0.3
PE_{max} (kPa)	9.8 (3.9)	10.1 (3.1)	0.7
PE_{max} % pred	86.5 (29.1)	88.1 (26.3)	1.0

Data reported as mean (standard deviation)

Legend to Table 1.
FEV_1 = forced expiratory volume in litres in 1 sec
FVC = forced vital capacity in litres
$PaCO_2$ = capillary blood pressure of carbon dioxide
$PaCO_2$ rest = $PaCO_2$ at rest/before tube breathing
$TBPaCO_2$ = $PaCO_2$ at the end of 10 minutes tube breathing
Delta $PaCO_2$ tube-rest = difference between $PaCO_2$ value during tube breathing and resting value
SaO_2 rest = oxygen saturation at rest
SaO_2 tube = oxygen saturation at the end of 10 minutes tube breathing
Delta SaO_2 tube-rest = difference between SaO_2 value during tube breathing and resting value
Borg = Borg-score at the end of tube breathing
S = slope of ventilatory response to CO_2
SIP_{max} = maximal sustainable inspiratory pressure in kilopascal
PI_{max} = maximal inspiratory pressure in kilopascal
PI_{max} % pred = maximal inspiratory pressure as percentage from reference value
PE_{max} = maximal expiratory pressure in kilopascal
PE_{max} % pred = maximal expiratory pressure as percentage from reference value

External dead space ventilation (tube-breathing)

The external dead space consisted of a wired bore spirometer-tube (internal diameter 3 cm, preliminary measured resistance of one meter of tube: 0.03 kPa/l/sec), connected to a mouthpiece. The length of the tube, representing the dead space, was adjusted to 60% of the forced vital capacity (FVC) [2], because during exercise, when minute ventilation rises, tidal volume increases to about 60% of the vital capacity and remains constant thereafter.[11] A capnograph (Drager, Type 8290000) was connected to the mouthpiece, to monitor the end-tidal PCO_2. The sampled gas was returned from the capnograph to the mouthpiece. The subjects breathed through the tube during 10 minutes, at an imposed frequency of 15 breaths/min, and at an inspiratory versus expiratory-time ratio of 1:2, using a metronome (Qwik Time QT5, quartz metronome). Before the experiment subjects were instructed to take deep breaths, to overcome the large dead space. They were seated and rested during 3 minutes. 30 seconds before the start of tube breathing ($PaCO_2$ rest) and 30 seconds before ending tube-breathing ($TBPaCO_2$), an arterialized capillary blood-gas sample

was taken from a warmed fingertip. Arterial oxygen saturation and heart rate were measured noninvasively by oximetry (Nonin Medical Inc. USA model 8500 MA). Perception of dyspnea at the end of tube-breathing was measured with a modified Borg-scale (BORG).[12]

Protocol

After the pulmonary function test, the hypercapnic ventilatory response was determined, followed by measurement of Pimax and Pemax. Next threshold loading was performed. The 3 hour session ended with tube-breathing. All experiments were performed in the late morning and early afternoon.

Subjects were resting for 20 minutes between each test.

Statistics

Pearson correlations between different parameters were determined. Furthermore, subjects were divided into two groups: normocapnic versus hypercapnic, which was dependent on their $TBPaCO_2$. A $PaCO_2 \leq 6.0$ kPa was defined as normocapnia. Mean values between groups were compared. Data are reported as mean ± SD. The Mann-Whitney U test was used to test significant differences between the two groups. Significance was set at $p<0.05$. Statistics were performed using SPSS.

RESULTS

Table 1 shows the characteristics and the results of the subjects.

Tube volumes ranged from 2.0 to 4.4 litres (=60% of FVC). During tube-breathing, 14 out of 20 subjects became hypercapnic ($TBPaCO_2 > 6$ kpa). Besides of dyspnea, there were neither severe complaints, nor adverse events. There were no significant

correlations between $PaCO_2$ and the ventilatory response to CO_2, PI_{max} , PE_{max} or SIP_{max}. Subsequently the subjects were divided into two groups to compare mean values: normocapnic versus hypercapnic at the end of tube-breathing. In the normocapnic group $PaCO_2$ remained constant: 5.1 (0.3) kPa [mean (± SD)] at rest, versus 5.2 (0.7) kPa at the end of 10 minutes tube-breathing (range during tube-breathing 4.2-6.0 kpa). In the hypercapnic group $PaCO_2$ showed a rise from 5.3 (0.4) kpa at rest, to 6.6 (0.4) kpa, p=0.001 (range during tube-breathing 6.1-7.7 kpa). A significant difference was found for oxygen saturation at rest as well as at the end of tube-breathing, p=0.02 (table 1). However, the change in oxygen saturation (tube-breathing value minus resting value) did not differ significantly between the groups: normocapnic group –0.7% versus hypercapnic group -0.2%, p=0.6. Clinically relevant desaturations did not occur in neither group. Lowest saturation in both groups was 94%.

No significant differences in heart rate at rest, heart rate during tube-breathing, or perception of dyspnea (BORG) were recorded among the normocapnic and hypercapnic groups. Subjects had no complaints during tube-breathing, besides of dyspnea.

Normocapnic and hypercapnic subjects showed no significant differences in the following characteristics: age, height, weight, FEV_1, FVC, $PaCO_2$ rest.

The ventilatory response to CO_2 (S) was not significantly different for the normocapnic (6.7 l/min/kPa (4.7)) versus the hypercapnic group (10.8 l/min/kPa (7.2)), p=0.2.

The normocapnic and hypercapnic subjects did not differ significantly in maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max}). Pimax was within a normal range in both groups: normocapnic: 82% (32%) predicted, versus hypercapnic 99% (28%) predicted, p=0,3.[8]

Inspiratory muscle endurance measured with incremental threshold loading, showed no significant differences between the normocapnic and hypercapnic subjects: SIP_{max} 3.6 (1.6) kpa versus 4.5 (1.9) kpa respectively, p=0.2.

DISCUSSION

The present study shows that tube-breathing in healthy volunteers is well tolerated. No clinically significant desaturations, severe complaints or adverse events occurred. It leads to hypercapnia in several subjects. Thus tube-breathing might be a feasible and inexpensive method to perform RMET, which suggests that it could become available to a large population. However, the potential development of hypercapnia must be considered when tube-breathing will be applied as endurance training for the respiratory muscles.

To our knowledge this is the first study, evaluating tube-breathing as a new method for RMET. Therefore we investigated the safety of this method, first of all in healthy subjects. Tube-breathing in our study did not lead to severe complaints, adverse events or relevant oxygen desaturations. A heart rate of 81 beats/minute at the end of 10 minutes tube-breathing does not reflect severe stress. Perception of dyspnea (Borg-score) was moderate to severe at the end of the tube-breathing session.

We also looked at the effects of tube-breathing on CO2-homeostasis. Strikingly, ventilation was not adapted to maintain a normal $PaCO_2$ during tube-breathing in all healthy subjects and consequently alveolar hypoventilation occurred. One of the limitations of this study is the fact that we did not measure tidal volumes and minute ventilation during tube breathing in our subjects. Thus, the question remains whether tidal volumes or probably the fixed respiratory rate (15 breaths/minute), or a combination of these two variables, were the limiting factors in achieving an adequate alveolar ventilation. On the other hand, the net effect of the alveolar ventilation was measured on end-tidal PCO_2. This partly obviates the necessity to measure minute ventilation as such. However, as a consequence, hypercapnia developed in this subset of subjects. Brief increases in $PaCO_2$ (lasting several minutes) produce a sensation of respiratory discomfort (air hunger), which is neither a harmful, nor a dangerous situation. Hypercapnia also leads to cerebral vasodilatation and it diminishes in- and expiratory upper airway resistance.[13,14] In several studies (in healthy subjects) the effect of induced acute hypercapnia on ventilation was evaluated.[15-17] However, the design of these studies was different from ours because, spontaneous breathing was compared to *mechanical ventilation*. It was shown that ventilation at the same level of hypercapnia, increased even more during spontaneous breathing, compared to mechanical ventilation. Furthermore, air hunger was much lower at the same level of hypercapnia during spontaneous breathing compared to mechanical ventilation. Mean levels of $PaCO_2$ ranged from 6,1 to 6,9 kpa. Thus it can be speculated that a small rise in $PaCO_2$ during tube-breathing might even lead to a more intense training stimulus. Moreover, even

prolonged exposure (5 days) to elevated levels of CO_2 in healthy subjects, did not alter the ventilatory chemosensitivity to subsequent acute hypercapnia.[18]

However, *chronic* hypercapnia due to respiratory muscle failure is an important complication and a poor prognostic marker, especially in patients with COPD.[19] On the other hand, especially these patients are eligible for respiratory muscle training to attempt to prevent or postpone this respiratory muscle failure, which is, among other things, caused by impaired respiratory muscle function.[20] Nevertheless, before applying RMET by means of tube breathing to patients with COPD, the safety, applicability and the appropriate training scheme of this technique have to be investigated in these patients.

In Jederlinic's classical study on resistance stress-testing and training of respiratory muscles in COPD-patients, these authors found that all patients hypoventilated, and desaturated.[21] However, some of their patients were already hypoxemic at the start of the test (SaO2 84%). When performing this resistive stress test, Jederlinic's patients hypoventilated. The 'wisdom of their bodies' had to make a choice between very strong exertion of their respiratory muscles versus accepting some degree of hypercapnia. Apparently they chose the latter. The subjects in our study, and also possibly future patients, face similar choices. As the resistive load in our study was distinctly lower than in Jederlinic's study, one might expect that the urge/need to trade off a heavy respiratory load for some degree of hypercapnia, might be less.

Dead space breathing or tube breathing has been studied in the past, however these studies are not comparable to our study design because our subjects were *instructed* to take deep breaths to overcome the large dead space (respiratory muscle

endurance training modality), whereas in the other tube-breathing studies the investigators looked at the spontaneous (physiological) effects of tube-breathing on ventilation.[22-25]

In determining the safety of tube-breathing we looked, among other things, at oxygen saturation. The upper part of the oxygen saturation curve levels off, which means that the partial pressure of O_2 might fall while the oxygen saturation is still normal. However, the lowest saturation measured was 94%, which is not associated with (relevant) hypoxemia. This observation, along with dyspnea scores and heart rate during tube-breathing, underlines that tube-breathing is a safe method.

The striking observation that hypercapnia developed in a large number of subjects could be explained by several mechanisms, which will be discussed below.
A difference in the sensitivity of the chemo receptors to a certain change in PaCO2 might be responsible for the development of hypercapnia during tube-breathing. This response to CO2 is mediated centrally by brainstem chemo receptors in the medulla and peripherally by the carotid and aortic bodies. A wide range of ventilatory responses to CO2 has been reported in the literature.[26] Our subjects also showed a wide variance and the results of the hypercapnic ventilatory response could not explain the difference in TBPaCO2 between the two groups.

Inspiratory muscle fatigue may lead to acute hypercapnic respiratory failure. One study investigated the effect of diaphragmatic fatigue on control of respiratory muscles and ventilation during CO2 rebreathing in healthy volunteers. It was concluded that diaphragmatic fatigue induces proportionally greater contributions of

inspiratory rib cage muscles, resulting in the preservation of ventilatory response to CO_2, despite impaired diaphragmatic contractility.[27] Diaphragmatic fatigue measured by cervical magnetic stimulation occurs following voluntary hyperpnea (until task failure), and lasts for at least one hour after hyperpnea.[28] The subjects in this study breathed at 60% MVV during 517±58 seconds with a respiratory rate of 89±5 breaths/min. Our subjects were healthy volunteers, breathing with a respiratory rate of 15 breaths/minute. Furthermore Pimax was within a normal range in both groups. Therefore respiratory muscle fatigue or weakness can not explain the difference in TBPaCO2 between both groups.

There was a wider range of ages and there were more females in the hypercapnic group. It is difficult to establish whether this might have played a role in becoming hypercapnic. Despite this, they were all healthy subjects of whom it is difficult to estimate retrospectively whether these factors may have played a role in becoming hypercapnic. This would require another study. Furthermore, the sample size in our study could have contributed to the absence of statistically significant differences between the different parameters.

Based on the knowledge that tube-breathing leads to a stimulation of ventilation because it increases the amplitude and leads to a change in the timing of the respiratory oscillations in arterial PCO_2, we would have expected our subjects to remain at least normocapnic, and possibly somewhat hypocapnic.[23-25] However, several subjects became hypercapnic. Neither respiratory muscle endurance, nor chemoreceptor sensitivity was significantly different between the groups, although the wide range in ventilatory responses to CO2 makes it hard to detect significant

differences. Especially when taken into account the small number of subjects that were studied, and therefore a type II error cannot be excluded. Despite these statistical remarks, these subjects “accepted” a higher $PaCO_2$ value, rather than increase their minute ventilation and thus their work of breathing, in spite of the fact that there still was a breathing reserve. The perception of the work of breathing at the end of tube-breathing was the same in both groups as shown by the Borg scores. Similar differences can be observed in patients with severe COPD. Some maintain a high ventilation in order to remain normocapnic (so called “pink puffers”), and others do not seem to be bothered by the hypercapnia (so called “blue bloaters”). This fits with the recently proposed theory of natural wisdom, that protects these patients from the detrimental consequences of their disease, but with the inevitable cost of hypercapnia.[29] It is, of course, extremely speculative to suggest that possibly these types of reactions may already be present in early life, before COPD ever develops. However, it is a known fact that there are great interindividual differences in ventilatory sensitivity to CO_2 and there are several reports suggesting that heredity plays a very important role.[25] Thus genetic set differences might determine the tendency to normocapnia or hypercapnia during tube-breathing.

The observation that tube-breathing is well tolerated in healthy subjects, might have important implications for the applicability of this training technique. Nevertheless, further studies are necessary before application of RMET by means of tube-breathing can be recommended as safe in healthy subjects and these findings need to be confirmed in patients with COPD. The equipment for tube-breathing is inexpensive and almost everywhere available. This means that RMET by means of tube-

breathing can be applied on a larger scale: in clinical research, and eventually in routine clinical use.

In summary, the results of this experiment show that tube-breathing is well tolerated in healthy subjects. It does not lead to complaints, adverse events or desaturations. It results in hypercapnia in a substantial number of subjects. This response could not be related to any characteristics of the subjects. When tube-breathing will be applied as a respiratory muscle training modality, this potential development of hypercapnia must be considered. Furthermore, the appropriate training scheme in healthy subjects and the safety and applicability of tube-breathing in patients with COPD needs further investigations.

REFERENCES

1. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther 1995; 75(11):996-1005.
2. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152.
3. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol 1992; 65(4):347-353.
4. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000; 162(5):1709-1714.
5. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:5-40.:5-40.
6. Smolders FD, Folgering HT, Bernards JA. Capnostat and oxystat. Electronic devices to automatically maintain the end-tidal PCO2 and PO2 of a subject connected to a closed respiratory circuit at adjustable levels. Pflugers Arch 1977; 372(3):289-290.

7. Wagenaar M, Vos PJ, Heijdra YF, Teppema LJ, Folgering HT. Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. Eur Respir J 2002; 20(5):1130-1137.

8. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39(7):535-538.

9. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. J Appl Physiol 1982; 52(3):768-772.

10. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. Am Rev Respir Dis 1987; 135(4):919-923.

11. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. Clin Chest Med 1994; 15(2):305-326.

12. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14(5):377-381.

13. Ito H, Kanno I, Ibaraki M, Hatazawa J, Miura S. Changes in human cerebral blood flow and cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. J Cereb Blood Flow Metab 2003; 23(6):665-670.

14. Verin E, Tardif C, Marie JP et al. Upper airway resistance during progressive hypercapnia and progressive hypoxia in normal awake subjects. Respir Physiol 2001; 124(1):35-42.

15. Bloch-Salisbury E, Shea SA, Brown R, Evans K, Banzett RB. Air hunger induced by acute increase in PCO2 adapts to chronic elevation of PCO2 in ventilated humans. J Appl Physiol 1996; 81(2):949-956.

16. Shea SA, Harty HR, Banzett RB. Self-control of level of mechanical ventilation to minimize CO2 induced air hunger. Respir Physiol 1996; 103(2):113-125.

17. Banzett RB, Lansing RW, Evans KC, Shea SA. Stimulus-response characteristics of CO2-induced air hunger in normal subjects. Respir Physiol 1996; 103(1):19-31.

18. Crosby A, Talbot NP, Balanos GM, Donoghue S, Fatemian M, Robbins PA. Respiratory effects in humans of a 5-day elevation of end-tidal PCO2 by 8 Torr. J Appl Physiol 2003; 95(5):1947-1954.

19. Calverley PM. Respiratory failure in chronic obstructive pulmonary disease. Eur Respir J Suppl 2003; 47:26s-30s.:26s-30s.

20. Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med 2003; 168(1):10-48.

21. Jederlinic P,Musspratt JA, Miller MJ. Inspiratory muscle training in clinical practice. Chest 1984;86:870-873

22. Sackner JD, Nixon AJ, Davis B, Atkins N, Sackner MA. Effects of breathing through external dead space on ventilation at rest and during exercise. II. Am Rev Respir Dis 1980; 122(6):933-940.

23. Fenner A, Jansson EH, Avery ME. Enhancement of the ventilatory response to carbon dioxide by tube breathing. Respir Physiol 1968; 4(1):91-100.

24. Goode RC, Brown EB, Jr., Howson MG, Cunningham DJ. Respiratory effects of breathing down a tube. Respir Physiol 1969; 6(3):343-359.

25. Cunningham DJ, Pearson SB, Marsh RH, Kellogg RH. The effects of various time patterns of alveolar CO 2 and O 2 on breathing in man. Acta Neurobiol Exp (Warsz) 1973; 33(1):123-138.

26. McGurk SP, Blanksby BA, Anderson MJ. The relationship of hypercapnic ventilatory responses to age, gender and athleticism. Sports Med 1995; 19(3):173-183.

27. Yan S, Lichros I, Zakynthinos S, Macklem PT. Effect of diaphragmatic fatigue on control of respiratory muscles and ventilation during CO2 rebreathing. J Appl Physiol 1993; 75(3):1364-1370.

28. Mador JM, Rodis A, Diaz J. Diaphragmatic fatigue following voluntary hyperpnea. Am J Respir Crit Care Med 1996; 154(1):63-67.

29. Roussos C, Koutsoukou A. Respiratory failure. Eur Respir J Suppl 2003; 47:3s-14s.

3

Respiratory Muscle Endurance Training by means of tube-breathing in Chronic Obstructive Pulmonary Disease: effect on CO_2-homeostasis

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ABSTRACT

The function of respiratory muscles can improve in response to training. Home-based endurance respiratory muscle training by means of tube-breathing is possibly a new training modality for respiratory muscles. The aim of this study was to investigate the effect of this tube-breathing on CO_2 homeostasis in patients with chronic obstructive pulmonary disease (COPD). We hypothesized that the ventilatory control system will stimulate ventilation during tube breathing, in order to preserve normocapnia.

Fourteen consecutive patients with moderate and severe COPD were included in the study. Pulmonary function test, hypercapnic ventilatory responses, endurance capacity of the respiratory muscles and tube-breathing with dyspnea scores (Borg) were performed.

Strikingly, four patients became hypercapnic ($PaCO_2$>6,0 kpa) during tube-breathing. These hypercapnic patients had significantly more severe COPD, more hyperinflation, a worse capacity of their respiratory muscles and more dyspnea during tube-breathing compared to the normocapnic patients. No significant difference was found for the hypercapnic ventilatory response.

This study shows that tube breathing may lead to hypercapnia and more dyspnea in severe COPD patients, especially in those with impaired respiratory muscle capacity. The ventilatory controlling system does not seem to play an important role in this situation.

INTRODUCTION

Impaired respiratory muscle function, due to respiratory muscle fatigue and weakness, leads to dyspnea and exercise intolerance in patients with chronic obstructive pulmonary disease (COPD).[1]

The function of respiratory muscles can improve in response to training. This improved function, in turn, can potentially decrease dyspnea, improve exercise capacity and increase the ability to perform daily activities in patients with COPD.[2-7] Different training protocols have been designed for improving respiratory muscle strength in COPD patients, including targeted inspiratory resistance training and threshold loading. Both techniques lead to an improvement of respiratory muscle *strength*, but the effect on exercise performance is less unambiguous.[6-11] However, the main function of the ventilatory muscles is to continuously perform low intensity contractions about 10 to 20 times per minute at rest. During exercise this frequency rises even up to 60 times per minute. Therefore specific *endurance* training may be much more effective. Respiratory Muscle Endurance Training (RMET) by means of normocapnic hyperpnea requires the individual to maintain a period of hyperpnea for about 15 minutes. This is probably the best technique for improving the *endurance* capacity of the respiratory muscles.[2] The only study that performed home-based RMET in COPD patients, indeed showed improvement in respiratory muscle function and exercise capacity.[12] However, the equipment needed to maintain a normocapnic situation during RMET is expensive and complicated. Therefore RMET, which is a technique with good prospects, is not applied on a large scale.

During hyperpnea, CO_2-homeostasis can be achieved by enlarging the dead space of the ventilatory system, which can be done by breathing through a tube. Thus tube-

breathing might be a simple and inexpensive way to perform RMET in a home based setting, enabling a widespread use of this promising training-method. However the effects of tube breathing on CO_2-homeostasis in patients with COPD have never been evaluated.

Therefore we investigated the effects of tube breathing on CO_2-homeostasis in patients with COPD. We hypothesized that the ventilatory control system will regulate ventilation during tube breathing at such a level that normocapnia will be maintained.

SUBJECTS AND METHODS

Fourteen consecutive patients (3 female and 11 male) with moderate and severe COPD, (FEV_1/FVC<70% and FEV_1 post-bronchodilatation between 80% and 30% predicted) from the out-patient clinic,[13] who were in a stable clinical condition for at least 6 weeks, participated in this study. Patients were excluded in case of recent exacerbation, hypoxemia or hypercapnia at rest, use of oral steroids and a medical history with thoracotomy. The subjects were informed about the purpose of this study and gave informed consent. The study was approved by the Ethics Committee of the University Hospital Nijmegen.

Pulmonary function test

Pulmonary function tests at rest were measured according to European Respiratory Society.[14] The characteristics of the pulmonary function tests are listed in table 1.

Hypercapnic ventilatory response

The steady state ventilatory response to CO_2 was measured. Subjects breathed in a closed spirometer circuit (Godant, Bilthoven, the Netherlands) in which the soda lime

absorber could be partially bypassed with a three way valve. Oxygen was supplemented. End-tidal PCO_2 was monitored (capnograph Drager, Typ 8290000). After at least 5 minutes, when the end-tidal PCO_2 value was stabilized, the soda lime absorber was partially bypassed. When the end-tidal PCO_2 increased by 1 kPa the bypass around the soda lime absorber was readjusted to prevent the end-tidal PCO_2 from rising further. After 5 minutes in this steady state, the test was ended. Tidal volume and breathing frequency were obtained from the spirometer and were converted to minute volume of ventilation (V_E). The ventilatory response (S) to carbon dioxide is the slope of the relationship of ventilation versus end-tidal PCO_2 (l/min/kPa).[15;16]

PI_{max}/PE_{max}

Maximal static inspiratory and expiratory mouth pressures (PI_{max} and PE_{max}) were measured using a flanged mouthpiece connected to a closed, rigid, plastic tube with a small air leak. The pressure inside the tube was measured with a pressure transducer (Validyne, Northridge, California, USA) and recorded on a chart recorder (Kipp & Zonen, Delft, the Netherlands). Plateau-levels were taken for analysis. PE_{max} was measured from total lung capacity (TLC), PI_{max} from residual volume (RV).[17]

Incremental Threshold loading

Incremental inspiratory threshold loading was used to measure respiratory muscle endurance.

Subjects, wearing a noseclip, were connected with a mouthpiece to a threshold loading device described by Nickerson and colleagues.[18] They inspired against a loaded inspiratory valve. Thus, a certain level of inspiratory pressure has to be

generated in order to overcome the threshold load and to initiate airflow. Pressure (Pth) was measured inside the mouthpiece with a pressure transducer(Validyne, Northridge, California, USA). Pth could be varied by adding weights to the plunger. The subjects started with a load equal to 10% of Pimax and 25 gram weights were added at 1.5 minute intervals.[19] Breathing was continued until inspiration could no longer be sustained. The pressure achieved during the heaviest load tolerated for at least 45 seconds was defined as the maximal sustainable inspiratory pressure (SIP_{max}).

External Dead space ventilation (tube breathing)

The external dead space consisted of a tube (internal diameter 3 cm) connected to a mouthpiece. A sampling capnograph (Drager, Typ 8290000) was connected to the mouthpiece, to monitor the end-tidal PCO_2. The sampled gas was returned from the capnograph to the mouthpiece. The external dead space was adjusted to 45% of the inspiratory vital capacity (IVC) of each individual patient. The subjects breathed trough the tube at an imposed frequency of 15/min and a Ti/Ttot ratio of 0.33, using a metronome (Qwik Time QT5, quartz metronome). Before the experiment, patients were instructed to take deep breaths, to overcome the large dead space. At the beginning and at the end of the tube breathing session an arterialized capillary blood-gas sample was taken from a warmed fingertip ($PaCO_2$-rest and $TBPaCO_2$-45% respectively) . Arterial oxygen saturation and heart rate were measured noninvasively by oximetry (Nonin Medical Inc. USA model 8500 MA) during tube breathing. Dyspnea during tube breathing was measured with a Borg-scale at regular intervals.[20]

Protocol

After pulmonary function testing, the hypercapnic ventilatory response was done, followed by measurement of Pimax and Pemax. Next incremental threshold loading was performed. The 3 hour session ended with tube breathing (45% IVC). All experiments were performed in the late morning and early afternoon.

Subjects were resting for 20 minutes between each test.

A $PaCO_2$>6.0 kPa was defined as hypercapnia.

Statistics

Correlations between the different parameters were determined. Furthermore, patients were divided into two groups: normocapnic versus hypercapnic, depending on their $TBPaCO_2$. Mean values ± SD were compared between the groups, by means of the Mann-Whitney U test. A value of $p \leq 0.05$ was considered statistically significant. Statistics were performed using SPSS 10.0 for Windows.

RESULTS

Table 1 shows the characteristics of the patients. 10 subjects remained normocapnic during tube breathing, whereas 4 subjects became hypercapnic. The correlation coefficients between $TBPaCO_2$ and the other parameters were determined and subsequently the subjects were divided into two groups, normocapnic versus hypercapnic group and mean values were compared.

Table 1. Variables for normocapnic versus hypercapnic group.

Variable	Normocapnic Mean (SD)	Hypercapnic Mean (SD)	P-value (between groups)
Female/male*	2/8	1/3	----------
Age (yr)	62 (8)	68 (9)	0.35
Height (cm)	177 (10)	173 (12)	0.52
Weight (kg)	79 (10)	64 (20)	0.22
FFMI	17.3 (1.2)	16.1 (3.2)	0.50
Packyears	20 (17)	38 (16)	0.11
FEV_1 (l)	2.0 (0.4)	1.0 (0.5)	0.02
FEV_1(%pred)	62 (12)	38 (16)	0.05
FVC (l)	4.4 (0.9)	3.2 (0.7)	0.02
FEV_1/FVC	48 (12)	36 (11)	0.13
FRC(%pred)	106 (22)	143 (18)	0.02
Kco (%pred)	80 (25)	53 (18)	0.07
S (l/min/kPa)	8.2 (6.4)	6.7 (4.9)	0.65
PI_{max} (kPa)	9.5 (1.9)	7.5 (1.5)	0.07
PI_{max} (%pred)	126 (25)	109 (27)	0.31
PE_{max} (kPa)	9.7 (3.9)	8.9 (3.1)	0.82
PE_{max} (%pred)	83 (21)	78 (47)	0.85
SIP_{max} (kPa)	2.4 (1.6)	1.5 (1.9)	0.04
$PaCO_{2rest}$ (kPa)	4.9 (0.3)	5.3 (1.2)	0.48
$PaCO_2$ 45% (kPa)	5.2 (0.6)	6.7 (1.0)	----
Oxygen saturation	95 (5)	92 (3)	0.22
Borg	6 (2)	9 (1)	0.007

Legend to table 1:
FFMI = fat free mass index
Packyears = number of years, smoking 20 cigarettes a day
FEV_1 (l) = forced expiratory volume in litres in 1 second
FEV_1 (%pred) = forced expiratory volume as percentage predicted
FVC (l) = forced vital capacity in litres
FRC (%pred) = functional residual capacity as percentage predicted
Kco(%pred) = transfer factor for carbon-monoxide/litre alveolar volume as percentage predicted
S = hypercapnic ventilatory response in litre per minute per kilopascal
PI_{max} = maximal inspiratory mouth pressure in kilopascal
PI_{max}(%pred) = maximal inspiratory mouth pressure as percentage predicted
PE_{max} = maximal expiratory mouth pressure in kilopascal
PE_{max}(%pred) = maximal expiratory mouth pressure as percentage predicted
SIP_{max} = maximal sustainable inspiratory pressure in kilopascal
$PaCO_2$ = pressure of carbon dioxide in arterialized capillary blood in kilopascal

$PaCO_{2rest}$ = $PaCO_2$ at rest/before tube breathing
$PaCO_2$ 45% = $PaCO_2$ at the end of tube breathing
Oxygen saturation = oxygen saturation at the end of tube breathing
Borg = Borg-score at the end of tube breathing

Correlations

The correlation coefficient for FEV_1 as percentage from predicted and $TBPaCO_2$ was –0.30, p=0.4. FEV_1/FVC showed no significant correlation with $PaCO_2$.

Functional residual capacity as percentage of predicted normal value (FRC%pred) showed a significant positive correlation with $TBPaCO_2$: r=0.60, p=0.05.

No significant correlations existed between $TBPaCO_2$ and the hypercapnic ventilatory response, r=0.13, p=0.7.

Correlation-coefficient for $TBPaCO_2$ and PI_{max}(kpa) was -0.64, p=0.02 and for $TBPaCO_2$ and PI_{max}(%predicted) r=-0.70, p=0.01. For $TBPaCO_2$ and PE_{max}(kpa) and $TBPaCO_2$ and PE_{max}(%pred) there was no significant correlation: r=-0.04, p=0.9 and r=-0.08, p=0.8 respectively.

Respiratory muscle endurance capacity (SIP_{max}) showed no significant correlation with $PaCO_2$, r=-0.30, p=0.4.

Borg score showed no significant correlation with $TBPaCO_2$: r=0.47, p=0.13.

Comparison of mean values

A significant difference between the normocapnic group and the hypercapnic group was found in FEV_1 as percentage from predicted; 62 (12)% versus 38 (16)%, p=0.05. However the amount of airway obstruction was not significantly different; in the normocapnic group and the hypercapnic group, FEV_1/FVC was 48 (12)% and 36 (11)% respectively, p=0.13.

FRC as percentage of predicted showed a significant difference between the groups: normocapnic 106 (22)% versus hypercapnic 143 (18)%, p=0.02. (table 1)
There was no significant difference in hypercapnic ventilatory response between the groups.

PI_{max} and PE_{max} were not statistically different between both groups. (table 1)

There was a significant difference between the normocapnic and the hypercapnic group for respiratory muscle endurance capacity (SIP_{max}); 2.4 (1.6) kPa versus 1.5 (1.9) kPa respectively, p=0.04. (table 1)

A statistically significant difference in the Borg score at the end of tube breathing was found between both groups: 6 (2) in the normocapnic group versus 9 (1) in the hypercapnic group. (table 1)

Oxygen saturation at the end of tube breathing did not differ significantly between the groups. (table 1)

DISCUSSION

The results of this study indicate that in patients with moderate and severe COPD, hyperinflation and diminished respiratory muscle endurance capacity are associated with hypercapnia during tube-breathing. Due to the high load on the respiratory muscles, and the increased chemical drive, the hypercapnic patients experienced more dyspnea.

To our knowledge, this is the first study evaluating the effect of tube-breathing, as a possible respiratory muscle endurance training modality, on CO_2-homeostasis in COPD patients. These patients may benefit from respiratory muscle endurance training, which requires complicated and expensive equipment. Tube-breathing is a simple and inexpensive way to perform RMET, which is accessible to almost all patients and chest-physicians.

Patients in the hypercapnic group had a lower FEV_1 (% predicted) compared to the normocapnic group. They also were more hyper-inflated as shown by a higher FRC (% predicted). Their diffusion capacity appeared to be lower, although not statistically significant. All these parameters point out that the patients in the hypercapnic group had more severe COPD. The increased FRC is of special importance in the explanation of the results of this study. It is well known that hyperinflation of the lungs leads to an unfavourable position of the diaphragm on its length-force diagram.[21] The lungs and thorax are in the upper horizontal part of the pressure-volume curve, and consequently are stiffer. Muscle fibres not only produce substantially less active force at shorter lengths than optimal length, they also fatigue more rapidly.[22] Fatigue is defined as a condition in which there is a loss in the capacity for developing force and/or velocity of a muscle, resulting from muscle activity under load, and which is reversible by rest.[22] The finding of the lower SIPmax in the hypercapnic group, as a parameter for respiratory muscle endurance capacity and the correlation between Pimax and TBPaCO2 supports this finding. Mador and colleagues have shown that contractile fatigue of the diaphragmatic occurs after voluntary hyperpnea until task failure, even in healthy subjects.[23] Voluntary hyperpnea is based on endurance exercise of the respiratory muscles. This is in accordance with our findings. These

factors all contribute to pump failure of the respiratory system, which leads to alveolar hypoventilation and thus hypercapnia.

Patients in the hypercapnic group experienced more dyspnea at the end of tube-breathing, compared to the normocapnic patients. This is reflected by a significant difference in the Borg score of 9 versus 6, p=0.007. Dyspnea is defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.[24] It is therefore a multi-factorial sensation that arises from different pathophysiological mechanisms. One of these mechanisms is the sense of respiratory muscular effort, which is related to the ratio of the pressure generated by the respiratory muscles to the maximum pressure-generating capacity of the muscles. This sense of effort may be the predominant factor contributing to breathlessness when the respiratory muscles are fatigued or weakened, or when the load on them is increased.[25] Another mechanism contributing to dyspnea is hypercapnia. Hypercapnia caused breathlessness in the absence of respiratory-muscle activity in paralysed (neuromuscular-blocking drug) healthy subjects. The same results were found in ventilator dependent patients with quadriplegia, who lack inspiratory muscle function and had air-hunger when end-tidal carbon dioxide was raised.[24] The effects of carbon dioxide on dyspnea are mediated through changes in pH at the level of (central) chemo receptors.[24] Patients in our study had the same ventilatory response to carbon dioxide. The difference in $paCO_2$ at the end of tube breathing therefore does not seem to be a result of a different sensitivity of the chemoreceptor-system for carbon dioxide. Hypercapnia thus is an indicator of a weak and fatigable respiratory pump. It could be hypothesized that these patients might benefit most from RMET. However, further studies will be needed to evaluate this.

In summary, it is likely that the increased load on the respiratory muscles had more impact on the patients with diminished respiratory muscle capacity (i.e. the hypercapnic group), than on the patients who stayed normocapnic during tube breathing. The (fast) change in $PaCO_2$ also contributes to the increased dyspnea. Thus, both factors led to a higher dyspnea sensation in the hypercapnic patients. Consequently, hyperinflated COPD patients with reduced capacity of the respiratory muscles, are probably prone to respiratory failure, hypercapnia and progressive dyspnea. Therefore they might be the most adequate patients for respiratory muscle endurance training.

One of the limitations of this study is the small number of patients. However, correlations and comparison of means even in this small group point in the same direction. Another limitation is the fact that we did not measure diaphragmatic fatigue strictly speaking. This can be done by cervical magnetic stimulation or transcutaneous phrenic nerve stimulation.[23] In our study we only looked at hypercapnia, which is caused by alveolar hypoventilation and thus is an indirect measurement of pump failure of the respiratory muscles. Our study was also not designed to look at dynamic hyperinflation. The protocol we used for tube-breathing, might have led to (more) dynamic hyperinflation, especially in those patients with more severe airflow obstruction. However, to minimize the possibility of dynamic hyperinflation we enforced patients (by means of the settings of the metronome) to breathe with a normal inspiratory ratio: expiratory ratio of 1:2 (Ti/Ttot= 0.33). Neither did we look at differences in lung compliance (loss of elastic recoil) between the subjects. Both factors might contribute to increased dyspnea and respiratory muscle fatigue.[24]

With the results of this study and the above mentioned remarks in mind, it would be interesting to find out whether diaphragmatic fatigue occurs during tube-breathing and whether hypercapnic patients would benefit more from endurance respiratory muscle training , than normocapnic patients.

In conclusion, the results of this study show that impaired respiratory muscle capacity leads to hypercapnia and a higher perception of dyspnea during tube-breathing in patients with moderate and severe COPD. The ventilatory controlling system does not seem to be an important factor in becoming hypercapnic (won't breathe). However the controlled system (respiratory pump) seems to be the determinant of hypercapnia during tube breathing (can't breathe). Further studies are needed to evaluate which patients will benefit most from RMET.

REFERENCES

1. Nici L. Mechanisms and measures of exercise intolerance in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):693-704.
2. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther 1995; 75(11):996-1005.
3. Larson JL, Kim MJ, Sharp JT, Larson DA. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988; 138(3):689-696.
4. Sonne LJ, Davis JA. Increased exercise performance in patients with severe COPD following inspiratory resistive training. Chest 1982; 81(4):436-439.
5. Wanke T, Formanek D, Lahrmann H, Brath H, Wild M, Wagner C et al. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD [see comments]. Eur Respir J 1994; 7(12):2205-2211.
6. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280.

7. Dekhuijzen PN, Folgering HT, van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. Chest 1991; 99(1):128-133.

8. Belman MJ, Shadmehr R. Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease. J Appl Physiol 1988; 65(6):2726-2735.

9. Berry MJ, Adair NE, Sevensky KS, Quinby A, Lever HM. Inspiratory muscle training and whole-body reconditioning in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996; 153:1812-1816.

10. Chen H, Dukes R, Martin BJ. Inspiratory muscle training in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1985; 131(2):251-255.

11. Goldstein R, De Rosie J, Long S, Dolmage T, Avendano MA. Applicability of a threshold loading device for inspiratory muscle testing and training in patients with COPD. Chest 1989; 96(3):564-571.

12. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life [In Process Citation]. Am J Respir Crit Care Med 2000; 162(5):1709-1714.

13. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care 2001; 46(8):798-825.

14. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:5-40.:5-40.

15. Smolders FD, Folgering HT, Bernards JA. Capnostat and oxystat. Electronic devices to automatically maintain the end-tidal PCO2 and PO2 of a subject connected to a closed respiratory circuit at adjustable levels. Pflugers Arch 1977; 372(3):289-290.

16. Wagenaar M, Vos PJ, Heijdra YF, Teppema LJ, Folgering HT. Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. Eur Respir J 2002; 20(5):1130-1137.

17. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39(7):535-538.

18. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. J Appl Physiol 1982; 52(3):768-772.

19. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. Am Rev Respir Dis 1987; 135(4):919-923.

20. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14(5):377-381.

21. Roussos C, Macklem PT. The respiratory muscles. N Engl J Med 1982; 307(13):786-797.

22. NHLBI Workshop summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. Am Rev Respir Dis 1990; 142(2):474-480.

23. Mador JM, Rodis A, Diaz J. Diaphragmatic fatigue following voluntary hyperpnea. Am J Respir Crit Care Med 1996; 154(1):63-67.

24. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1999; 159(1):321-340.

25. Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med 1995; 333(23):1547-1553.

4

Exercise performance improves in patients with Chronic Obstructive Pulmonary Disease due to Respiratory Muscle Endurance Training

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ABSTRACT

Background: Impaired exercise tolerance is frequently observed in patients with chronic obstructive pulmonary disease (COPD). Respiratory muscle *strength* training has been applied in COPD patients, to improve respiratory muscle function and exercise performance. Respiratory Muscle *Endurance* Training (RMET) by means of normocapnic hyperpnea is probably a better technique for improving *endurance* respiratory muscle function, which is required during exercise. This technique is not applied on a large scale because complicated and expensive equipment is needed to maintain CO_2 homeostasis. This CO_2 homeostasis can be preserved during hyperpnea by enlarging the dead space of the ventilatory system by breathing through a tube. Therefore, tube-breathing might be a new, inexpensive method for home-based RMET.

The aim of this study was to asses whether home-based RMET by means of tube breathing improves endurance exercise performance and perception-of-dyspnea in patients with COPD.

Methods: We randomised 36 patients with moderate and severe COPD (GOLD II and III) to RMET (n=18) by means of paced tube-breathing or to sham training (control: n=18). Both groups trained twice daily for 15 minutes, 7 days per week, during 5 weeks.

Results: Endurance exercise capacity, determined by constant-load exercise testing on a cycle-ergometer, showed a significant increase of endurance time in the RMET-group: 18 minutes ±648 seconds to 28 minutes ±894 seconds (mean±SD), $p<0.001$, whereas perception-of-dyspnea (Borg-score) decreased from 8.4±1.9 to 5.4±1.3, $p<0.001$. Respiratory muscle endurance capacity significantly increased in the RMET-group: sustainable inspiratory pressure increased from 25±9 to 31±14 cm H_2O

, p=0.005. Quality of life (Chronic Respiratory Disease Questionnaire) improved from 78.7±20.6 to 86.6±18.4, p=0.001. The control group showed no significant changes.

Conclusion: Home-based RMET by means of tube-breathing leads to a significant improvement of endurance exercise capacity, a reduction in perception-of-dyspnea and an improvement in quality of life in patients with moderate to severe COPD.

INTRODUCTION

Impaired exercise tolerance and diminished ventilatory efficiency are frequently observed in patients with chronic obstructive pulmonary disease (COPD). Airflow limitation leads to altered ventilation-perfusion matching and hyperinflation, which decreases effective alveolar ventilation and reduces ventilatory efficiency. Increased airway resistance also leads to increased work of breathing.[1] In COPD patients, low maximal respiratory pressures have been observed.[2] This is indicative of diminished respiratory muscle function, due to respiratory muscle weakness, due to hyperinflation, or a combination of these, which contributes to impaired exercise tolerance and dyspnea.

Several forms of respiratory muscle training have been applied in patients with COPD, to improve respiratory muscle function and, to some extent, dyspnea and exercise performance. Most of these studies used respiratory muscle *strength* training and showed inconsistent results regarding improvements of dyspnea and exercise capacity.[3-9] Respiratory Muscle *Endurance* Training (RMET) by means of normocapnic hyperpnea is probably a better technique for improving respiratory muscle *endurance* capacity, which is required during exercise.[10] This technique is not applied on a large scale because complicated and expensive equipment is needed to maintain CO_2 homeostasis during a period of hyperpnea.[11-13] This CO_2 homeostasis can also be preserved during hyperpnea by enlarging the dead space of the ventilatory system by breathing through a tube.

We therefore hypothesized that RMET by means of tube-breathing might be a simple and inexpensive technique to improve respiratory muscle performance and exercise

capacity in patients with COPD, and thus might become available for routine clinical use.

The aim of this randomised controlled trial was to test the effectiveness of RMET by means of tube-breathing on *endurance* exercise capacity in patients with moderate to severe COPD. The effects on respiratory muscle function, perception of dyspnea and quality of life were also evaluated.

SUBJECTS AND METHODS

Subjects

Subjects were recruited from the waiting list of participants for pulmonary rehabilitation in the Department of Pulmonology Dekkerswald, University Medical Center Nijmegen. Consecutive patients, who met the inclusion criteria, agreed to participate and had signed the informed consent form were randomly assigned to an RMET group or a control group (sham training). The study protocol was approved by the Ethics Committee of the University Hospital Nijmegen. Inclusion criteria were: 1) Chronic airflow obstruction defined as an $FEV_1/FVC<70\%$, FEV_1: 30-80% predicted, post bronchodilatation. 2) Stable clinical condition for at least 6 weeks. Exclusion criteria were: 1) Hypoxemia at rest or during exercise. 2) Cardiac or orthopaedic disease. 3) Body Mass Index (BMI) > 30 kg/m^2.

All patients on the waiting list for pulmonary rehabilitation (n=92) were screened between July 2001 and November 2002. Three patients refused to participate and 50 patients met the exclusion criteria. (FEV_1<30%predicted and/or hypoxemia at rest or during exercise : n=46, BMI>30: n=3 , orthopaedic disease: n=1). Initially 39 patients

were included in the study. Three patients dropped out of the study (severe exacerbation requiring hospitalization, 2 controls and 1 study-group). Thirty-six patients completed the study.

Table 1 shows the baseline characteristics of the subjects. There were no significant differences between the groups. Age ranged from 38 to 73 years (56±8) (mean±SD). All patients used bronchodilators (long acting beta-agonists and short or long acting anti-cholinergics). Inhaled corticosteroids were used by 13 patients in the RMET group versus 12 in control group, and aminophylline was used by 2 patients in both groups. The use of medication did not differ significantly between groups. Medication was not changed during the study period. None of the patients had participated in a previous rehabilitation program.

Study protocol

Standardized tests were performed before the start (baseline), and in the last week of the training-period. Baseline testing was performed by the investigator. All other tests were performed by a doctor and physiotherapist, who were not aware of baseline results, nor the training device that was used by the patient.

Pulmonary function testing, measurement of peak oxygen consumption (Vo_{2peak}), maximal respiratory muscle strength and BMI were performed during the screening for pulmonary rehabilitation. If patients were suitable for participation, supplementary tests were performed within 1 week.

On the first day of the study patients performed an inspiratory muscle endurance test (Incremental Threshold Loading).[14] After 30 minutes of rest a hyperpnea endurance

test was done . After another 30 minutes of rest a 6-minutes walking distance test was carried out.[15] The chronic respiratory disease questionnaire (CRQ) for measurement of health-related quality of life was completed.[16]

On the second day Incremental Threshold Loading (30 minutes rest), hyperpnea endurance test (30 minutes rest) and 6-minutes walking distance test were repeated followed by (30 minutes rest) an endurance test on a cycle-ergometer.
The best results were taken for analysis.

Patients of both groups were told that they were undergoing respiratory muscle exercises, and that two different devices were being compared for this purpose.

Testing

Pulmonary function testing:

A complete pulmonary function study was performed according to the statement of the European Respiratory Society.[17]

Measurement of respiratory muscle performance:

Maximal inspiratory and expiratory pressures (Pimax, Pemax) were measured in sitting position at residual volume and total lung capacity, respectively, using a flanged mouthpiece with a small air leak. The pressure was measured with a transducer (Validyne DP103-32, Northridge, California, USA) and recorded (Kipp & Zonen, BD 101, Delft, the Netherlands). Measurements of plateau values were taken. Reference normal values were taken from Wilson.[18]

Table 1: Baseline characteristics

	RMET	**Control-group**	**P value**
N	18	18	
age (yrs)	54.4 (7.7)	57.0 (8.5)	0.35
sex M/F	8/10	9/9	0.75
BMI (kg/m^2)	26.7 (5.0)	27.5 (3.3)	0.61
FEV1 (litres)	1.5 (0.4)	1.7 (0.5)	0.15
FEV1 %pred	50 (14)	58 (15)	0.10
FEV1/IVC	46 (13)	50 (14)	0.47
RV %pred	137 (38)	127 (26)	0.36
Pimax (cm H_2O)	69 (29)	72 (23)	0.69
Pimax %pred	89 (34)	93 (28)	0.73
HET (sec)	534 (349)	389 (265)	0.17
SIPmax (cm H_2O)	25 (9)	29 (12)	0.37
Wmax CPET	111 (33)	123 (35)	0.29
Wmax %pred CPET	65 (16)	67 (15)	0.66
VO2peak (ml/min/kg)	19.6 (4.5)	19.3 (4.0)	0.85
6-MWD (metres)	519 (89)	550 (75)	0.27
6-MWD %pred	92 (15)	100 (12)	0.09
CLET (minutes ^{seconds})	17 ^{51} (10 ^{48})	16 ^{24} (15 ^{30})	0.75
BORG dyspnea CLET: iso-time 80%	8.4 (1.9)	8.3 (1.7)	0.78
CRQ	78.7 (20.6)	82.4 (14.7)	0.5

Data are expressed as means (SD)

Legend to Table 1.
BMI = body mass index;
FEV_1 = forced expiratory volume in 1 second;
%pred = percentage predicted of reference values;
IVC = inspiratory vital capacity;
RV = residual volume;
Pimax = maximal inspiratory mouth pressure;
HET = hyperpnea endurance test;
SIPmax = maximal sustainable inspiratory mouth pressure;
Wmax = maximal work load in watt;
CPET = cardio pulmonary exercise testing;
VO2peak = peak oxygen uptake;
6-MWD = 6-minutes walking distance;
CLET = constant load exercise test on cycle ergometer;
CRQ = Chronic Respiratory Disease Questionnaire

Inspiratory muscle endurance was measured by Incremental Threshold Loading.[19] Patients inspired against a weighted inspiratory valve, of which the load was increased at regular intervals. Threshold pressure was measured with a pressure transducer (Validyne DP103-32, Northridge, California, USA). The pressure achieved during the heaviest load tolerated for at least 45 seconds was defined as the maximal sustainable inspiratory pressure (SIPmax).[14]

A hyperpnea endurance test (HET) was used to assess endurance performance of respiratory muscles. Subjects, wearing a nose-clip, breathed in a closed spirometer circuit (Godart, Bilthoven, the Netherlands) in which the soda lime absorber could be partially bypassed to maintain an isocapnic situation during the test . Oxygen was supplemented. End-tidal PCO_2 (Pet_{CO2}) was measured at the mouth (Drager, Typ 8290000) and oxygen saturation was monitored with a pulse oximeter. Patients breathed with a fixed frequency of 30 times a minute, Ti/Ttot=1:3, using an electronic metronome (Qwik Time QT5) and with a tidal volume of 45% of their vital capacity (IVC). They had visual feedback of their tidal volumes on the spirometer and were not encouraged during the test. The test was terminated when the patient could no longer sustain the respiratory frequency or tidal volume during 3 consecutive breaths or after a maximum of 20 minutes and this time was recorded.

Exercise testing:

Maximal incremental cardio-pulmonary exercise testing (CPET) was performed on an electrically-braked cycle ergometer (Lode, Groningen, The Netherlands). During this symptom-limited test the work rate increased every 30 seconds by 5% of the predicted maximal work load [20] and pedalling rate was set at about 60 revolutions per

minute. Ventilatory parameters were measured breath by breath (sensormedics Vmax 29). Arterial blood samples were taken at regular intervals. Heart rate was monitored by ECG recording. At the end of the test Vo_{2peak} and Wmax were recorded. Results were compared (pre- and post- training) at identical levels of exercise: iso-work-load. Wmax of the first CPET was set at 100%.

Endurance test or constant-load exercise testing (CLET) was performed on the same cycle-ergometer. Patients exercised at a work rate of 50% of the individual Wmax, pedalling rate 60 revolutions per minute. They were not encouraged during the test. The test was terminated when patients indicated that they were exhausted and were unable to maintain a pedalling frequency of 60 revolutions per minute. This time was recorded as cycle-endurance time. Ventilatory parameters were measured. Perception of dyspnea was measured by Borg scores at regular intervals.[21] Results (pre- and post- training) were compared at identical time-points of exercise: iso-work-time. The endurance time of the first CLET was set at 100%.

Six-minute walking test was performed in a standardized way [15] in a corridor of 50 meters length.

Endurance respiratory muscle training and sham-training

Respiratory muscle endurance training

RMET was performed by means of tube-breathing. A tube (internal diameter 3 cm), connected to a mouthpiece, was added to the respiratory system to re-breathe exhaled carbon dioxide. Maximum ventilatory capacity that can be sustained for 15

minutes is about 60% of MVV. [22] Therefore, the aimed level of ventilation during training was set at 60% of Maximum Voluntary Ventilation (MVV) which was calculated from 35 times FEV_1 (60% MVV= 0.6 x 35 x FEV_1). The dead space was adjusted to 60% of the patients inspiratory vital capacity (IVC) + the resting tidal volume [23], because during exercise, when minute ventilation rises, tidal volume increases to about 60% of the vital capacity and remains constant thereafter.[24] Breathing frequency (F_{resp}) was calculated: 60% MVV= F_{resp} x (0.6 x IVC + resting tidal volume) and was increased during training to a maximum of 20 breaths per minute. Breathing frequency was imposed by an electronic metronome: Ti/Ttot ratio of 0.33 (Qwik Time QT5). Patients wore a nose-clip and were instructed to take deep breaths. End-tidal CO2 (PetCO2) was analysed with a sampling capnograph (Drager, Type 8290000) which was connected to the mouthpiece.

Sham training

Sham training was performed by breathing 6-7 times/minute through an incentive flowmeter (Inspirx, Resprecare Medical Inc, The Hague, The Netherlands). Airflow resistance was set at ± 5%Pimax.

Training intensity

Patients in both groups trained twice daily for 15 minutes, 7 days a week, during 5 weeks. All patients were seen weekly at the pulmonary laboratory to check whether training was performed correctly. Furthermore, patients completed a diary in which they reported training regimen.

Statistics

Data are reported as mean ± standard deviation (SD).

Training induced changes (post- minus pre-training values: delta) were compared between groups using Analysis of Covariance (ANCOVA) with baseline as covariable (P-delta). The Students t-test for paired samples was used to evaluate differences within groups (pre- versus post- training). Significance was set at $p \leq 0.05$. SPSS 10.0 for Windows was used for analysis. Endurance time of the CLET will be the primary endpoint. This study was initially powered to detect differences between 3 treatment arms. To demonstrate a difference in change of CLET of 15% between either of 2 active treatments and no treatment, 20 subjects per group are needed, assuming a standard deviation of 15% in the change, a significance level of 2.5% per comparison and a power of 80%. Since one active treatment arm was dropped soon after start of the study (for financial reasons only), the significance level for the final analysis was raised to 5%. Hence, 17 subjects per group would suffice to attain a power of 80%.

RESULTS

Respiratory muscle performance

Table 2 shows the effects of 5 weeks of home-based RMET on respiratory muscle performance. HET and SIPmax significantly increased in the RMET-group. The control group showed a decrease of these parameters. Pimax and Pemax showed no significant changes. Subset analysis of patients with a low Pimax (<75% predicted, n=6 in RMET-group and n=5 in control group), as indicative of respiratory muscle weakness, showed the same results in HET and SIPmax and moreover Pimax increased significantly in the RMET-group from 39 cm H_2O (=54% pred) to 58 cm H_2O (=80% pred), p=0.049. No changes occurred in the control group.

Exercise performance and quality of life

The effects of home-based RMET on exercise performance and quality of life are shown in table 2.

Endurance exercise capacity (CLET) significantly increased by 58% in the RMET-group, whereas no change was found in the control group. 6-MWD and quality of life also showed a significant increase in the RMET-group, without a change in the control group.

At an iso-work-time of 80% of the initial endurance time there were significant changes in the RMET-group for the following variables (table 3): Ventilation decreased from 42.8±10.5 to 39.6±10.0 litres/minute; p=0.034, respiratory frequency decreased from 37±7 to 30±7 breaths/minute; p<0.001 and tidal volume increased from 1.2±0.3 to 1.4±0.5 litre; p=0.035. Borg score for exercise dyspnea at iso-work-time significantly decreased in the RMET-group from 8.4±1.9 to 5.4±1.3, p<0.001. In the control group there were no significant changes for these parameters.

CPET showed a significant increase in maximal work-load in the RMET-group. (table 2) Vo_{2peak} did not change. At an iso-work load of 80% the following changes were observed in the RMET-group: Minute ventilation, respiratory rate, Vo_2 and heart-rate all significantly decreased. No significant changes were observed in the control group. (table 4)

Table 2: Pre and post training values and significance of training induced changes

	RMET			**Control-group**			
	pre	**post**	**P-value** within group	**pre**	**post**	**P-value** within group	**P-delta**
Pulmonary function tests							
FEV1 (litres)	1.5(0.4)	1.6(0.5)	0.12	1.7(0.5)	1.8(0.5)	0.18	0.84
IVC (litres)	3.3(0.7)	3.3(0.7)	0.26	3.6(0.9)	3.7(0.9)	0.10	0.52
Respiratory muscle performance							
Pimax (H_2O)	66(29)	73(28)	0.10	72(23)	75(30)	0.72	0.53
Pemax (H_2O)	75(34)	88(42)	0.13	82(34)	92(41)	0.38	0.94
HET (sec)	534(349)	833(348)	<0.001	389(265)	343(259)	0.05	<0.001
Sipmax (H_2O)	25(09)	31(14)	0.005	29(12)	26(12)	0.04	<0.001
Exercise performance and CRQ							
CLET (min^{sec})	$17^{51}(10^{48})$	$28^{16}(14^{54})$	<0.001	$16^{24}(15^{30})$	$16^{35}(14^{02})$	0.85	<0.001
6-MWD (m)	512(86)	535(77)	0.007	549(75)	544(85)	0.48	0.02
Wmax CPET	111 (33)	120 (38)	0.02	123 (35)	126 (42)	0.5	0.07
VO2peak (ml/min/kg)	19.6(4.5)	19.9(4.7)	0.33	19.3(4.0)	19.9(5.1)	0.51	0.93
CRQ	78.7(20.6)	86.6(18.4)	0.001	82.4(14.7)	85.0(15.0)	0.2	0.07

Data are expressed as means (SD). P delta: significance of training induced changes (post-minus pre-training values: delta) between groups by ANCOVA.

Legend to table 2.
FEV_1 = forced expiratory volume in 1 second;
IVC = inspiratory vital capacity;
Pimax = maximal inspiratory mouth pressure;
Pemax = maximal expiratory mouth pressure;
HET = hyperpnea endurance test;
SIPmax = maximal sustainable inspiratory mouth pressure;
6-MWD = 6-minutes walking distance;
CLET = constant load exercise test on cycle ergometer;
Wmax = maximal work load in watt;
CPET = cardio pulmonary exercise testing;
VO2peak = peak oxygen uptake;
CRQ = Chronic Respiratory Disease Questionnaire

Table 3: CLET: iso-work-time 80%

Pre and post training values and significance of training induced changes

	RMET			**Control-group**			
	pre	**post**	**P-value** within group	**pre**	**post**	**P-value** within group	**P-delta**
Ventilation l/min	42.8 (10.5)	39.6 (10.0)	0.034	40.9 (8.6)	43.3 (8.9)	0.33	0.03
Resp. rate	37 (7)	30 (7)	<0.001	32 (6)	32 (6)	0.50	0.05
Tidal volume (l)	1.2 (0.3)	1.4 (0.5)	0.035	1.3 (0.3)	1.3 (0.3)	0.45	0.6
BORG dyspnea	8.4 (1.9)	5.4 (1.3)	<0.001	8.3 (1.7)	7.2 (2.2)	0.23	0.02

Data are expressed as means (SD).
P delta: significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA.
Endurance time of first CLET=100%
Resp. rate = respiratory rate in breaths per minute

Table 4: CPET: iso-work-load 80% Wmax

Pre and post training values and significance of training induced changes

	RMET			**Control-group**			
	pre	**post**	**P-value** within group	**pre**	**post**	**P-value** within group	**P-delta**
Ventilation l/min	53.5 (14.8)	47.9 (15.1)	0.01	53.7 (10.4)	52.0 (12.7)	0.16	0.09
Resp. rate	40 (7)	32 (5)	0.002	36 (5)	34 (5)	0.13	0.12
Vo_2 l/min	1.52 (0.41)	1.42 (0.41)	0.01	1.52 (0.42)	1.50 (0.47)	0.67	0.33
Heart rate BPM	150 (17)	135 (16)	0.005	144 (17)	142 (17)	0.65	0.05

Data are expressed as means (SD).
P delta: significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA.
Maximal work-load of first CPET=100%
Resp. rate = respiratory rate in breaths per minute;
BPM = beats per minute

DISCUSSION

The present study shows that home-based RMET by means of tube-breathing leads to a substantial improvement of *endurance* exercise capacity by 58%, an improvement in quality of life and a reduction in the perception of dyspnea, in patients with moderate and severe COPD. These findings suggest that this inexpensive technique can be a clinically relevant and easy applicable training intervention for COPD patients.

To our knowledge, this is the first study using tube-breathing as home based respiratory muscle endurance training in COPD patients. We found an improvement in exercise endurance capacity of 58%. One other study showed an increase of 54% in submaximal cycling endurance exercise, after RMET in COPD patients. However RMET was not performed in a home-based setting and that study had no control group.[25] Another study, performing *home-based* RMET in COPD, with a specially developed, expensive electromechanical device, reported an increase in submaximal treadmill exercise in the study-group compared to the control-group, that did not reach statistical significance.[13] Furthermore, submaximal exercise on a treadmill has never been validated in COPD, whereas constant load exercise testing (CLET) on cycle ergometer has been proven to be a reproducible, reliable and valid method to assess endurance exercise capacity in patients with COPD.[26,27] CLET can not only be used to measure endurance exercise time, but also to compare ventilatory and metabolic parameters at the same work-rate, before and after intervention. The latter being an effort independent measurement of training effects. Our study shows a change in breathing pattern after RMET. We found a lower minute ventilation, a lower breathing frequency and a larger tidal volume during CLET at iso-work-time 80%.

This change of breathing pattern has two major advantages. First, the ratio of dead space to tidal volume (Vd/Vt) decreases, which leads to an increase in effective alveolar ventilation. Secondly, it diminishes the work-of-breathing.[1] It also indicates that respiratory muscle fatigue, leading to a rapid, shallow breathing pattern is delayed.[28,29] These observations are supported by the finding that Borg-scores were significantly lower in the RMET-group at iso-time during CLET. This can be an additional explanation for the better performance during endurance exercise.[30] Other studies using RMET in patients with COPD [13,25,31,32] do not report ventilatory parameters at iso-work-time. One study reported a decrease in strain index for ventilation, which means that a lower percentage of Vemax was necessary for a given workload.[25] In accordance with the above mentioned clinical and home-based trial our results show improvement in endurance exercise time and improvements in ventilatory parameters. However, our study is the first to show that home based RMET by means of tube breathing, leads to a significant and clinically relevant improvement in endurance exercise capacity.

Remarkably, maximal exercise capacity (Wmax) improved in the RMET-group by 8%, without a change in VO2peak. This can be explained by comparing parameters of CPET at iso-work load 80%, showing that minute ventilation, respiratory rate, VO2 and heart-rate are significantly less after training, as a result of a more efficient way of breathing and less work of breathing. The reduction of minute ventilation and respiratory rate and their mutual relationship leads to an improvement of Vd/Vt. The decrease of VO2 by 100 ml/min at the same work-load can be a result of a better trained respiratory system in terms of oxidative capacity, requiring less oxygen for the same amount of work and thus a lower heart-rate. Translating these data to maximal

exercise capacity leads to an improvement of work-load at the same oxygen-consumption. An increase in VO2peak of 19% was found in the only other study on home-based RMET in COPD patients. However, they did not speculate on the mechanism explaining this increase.[13] Thus our results show effort independent improvements in cardio-circulatory and ventilatory parameters as a result of RMET.

In accordance with improvements in endurance and maximal exercise capacity, patients in our RMET-group significantly improved 6-minutes walking distance by 5% (23 meters). Other studies showed improvements of 8 to 12 %. Although the improvement in 6-MWD was statistically significant, 23 meters do not seem to be clinically relevant.[15] However, our patients had base-line values of 92% and 100% of reference values for 6-MWD (RMET and control respectively)[33], and therefore great improvements were not expected. The fact that the RMET-group, in contrast to the control-group, significantly increased, in combination with a significant P-delta, indicates a true training effect. Therefore, functional exercise capacity, which is a useful outcome in evaluating the effects of respiratory muscle training[34], improved as a result of home-based RMET.

Improvements in exercise capacity can, in part, be explained by improved respiratory muscle function. Indeed, respiratory muscle endurance, measured by HET, significantly improved by 56% in the RMET-group. Previous studies using endurance respiratory muscle training as a training mode in patients with COPD showed improvements in maximal sustained ventilatory capacity (MSVC) of 29% [32] to 47% [35]. Our results are comparable with these studies. Scherer reported an increase of 258% in sustained ventilation[13], using a different protocol. We terminated the

respiratory muscle endurance test after 20 minutes, because we were looking for improvements in respiratory muscle endurance capacity, and not for maximal results. The improvement in HET was confirmed by a significant improvement in incremental threshold loading. Therefore RMET by means of tube breathing leads to an improvement in respiratory muscle function.

General exercise training, compared to isolated respiratory muscle training, is another way to train the respiratory muscles in a very specific way. General exercise training during 6 weeks indeed showed an improvement of exercise performance and respiratory muscle function.[36] However, our study showed that training of the respiratory muscles without any other intervention, leads to an improvement of exercise capacity and respiratory muscle endurance performance. RMET can be performed in a home-based setting with minimal supervision, whereas general exercise training has to be performed in an institute. Furthermore, RMET can be seen as an add-on therapy to general exercise training. Ries et al. indeed showed that adding RMET to a rehabilitation program leads to an improvement in exercise capacity compared to a control-group receiving general exercise training only.[32] Future investigations are needed to evaluate whether starting RMET before the start of general exercise training or pulmonary rehabilitation leads to better outcomes of these programs in terms of exercise performance.

One of the limitations of this study is the possibility of introducing a bias because patients included in our study were selected on the basis of an intended rehabilitation treatment for COPD, GOLD stage II and III. This means that these patients were highly motivated to improve their health status. However, motivation to perform this

time and energy consuming training is very important.[13] Furthermore, neither respiratory muscle weakness nor ventilatory limitation were inclusion criteria. Analysis of our data shows only a slightly lowered Pimax compared to reference values. However, other studies even found improvements of respiratory muscle function and exercise capacity in normal sedentary subjects[23] and in normal trained subjects [37,38] after endurance training of the respiratory muscles. Therefore RMET is also useful in subjects with normal respiratory muscle performance.

The results of this study may have important clinical implications for the treatment of COPD patients. This easy applicable and inexpensive technique can be applied on a large scale. In this light, it can be added to the non-pharmacological therapeutic interventions in COPD, whereas respiratory muscle training until now is indicated, only along with a pulmonary rehabilitation program for selected patients with decreased respiratory muscle strength.[39] Furthermore, when pulmonary rehabilitation, or even general exercise training is not available, home based RMET by means of tube breathing, can be a good alternative. In addition, home-based RMET resulted in a significant improvement in health-related quality of life, which is an important clinical outcome parameter in COPD patients.[40]

In conclusion, the results of this study show that home-based RMET by means of tube breathing substantially improves endurance exercise capacity. It also improves quality of life and leads to a decrease of dyspnea in patients with moderate and severe COPD. Future investigations are needed to determine the effects of RMET in patients with very severe COPD, GOLD IV. Furthermore, it will be interesting to find out whether adding RMET to a pulmonary rehabilitation program might result in improvements of the outcomes of such a program.

REFERENCES

1. Nici L. Mechanisms and measures of exercise intolerance in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):693-704
2. Wijkstra PJ, van der Mark TW, Boezen M, et al. Peak inspiratory mouth pressure in healthy subjects and in patients with COPD. Chest 1995; 107(3):652-656
3. Weiner P, Magadle R, Beckerman M, et al. Specific expiratory muscle training in COPD. Chest 2003; 124(2):468-473
4. Weiner P, Magadle R, Beckerman M, et al. Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. Chest 2003; 124(4):1357-1364
5. Sanchez RH, Montemayor RT, Ortega RF, et al. Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life. Chest 2001; 120(3):748-756
6. Lisboa C, Munoz V, Beroiza T, et al. Inspiratory muscle training in chronic airflow limitation: comparison of two different training loads with a threshold device. Eur Respir J 1994; 7(7):1266-1274
7. Larson JL, Kim MJ, Sharp JT, et al. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988; 138(3):689-696
8. Lisboa C, Villafranca C, Leiva A, et al. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. Eur Respir J 1997; 10(3):537-542
9. Flynn MG, Barter CE, Nosworthy JC, et al. Threshold pressure training, breathing pattern, and exercise performance in chronic airflow obstruction. Chest 1989; 95(3):535-540
10. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther 1995; 75(11):996-1005
11. Bourjeily G, Rochester CL. Exercise training in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):763-781
12. Gosselink R, Decramer M. Inspiratory muscle training: where are we? Eur Respir J 1994; 7(12):2103-2105
13. Scherer TA, Spengler CM, Owassapian D, et al. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000; 162(5):1709-1714
14. Martyn JB, Moreno RH, Pare PD, et al. Measurement of inspiratory muscle performance with incremental threshold loading. Am Rev Respir Dis 1987; 135(4):919-923
15. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1):111-117

16. Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987; 42(10):773-778.

17. Standardized lung function testing. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:1-100

18. Wilson SH, Cooke NT, Edwards RH, et al. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39(7):535-538

19. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. J Appl Physiol 1982; 52(3):768-772

20. Folgering HThM, Doorn van P, Cox NJM. A prediction equation for Wmax in COPD-patients. Eur Respir J 1988; 1:67s

21. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982; 14(5):377-381

22. Goldstein RS. Pulmonary rehabilitation in chronic respiratory insufficiency. 3. Ventilatory muscle training. Thorax 1993; 48(10):1025-1033

23. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152

24. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. Clin Chest Med 1994; 15(2):305-326

25. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280

26. Hul van 't HA, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. J Cardiopulm Rehabil 2003; 23(2):143-150

27. Covey MK, Larson JL, Wirtz S. Reliability of submaximal exercise tests in patients with COPD. Chronic obstructive pulmonary disease. Med Sci Sports Exerc 1999; 31(9):1257-1264

28. Larson JL, Kim MJ. Ineffective breathing pattern related to respiratory muscle fatigue. Nurs Clin North Am 1987; 22(1):207-223

29. Mador MJ. Respiratory muscle fatigue and breathing pattern. Chest 1991; 100(5):1430-1435

30. O'Donnell DE, Lam M, Webb KA. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998; 158(5 Pt 1):1557-1565

31. Levine S, Weiser P, Gillen J. Evaluation of a ventilatory muscle endurance training program in the rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1986; 133(3):400-406

32. Ries AL, Moser KM. Comparison of isocapnic hyperventilation and walking exercise training at home in pulmonary rehabilitation. Chest 1986; 90(2):285-289

33. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998; 158(5 Pt 1):1384-1387

34. Polkey MI, Moxham J. Improvement in volitional tests of muscle function alone may not be adequate evidence that inspiratory muscle training is effective. Eur Respir J 2004; 23:5-6

35. Keens TG, Krastins IR, Wannamaker EM, et al. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. Am Rev Respir Dis 1977; 116(5):853-860

36. O'Donnell DE, McGuire M, Samis L, et al. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. Am J Respir Crit Care Med 1998; 157:1489-1497

37. Boutellier U, Buchel R, Kundert A, et al. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol 1992; 65(4):347-353

38. Holm P, Sattler A, Fregosi RF. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. BMC Physiol 2004; 4(1):9

39. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest 1997; 112(5):1363-1396

40. Guyatt G. Measuring health status in chronic airflow limitation. Eur Respir J 1988; 1(6):560-564

5

Respiratory Muscle Endurance Training improves Dyspnea and Quality of Life in patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Respiratory muscle weakness may contribute to dyspnea in patients with Chronic Obstructive Pulmonary Disease (COPD). Dyspnea leads to impaired exercise tolerance and adversely affects quality of life. Home-based respiratory muscle endurance training by means of tube-breathing is a new training mode, based on the principle of normocapnic hyperpnea. We hypothesized that home-based Respiratory Muscle Endurance Training (RMET) leads to an improvement of respiratory muscle endurance capacity, a reduction of dyspnea and an improvement in quality of life.

Methods: Thirty-six patients with moderate to severe COPD (GOLD II and III) were randomized into two groups: RMET by means of tube-breathing (n=18) and sham training with an incentive spirometer (control: n=18). Patients in both groups trained twice daily, 15 minutes, 7 days a week during 5 weeks. Pulmonary function tests, respiratory muscle performance, dyspnea scores (BDI/TDI), and health-related quality of life (CRQ) were measured before and after training.

Results: Patients in the RMET-group showed significant improvement of respiratory muscle endurance capacity. There was also a significant improvement in dyspnea and quality of life in the RMET-group: TDI-focal score increased by 2.8±2.5 points [mean±SD], p=0.001, CRQ-total score increased from 78.7±20.6 to 86.6±18.4, p=0.001. The control group showed no significant changes.

Conclusions: Home-based RMET by means of tube breathing is a new method for endurance training of the respiratory muscles and it leads to an improvement of respiratory muscle endurance capacity, a reduction in dyspnea during daily activities, as well as an improvement in quality of life.

List of abbreviations

BDI = baseline dyspnea index

CO_2 = carbon dioxide

COPD = Chronic Obstructive Pulmonary Disease

CRQ = Chronic Respiratory Disease Questionnaire

RMET = Respiratory Muscle Endurance Training

ERS = European Respiratory Society

FEV_1 = forced expiratory volume in 1 second

Fresp = respiratory frequency in breaths per minute

FVC = forced vital capacity

GOLD = Global Initiative for Chronic Obstructive Pulmonary Disease

ITLet = incremental threshold loading endurance time

IVC = inspiratory vital capacity

MCID = minimum clinically important difference

M/F = male/female

MVV = maximum voluntary volume

N = number of patients

Pemax = maximal expiratory mouth pressure

$PetCO_2$ = end tidal CO_2

Pimax = maximal inspiratory mouth pressure

QOL = Quality of Life

RV = residual volume

SD = standard deviation

TDI = transition dyspnea index

Ti = inspiratory time

Ttot = total time of 1 respiratory cycle (in- and expiration)

Yrs = years

%pred = % of predicted value

INTRODUCTION

Patients with Chronic Obstructive Pulmonary Disease (COPD) often seek medical help because of dyspnea. These patients become concerned when difficulty in breathing interferes with their ability to perform various daily activities and adversely affects their quality of life (QOL). One of the most important factors contributing to dyspnea is the work of breathing and the load on the respiratory muscles.[1] Impairment of expiratory flow, hyperinflation, increased work of breathing and increased dead space ventilation, also contribute to dyspnea.[2] Respiratory muscle weakness is frequently observed in patients with COPD. This is reflected by lower maximal respiratory pressures in these patients[3] and diminished respiratory muscle endurance.[4] In summary, on the one hand there is an increased load on the respiratory muscles whereas on the other their capacity is less. These factors will aggravate the perception of dyspnea.

Respiratory muscles can improve their capacity in response to training, and thus dyspnea and QOL might also improve. Indeed, respiratory muscle *strength* training by means of resistive training, may lead to a reduction of dyspnea[5-9] and an improvement of QOL[7] However, since natural breathing is non-resistive and since breathing frequencies during exercise may increase up to 60 breaths per minute, specific respiratory muscle *endurance* training (RMET) might be a much better training modality.[10] RMET is based on normocapnic hyperpnea. Only one study looked at the effects of home-based RMET on dyspnea and quality of life. Indeed dyspnea and QOL improved, however the equipment that was used to remain normocapnic during a period of hyperpnea is very expensive[11] and this prevents widespread use of this promising technique. CO_2-homeostasis during hyperpnea can also be preserved by enlarging the dead space of the ventilatory system by breathing

through a tube. Tube breathing might be a very easy and inexpensive way to perform RMET.

We hypothesized that tube-breathing, being a new and inexpensive method for home-based Respiratory Muscle Endurance Training, leads to an improvement of respiratory muscle function, a reduction of dyspnea and an improvement of Quality of Life in patients with COPD.

SUBJECTS AND METHODS

Subjects

Thirty-six patients with moderate to severe COPD (FEV1/FVC<70%, FEV1 30%-80% predicted, post bronchodilatation), according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[12] were recruited for the study. All patients were on the waiting list of participants for pulmonary rehabilitation in the Department of Pulmonology Dekkerswald, University of Nijmegen. They were in a stable clinical condition for at least 6 weeks. Patients with hypoxemia at rest or during exercise or cardiac disease and poor compliance were excluded from participation. Patients who agreed to participate and had signed the informed consent form were randomly assigned to Respiratory Muscle Endurance Training (RMET-group) or to sham training (control-group). The study protocol was approved by the Ethics Committee of the University Hospital Nijmegen. Medication was not changed during the study period. Table 1 shows the baseline characteristics of the subjects. There were no significant differences in baseline characteristics between the two groups at the start of the study.

Table 1: Baseline characteristics

	RMET-group	**Control-group**	**P value** between groups
n	18	18	
age (years)	54.4 (7.7)	57.0 (8.5)	0.4
sex Male/Female	8/10	9/9	0.8
Smoking (packyears)	33 (22)	34 (16)	0.9
FEV1 (litres)	1.5 (0.4)	1.7 (0.5)	0.2
FEV1(%predicted)	50 (14)	58 (15)	0.1
FEV1/IVC	46 (13)	50 (14)	0.5
RV (%predicted)	137 (38)	127 (26)	0.4
Pimax (%predicted)	89 (34)	93 (28)	0.7
ITLet (seconds)	760 (267)	892 (377)	0.2
CRQ total	78.7 (20.6)	82.4 (14.7)	0.5
CRQ dyspnea	18.1 (5.0)	19.6 (5.1)	0.4
CRQ fatigue	14.1 (4.1)	14.8 (3.6)	0.6
CRQ emotional function	29.1 (8.6)	29.4 (7.4)	0.9
CRQ mastery	17.4 (5.2)	18.6 (4.9)	0.5
BDI Focal score	5.0 (2.1)	5.7 (1.5)	0.3
BDI functional impairment	1.5(1.0)	2.0 (0.6)	0.1
BDI magnitude of task	1.8 (0.6)	1.9 (0.7)	0.4
BDI magnitude of effort	1.8 (0.8)	1.8 (0.6)	0.95

Data are expressed as mean (SD)

Legend to table 1:

RMET: Respiratory Muscle Endurance Training
n: number of patients
packyears: number of years that a subject smokes a mean of 20 cigarettes per day
FEV_1: Forced Expiratory Volume in 1 second
IVC: Inspiratory Vital Capacity
RV: Residual Volume
Pimax: Maximal Inspiratory Pressure
ITLet: Incremental Threshold Loading endurance time
CRQ: Chronic Respiratory Disease Questionnaire
BDI: Baseline Dyspnea Index

Study protocol

Baseline tests were performed before the start of the study. Subsequently patients exercised their respiratory muscles during 5 weeks by means of RMET or sham-training. In the last week of this period patients were tested again. Testing was standardized.

Patients performed pulmonary function tests, tests to asses respiratory muscle performance, followed by an interview and a questionnaire to assess dyspnea and health related quality of life.

Patients of both groups were told that they were undergoing respiratory muscle exercises, and that two different devices were being compared for this purpose.

TESTS

Pulmonary function tests

A complete pulmonary function study was performed according to ERS-standards.[13]

Measurement of respiratory muscle performance

Maximal in-and expiratory pressures (Pimax and Pemax) were measured in sitting position at residual volume and total lung capacity respectively. A flanged mouthpiece with a small air leak was connected to a pressure transducer (Validyne DP103-32, Northridge, California, USA). Mouth pressures were recorded on a chart recorder (Kipp & Zonen, BD 101, Delft, the Netherlands) and plateau values were taken for analysis. Reference values were taken from Wilson[14]

Incremental Threshold Loading was used to measure inspiratory muscle endurance. Patients inspired against a weighted inspiratory valve. They started with a load of 10% of their Pimax and 25 gram weights were added at 1.5 minute intervals.[15] The time during which a patient was able to breathe through the threshold device was defined as incremental threshold loading endurance time (ITLet). Borg scores were taken at regular intervals. Borg scores (pre- and post- training) were compared at identical time-points during the Incremental Threshold Loading test: iso-endurance time. The maximal endurance time of the first test was set at 100%.

Assessment of dyspnea and health-related QOL

Dyspnea during daily activities was assessed by Mahler's Baseline and Transition Dyspnea Index (BDI/TDI).[16;17]

Health-related quality of life was measured by the Chronic Respiratory Disease Questionnaire (CRQ). This questionnaire measures health-related quality of life in patients with COPD in four dimensions: dyspnea, fatigue, emotional function and mastery. The dyspnea category is strictly individualized. Altogether 20 items are scored on a seven-point scale (a higher score indicates a better quality of life).[18;19]

Training protocol

Patients in both groups trained twice daily for 15 minutes, 7 days a week, during 5 weeks. All patients were checked in the pulmonary laboratory by means of a 15 minute trial-run on adjustment and once a week thereafter. In the RMET-group, end-tidal CO2 was analysed with a sampling capnograph (Drager, Typ 8290000) which was connected to the mouthpiece. Arterial oxygen saturation and heart rate were measured noninvasively by oximetry (Nonin Medical Inc. USA model 8500 MA).

Respiratory Muscle Endurance Training

RMET was performed by means of tube breathing. We added an external dead space (mouthpiece+tube, internal diameter 3 cm) to the respiratory system, in order to maintain the partial pressure of arterial carbon dioxide within a normal range during voluntary hyperpnea. The aimed level of ventilation during training was set at 60% of Maximum Voluntary Ventilation (MVV) which was calculated from 35 times FEV_1 (60% MVV= 0.6x35xFEV_1). The dead space was adjusted to 60% of the patient's inspiratory vital capacity (IVC) + the resting tidal volume.[20] Breathing frequency (F_{resp}) was calculated: 60% MVV= F_{resp} x (0.6 x IVC+ resting tidal volume) and was increased during training to a maximum of 20 breaths per minute. Breathing frequency was imposed by a metronome: Ti/Ttot ratio of 0.33 (Qwik Time QT5). Patients wore a nose-clip and were instructed to take deep breaths to overcome the large dead space.

Sham training

Sham training consisted of breathing exercises, 6-7 times a minute, on an incentive target-flowmeter (Inspirx, Resprecare Medical Inc, The Hague, The Netherlands). Airflow resistance was ± 5% of Pimax.

Data Analysis

Data are reported as mean ± standard deviation (SD). Training induced changes (post- minus pre-training values: delta) were compared between groups using Analysis of Covariance (ANCOVA) with baseline as covariable (P-delta). The Students t-test for paired samples was used to evaluate differences within groups

(pre- versus post- training). Significance was set at p≤0.05. SPSS 10.0 for Windows was used for analysis.

RESULTS

Pulmonary function tests

Pulmonary function tests showed no significant change after the training period. (table 2)

Table 2: Pulmonary function and respiratory muscle performance

	RMET			**Controls**			
	pre	**post**	P-value within group	**pre**	**post**	P-value within group	P-Delta
FEV1 (litres)	1.5(0.4)	1.6(0.5)	0.1	1.7(0.5)	1.8(0.5)	0.2	
IVC (litres)	3.3(0.7)	3.3(0.7)	0.3	3.6(0.9)	3.7(0.9)	0.1	
Pimax (kpa)	6.6(2.9)	7.3(2.8)	0.1	7.2(2.3)	7.5(3.0)	0.7	0.53
Pemax (kpa)	7.5(3.4)	8.8(4.2)	0.1	8.2(3.4)	9.2(4.1)	0.4	0.94
ITLet (seconds)	760(267)	974(434)	0.001	892(377)	790(381)	0.01	< 0.001
Borg iso-80%	8.9(1.5)	8.1(1.5)	0.04	9.0(1.6)	8.6(1.5)	0.5	0.7

pre and post training values: data are expressed as mean (SD)

Legend to table 2:

RMET: *Respiratory Muscle Endurance Training*
FEV_1: *Forced Expiratory Volume in 1 second*
IVC: *Inspiratory Vital Capacity*
Pimax: *Maximal Inspiratory Pressure*
Pemax: *Maximal Expiratory Pressure*
Kpa: *kilopascal*
ITLet: *Incremental Threshold Loading endurance time*
Borg iso-80%: *Borg score for dyspnea at 80% of maximal time of the first Incremental Threshold Loading Test*
P-Delta: *significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA*

Respiratory muscle performance

Respiratory muscle strength, measured by Pimax and Pemax showed no significant changes after training. (table 2)

Respiratory muscle endurance performance, measured by incremental threshold loading (ITLet), significantly increased by 29% in the RMET-group from 12.6 to 16.2 minutes. A significant *decrease* of 11% was observed in the control group. (table 2) The Borg-score at iso-endurance time 80% was significantly lower in the RMET-group after training. Borg score decreased from 8.9±1.5 to 8.1±1.5, p=0.04. No change occurred in the control group. (table 2)

Dyspnea

Baseline Dyspnea Index values showed no significant differences between the two groups. Transitional Dyspnea Index (focal score) showed a significant improvement of dyspnea in daily activities in the RMET-group versus the control group: 2.8±2.5 versus –0.2±1.6; p=0.001. There were also significant differences between the two groups for each category of the TDI. (table 3)

Health-related quality of life

The Chronic Respiratory Disease Questionnaire showed a significant improvement in total score and also in the domains dyspnea, fatigue and mastery in the RMET-group. (table 4) The control group showed no significant changes.

Table 3: Transition Dyspnea Index

	RMET	**Controls**	
	TDI	**TDI**	**P-Delta**
Functional impairment	+1.1 (0.9)	+0.0 (0.6)	0.001
Magnitude of task	+0.9 (0.8)	+0.1 (0.4)	0.001
Magnitude of effort	+0.8 (1.0)	-0.3 (0.9)	0.005
Focal score	+2.8 (2.5)	-0.2 (1.6)	<0.001

Post training values TDI: data are expressed as mean (SD)

Legend to table 3:

RMET: Respiratory Muscle Endurance Training

TDI: Transition Dyspnea Index

P-Delta: significance of training induced changes (delta) between groups by ANCOVA

Table 4: Quality of life: CRQ

	RMET			**Controls**			
	pre	**post**	P-value within group	pre	**post**	P-value within group	P-Delta
CRQ total	78.7(20.6)	86.6(18.4)	0.001	82.4(14.7)	85(15)	0.2	0.07
CRQ dyspnea	18.1(4.9)	20.9(4.8)	0.01	19.6(5.1)	19.9(5.0)	0.5	0.04
CRQ fatigue	14.1(4.1)	15.7(4.4)	0.04	14.8(3.6)	15.5(3.7)	0.3	0.46
CRQ emotional function	29.1(8.6)	30.4(7.8)	0.1	29.4(7.4)	30.2(8.2)	0.2	0.58
CRQ mastery	17.4(5.2)	19.4(4.7)	<0.001	18.6(4.9)	19.3(5.0)	0.3	0.21

pre and post training values: data are expressed as mean (SD)

Legend to table 4:

CRQ: Chronic Respiratory Disease Questionnaire

RMET: Respiratory Muscle Endurance Training

P-Delta: significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA

DISCUSSION

The present study demonstrates that dyspnea during daily activities, quality of life and respiratory muscle function improve as a result of home-based RMET in patients with moderate to severe COPD. This implicates that specific endurance training of the respiratory muscles by means of tube-breathing, which is very easy applicable and inexpensive, contributes to an improvement in health-status in COPD patients.

To our knowledge, this is the first study evaluating the effects of home-based-RMET by means of tube-breathing on dyspnea, QOL and respiratory muscle performance. Inspiratory muscle endurance as measured by incremental threshold loading, improved by 29% in the RMET-group. Previous studies also showed improvement of respiratory muscle endurance capacity after endurance training of the respiratory muscles. Improvements ranged from 29% to 47% and in one study even 258%[11; 21-23] However, different endurance tests of the respiratory muscles were used and therefore direct comparison of these results is not possible. Nevertheless, it can be concluded that respiratory muscle endurance capacity improves significantly as a result of specific endurance training. This improvement has its repercussion on the sensation of dyspnea. Comparing the post-training Borg scores with the ones reported at 80% of the first ITL (iso-endurance time 80%), shows that subjects in the RMET-group also experienced less dyspnea at the same time-point. This means that less dyspnea is perceived while the work-load for the respiratory muscles is the same. Thus, RMET by means of tube-breathing improves the endurance capacity of the respiratory muscles, and reduces the perception of dyspnea.

Furthermore, dyspnea in daily activities significantly improved in the RMET-group, as reflected by a TDI of +2.8. (table 3). There were also significant differences between

the two groups for each category of the TDI, which means that patients were able to resume some of their daily activities they had abandoned because of dyspnea and perform greater efforts and tasks than prior to RMET. (table 3) The only other study that performed home-based endurance training of the respiratory muscles in COPD patients, also showed an increase in TDI, however there was no significant difference between the study group and the control group.[11] Thus our study shows that significant improvements in dyspnea during daily activities can be obtained by RMET by means of tube-breathing.

With these results in mind, the question still remains whether dyspnea improved only as a result of better respiratory muscle performance. It is well known that dyspnea is a multi-factorial problem, not solely dependent on respiratory muscle function. Dyspnea originates in the central nervous system because of an imbalance between the motor neural output to the respiratory muscles and the magnitude of ventilation resulting from it. Patients in the study group were enforced to increase their motor neural output daily during RMET. This may have led to an adaptation to this higher output, and thus a contribution to the reduction in dyspnea. This adaptation aspect cannot be excluded in our patients. Our findings of increased performance of the respiratory muscles support the concept that the balance between the load on the respiratory muscles, versus the working capacity of those muscles, is a major determinant of dyspnea.

Health related quality of life, measured by CRQ total score, significantly increased in the RMET-group, whereas no significant change was found in the control group. Looking at the different subsets of the CRQ, the domain dyspnea showed a

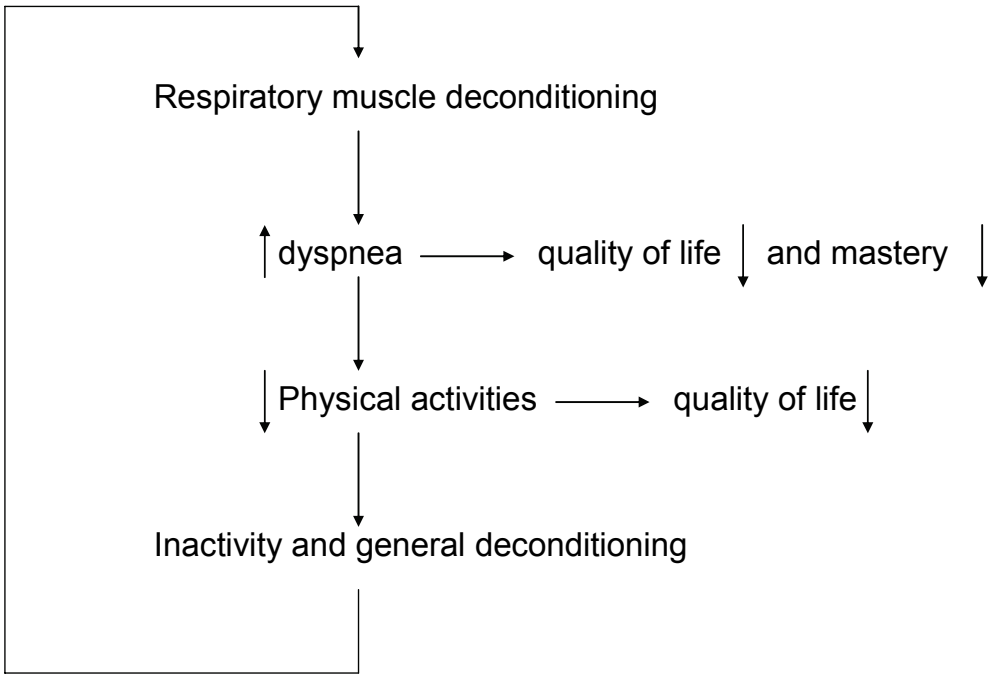
significantly and clinically relevant improvement. This is in accordance with our results of the TDI. Patients not only experienced less dyspnea, they also had more feeling of control over their disease, reflected by a significant and clinically relevant increase in the domain mastery. Furthermore patients felt less fatigued.

Other studies using RMET, did not measure quality of life[21;23] except for Scherer et al. who used the SF-12 health questionnaire, consisting of a physical and mental component. Only the physical, but not the mental component of the SF-12 health survey, showed a significant increase in the study group.[11] Some studies using resistive breathing, also measured quality of life. Larson and co-workers evaluated the effects of inspiratory (threshold) muscle training with and without cycle ergometry training on the domains dyspnea and fatigue of the CRQ. A control group received education only. They found a significant improvement of dyspnea in all groups, but no differences between the groups. Furthermore, there were no significant changes in the CRQ-fatigue domain.[24] In another study patients were trained with inspiratory (threshold) muscle training. Two different training loads, 15% and 30% of Pimax, were compared. There were no changes in patients' reports of functional impairment (Sickness Impact Profile), mood (Profile of Mood States) and health status (Health Perceptions Questionnaire).[25] Thus, previous studies have shown that aspects of quality of life questionnaires can improve after respiratory muscle training. However, our study is the first to show an improvement of health-related quality of life after home-based RMET by means of tube-breathing.

Irrespective of whether dyspnea or respiratory muscle deconditioning is the first phenomenon in patients with COPD, both aspects lead to a further decline in health status. The following model might explain this. (figure 1) Respiratory muscle

deconditioning contributes to dyspnea, which influences quality of life and mastery in a negative way. Dyspnea itself, leads to a decrease in physical activities, which acts negatively upon quality of life. A decline in physical activity leads to further deconditioning of the organism as a whole and consequently also of the respiratory muscles. In this way a negative loop is created that is intensifying itself. This finally leads to progressive dyspnea and severe impairment of quality of life. Our study validates this model, and shows that RMET interrupts this negative loop. RMET leads to an increased respiratory muscle endurance capacity, a reduction of dyspnea and an improvement of quality of life.

Figure 1: relation of respiratory muscle function to dyspnea and quality of life in COPD patients: a model



One of the limitations of this study is the fact that patients were selected from the waiting-list for pulmonary rehabilitation. This may have led to a bias because these patients are motivated to improve their health status. However, patients need to be motivated to perform this kind of endurance training of the respiratory muscles, which is time and energy consuming.

The present findings may have implications for the non-pharmacological management of patients with moderate and severe COPD (GOLD II and III). It appears that home-based RMET by means of tube-breathing is successful in reducing dyspnea and improving quality of life. Furthermore it is not expensive and easy to perform. This enables its wide-spread use, even apart from a pulmonary rehabilitation program, whereas until now respiratory muscle training is only recommended for selected patients within a pulmonary rehabilitation program.[26]

In summary, the results of this study show that home-based endurance training of the respiratory muscles by means of tube-breathing results in improvement of respiratory muscle endurance performance, dyspnea and health related quality of life in patients with moderate and severe COPD. Future investigations are needed to establish its role in conjunction with a pulmonary rehabilitation program and the role of adaptation of the patient to sensory perceptions from the respiratory muscles. Furthermore, it will be interesting to evaluate the effects of this training modality in very severe COPD (GOLD IV).

REFERENCES

1. Cloosterman SG, Hofland ID, van Schayck CP, Folgering HT. Exertional dyspnoea in patients with airway obstruction, with and without CO2 retention. Thorax 1998; 53(9):768-774.
2. Nici L. Mechanisms and measures of exercise intolerance in chronic obstructive pulmonary disease. Clin Chest Med 2000; 21(4):693-704.
3. Wijkstra PJ, van der Mark TW, Boezen M, Van Altena R, Postma DS, Koeter GH. Peak inspiratory mouth pressure in healthy subjects and in patients with COPD. Chest 1995; 107(3):652-656.
4. Manning HL, Schwartzstein RM. Pathophysiology of dyspnea. N Engl J Med 1995; 333(23):1547-1553.
5. Lisboa C, Villafranca C, Leiva A, Cruz E, Pertuze J, Borzone G. Inspiratory muscle training in chronic airflow limitation: effect on exercise performance. Eur Respir J 1997; 10(3):537-542.
6. Lisboa C, Munoz V, Beroiza T, Leiva A, Cruz E. Inspiratory muscle training in chronic airflow limitation: comparison of two different training loads with a threshold device. Eur Respir J 1994; 7(7):1266-1274.
7. Sanchez RH, Montemayor RT, Ortega RF, Cejudo RP, Del Castillo OD, Elias HT et al. Inspiratory muscle training in patients with COPD: effect on dyspnea, exercise performance, and quality of life. Chest 2001; 120(3):748-756.
8. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. Chest 2003; 124(4):1357-1364.
9. Harver A, Mahler DA, Daubenspeck JA. Targeted inspiratory muscle training improves respiratory muscle function and reduces dyspnea in patients with chronic obstructive pulmonary disease. Ann Intern Med 1989; 111(2):117-124.
10. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther 1995; 75(11):996-1005.
11. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life [In Process Citation]. Am J Respir Crit Care Med 2000; 162(5):1709-1714.
12. Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care 2001; 46(8):798-825.
13. Standardized lung function testing. Official statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:1-100.:1-100.

14. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. Thorax 1984; 39(7):535-538.

15. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. Am Rev Respir Dis 1987; 135(4):919-923.

16. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3):580-586.

17. Mahler DA, Tomlinson D, Olmstead EM, Tosteson AN, O'Connor GT. Changes in dyspnea, health status, and lung function in chronic airway disease. Am J Respir Crit Care Med 1995; 151(1):61-65.

18. Guyatt G. Measuring health status in chronic airflow limitation. Eur Respir J 1988; 1(6):560-564.

19. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. Thorax 1987; 42(10):773-778.

20. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152.

21. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280.

22. Levine S, Weiser P, Gillen J. Evaluation of a ventilatory muscle endurance training program in the rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1986; 133(3):400-406.

23. Ries AL, Moser KM. Comparison of isocapnic hyperventilation and walking exercise training at home in pulmonary rehabilitation. Chest 1986; 90(2):285-289.

24. Larson JL, Covey MK, Wirtz SE, Berry JK, Alex CG, Langbein WE et al. Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999; 160(2):500-507.

25. Larson JL, Kim MJ, Sharp JT, Larson DA. Inspiratory muscle training with a pressure threshold breathing device in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1988; 138(3):689-696.

26. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest 1997; 112(5):1363-1396.

6

Respiratory muscle endurance training prior to pulmonary rehabilitation in chronic obstructive pulmonary disease improves outcome measurements

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ABSTRACT

***Background*:** Respiratory muscle training can be used in pulmonary rehabilitation of patients with Chronic Obstructive Pulmonary Disease (COPD). Endurance training of the respiratory muscles, without any other intervention like general exercise training, results in improvement of exercise capacity. We therefore hypothesized that optimising the condition of the respiratory muscles by means of respiratory muscle endurance training *before* the start of pulmonary rehabilitation might lead to a better improvement of endurance exercise capacity after pulmonary rehabilitation.

***Methods*:** We randomised 36 patients with moderate to severe COPD to home-based Respiratory Muscle Endurance Training (RMET: n=18) by paced tube-breathing or sham training with an incentive flowmeter (control: n=18). Both groups trained twice daily for 15 minutes, during 17 weeks. Training started 5 weeks prior to the start of pulmonary rehabilitation and was continued until the end of rehabilitation.

***Results*:** Improvements in respiratory muscle capacity and exercise performance *during* the rehabilitation period were not statistically different between the groups. Quality of life and dyspnea during daily activities also improved to the same extent *during* rehabilitation in both groups. However, the improvement over the *complete* period of preceding respiratory muscle training *and* subsequent pulmonary rehabilitation was significantly better in patients who received RMET compared to the control group for the following variables: respiratory muscle endurance capacity, $p<0.001$; 6-minutes walking distance, $p=0.02$; endurance exercise capacity, $p=0.03$ and dyspnea during exercise (Borg-score), $p=0.01$

***Conclusion*:** Optimising the respiratory muscles by means of RMET before the start of pulmonary rehabilitation, leads to a better outcome of such a program in terms of

improved exercise endurance capacity and a reduction of dyspnea during exercise in patients with moderate to severe COPD.

INTRODUCTION

Respiratory muscle training can be considered within a pulmonary rehabilitation program especially in patients with Chronic Obstructive Pulmonary Disease (COPD) who have decreased ventilatory muscle strength.[1] Studies have reported that addition of respiratory muscle training to a pulmonary rehabilitation program results in an increased strength and endurance of these muscles.[2-4] However, the addition of respiratory muscle training to a pulmonary rehabilitation program does not always result in improvement of (maximal) exercise capacity.[2-6] Patient selection, respiratory training modality and intensity may all have contributed to these diverse results. Furthermore, all studies investigated effects of respiratory muscle training as part of the pulmonary rehabilitation program. This may have less effect than applying respiratory muscle training *before* the start of the pulmonary rehabilitation program, since this may enhance training intensity due to a better trained ventilatory system and less dyspnea. Indeed, isolated home-based Respiratory Muscle Endurance Training (RMET) in patients with COPD has been shown to improve respiratory muscle function and reduce dyspnea.[7] Both factors can contribute to higher tolerable training loads and thus may lead to better outcomes of exercise capacity after pulmonary rehabilitation. Furthermore, since the prevalence of COPD and therefore the need for pulmonary rehabilitation will increase dramatically over the coming years, the burden on rehabilitation programs will also increase.[8] At present, many rehabilitation institutes in the Netherlands deal with considerable waiting lists. During such a period, home-based RMET can easily be applied.

So far no studies have been reported assessing the effects of optimising the respiratory muscles before the start of the pulmonary rehabilitation program.

We hypothesized that optimising the condition of the respiratory muscles *before* the start of pulmonary rehabilitation results in an improved exercise capacity because the efficiency of breathing improves and dyspnea decreases after RMET.

We conducted a randomised controlled trial with home-based RMET before the start of pulmonary rehabilitation in patients with COPD and evaluated its effect on endurance exercise capacity, health related quality of life and dyspnea.

METHODS

Patients

Patients were recruited from the waiting list for pulmonary rehabilitation in the Department of Pulmonary Diseases Dekkerswald, University of Nijmegen. Patients with moderate to severe COPD ($FEV_1/FVC<70\%$ and FEV_1 post-bronchodilatation between 30 and 80% predicted: GOLD II and III), in a stable clinical condition, were randomly assigned to a RMET group or a control group (sham training). Patients were not hypoxemic, neither at rest nor during maximal incremental exercise testing. They were free of any clinical evidence of cardiovascular or musculoskeletal disease and had a Body Mass Index (BMI) < 30 kg/m^2. Initially 39 patients were included in the study. Three patients dropped out of the study (severe exacerbation requiring hospitalization, 2 controls and 1 in the study-group). Thirty-six patients completed the study.

The protocol was approved by the Ethics Committee of the University Hospital Nijmegen and all patients gave written informed consent.

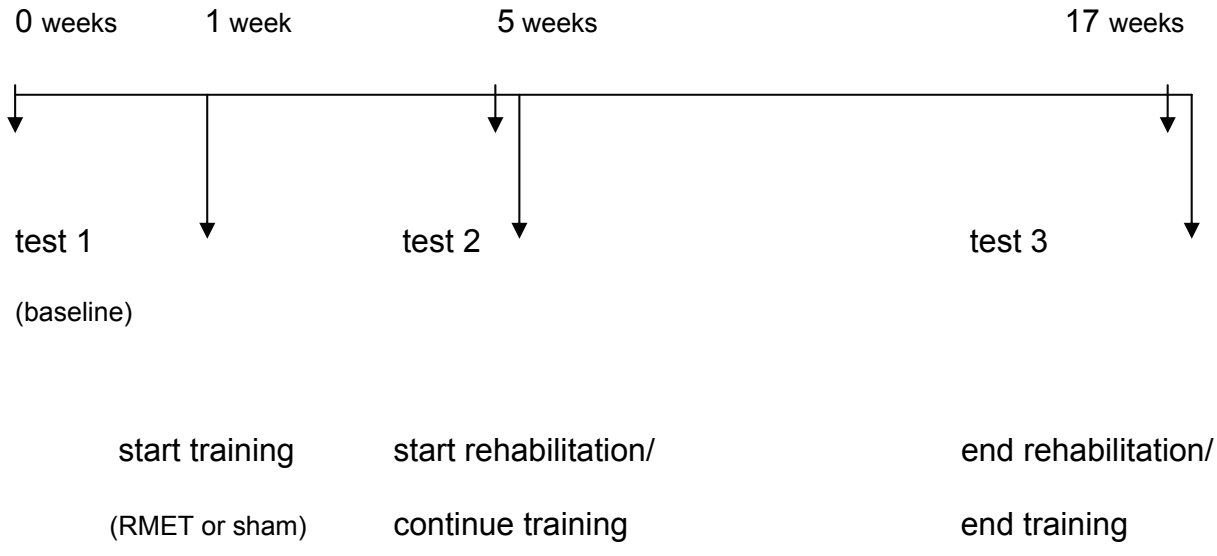
Pulmonary rehabilitation program

Patients participated in a multidisciplinary in-patient program for 12 weeks, which consisted of exercise training, peripheral muscle training, education, nutritional and psycho-social support.[9]

Study protocol

Patients trained their respiratory muscles (RMET or sham training), in a standardised way after instruction by the investigator, from 5 weeks *prior* to the start of the pulmonary rehabilitation program until the end of this rehab-program. (Figure 1)

Figure 1: Study protocol



Patients were clinically evaluated at baseline before the start of home-based RMET (test 1), 2 days before the start of pulmonary rehabilitation (test 2), and in the last week of the rehabilitation program (test 3).

Every test took three days. On the first day, pulmonary function testing,[10] measurement of maximal respiratory muscle strength, evaluation of nutritional status and measurement of Vo_{2peak} were performed. On the second day patients performed respiratory muscle endurance tests. A quality of life questionnaire and a dyspnea questionnaire were completed. 6-minutes walking distance was performed.

On the third day respiratory muscle endurance tests and the 6-minutes walking distance were repeated. Endurance testing on a cycle-ergometer was performed. Between all tests patients rested for 30 minutes.

The best results of the tests were used for analysis.

MEASUREMENTS

Measurement of respiratory muscle performance

Inspiratory muscle endurance: Incremental Threshold Loading was used to determine inspiratory muscle endurance.[11;12] The pressure achieved during the heaviest load tolerated for at least 45 seconds was defined as the maximal sustainable inspiratory pressure (SIPmax).

Respiratory muscle strength: Maximal inspiratory and expiratory plateau pressures (Pimax, Pemax) were measured at the mouth from RV and TLC, respectively. A flanged mouthpiece was connected to a transducer (Validyne DP103-32, Northridge, California, USA). The highest of at least 9 measurements was taken for analysis.[13] Reference values were taken from Wilson.[14]

Respiratory muscle endurance: Performance of in- and expiratory muscles was assessed by a hyperpnea endurance test (HET). Patients breathed in a closed spirometer circuit (Godart, Bilthoven, the Netherlands) in which the soda lime absorber could be partially bypassed with a three way valve to maintain an isocapnic situation during the test . Oxygen was supplemented in quantities that kept the level of the spirometer constant. End-tidal PCO_2 (Pet_{CO2}) was monitored at the mouth by a capnograph (Drager, Type 8290000). Arterial oxygen saturation (SaO_2) was monitored with a pulse oximeter (Oxyshuttle, Sensor Medics, Bilthoven, The Netherlands). Patients were instructed to hyperventilate at 30 breaths/minute, Ti/Ttot=1:2. Visual feedback of the tidal volume (45% of their inspiratory vital capacity) was given on the spirometer. The test was stopped when the patient could no longer sustain the respiratory frequency or tidal volume during 3 consecutive breaths or after a maximum of 20 minutes. Time until the end of the test was recorded as hyperpnea endurance time (HET). Patients were not encouraged during the test.

Health-related quality of life and Dyspnea

Health-related quality of life and *dyspnea* were assessed by means of the Chronic Respiratory Disease Questionnaire (CRQ)[15] and Mahler Transition Dyspnea Index (TDI).[16;17]

Measurement of exercise performance

Maximal exercise test: Maximal incremental cardio-pulmonary exercise testing (CPET) was performed. Work rate increased each 30 seconds by 5% of the predicted value.[18] Minute ventilation, respiratory frequency, oxygen consumption and

carbon dioxide production as well as oxygen saturation were measured continuously (Sensormedics Vmax 29). Heart rate and blood-pressure were monitored.

Endurance exercise test: constant-load bicycle exercise testing (CLET) was performed at a work rate of 50% of the individual Wmax. The test was stopped when patients were exhausted and could not maintain a pedalling frequency of 60/minute. This time was recorded as cycle-endurance time. Measurements of minute ventilation, respiratory frequency, oxygen consumption, carbon dioxide production and heart rate were performed. Perception of dyspnea was measured by means of Borg scores which were taken at the end of the test (CLET BORG).[19] Patients were not encouraged during the test.

6 minutes walking distance (6 MWD): 6 MWD was determined in a straight corridor of 50 meters.[20]

Respiratory muscle endurance training and sham-training

Respiratory muscle endurance training (RMET)

RMET was performed by means of paced tube breathing. $PaCO_2$ was kept within a normal range during hyperpnea by adding an external dead space (tube, internal diameter 3 cm) to the respiratory system. The aimed level of ventilation was set at 60% of Maximum Voluntary Ventilation (MVV), calculated from 35 times FEV_1 (60% MVV= 0.6 x 35 x FEV_1). The dead space was adjusted to 60% of the patient's inspiratory vital capacity (IVC) + the resting tidal volume,[21] because during exercise, when minute ventilation rises, tidal volume increases to about 60% of the vital capacity and remains constant thereafter.[22] Breathing frequency (F_{resp}) was

calculated: 60% MVV= F_{resp} x (0.6 x IVC+ resting tidal volume) and was increased during training to a maximum of 20 breaths per minute. Breathing frequency was imposed by a metronome: Ti/Ttot ratio of 0.33 (Qwik Time QT5). Patients wore a nose-clip and were instructed to take deep breaths. End-tidal CO2 (PetCO2) at the mouth was analysed with a sampling capnograph (Drager, Type 8290000). Arterial oxygen saturation and heart rate were measured (Nonin Medical Inc. USA model 8500 MA).

Sham training

Sham training was performed by breathing 6-7 times/minute through an incentive flowmeter (Inspirx, Resprecare Medical Inc, The Hague, The Netherlands). Airflow resistance was set at ± 5%Pimax.

All patients were instructed in the pulmonary laboratory by means of a 15 minute trial-run at the beginning of the study and weekly thereafter. They trained twice daily for 15 minutes, 7 days a week, during 5 weeks prior to pulmonary rehabilitation and subsequently during the 12-week in-patient pulmonary rehabilitation program.

Statistical analysis

Data are reported as mean ± standard deviation (SD), since values were normally distributed. For descriptive purposes, the Student's t-test for paired samples was used to evaluate differences within groups. Training induced changes (post- minus pre-training values: test 3 minus test 1) were compared between groups using Analysis of Covariance (ANCOVA) with baseline as covariable and reflected as

'delta' (P-Delta). Significance was set at $p \leq 0.05$. SPSS 10.0 for Windows was used for analysis.

RESULTS

Baseline demographic data showed no significant differences between the groups (table 1).

After the period of isolated home-based RMET and before the start of the rehabilitation (test 2) there were no significant differences between the RMET-group and the control-group in pulmonary function tests, respiratory muscle strength, SIPmax, 6-MWD, maximal exercise capacity, CRQ and TDI. However, respiratory muscle endurance capacity (HET), constant load exercise test (CLET) and perception of dyspnea at 80% iso-time during CLET (CLET BORG dyspnea) were significantly different between the groups in favour of the RMET-group (table 2).

Respiratory muscle endurance capacity (HET), constant load exercise test (CLET) and 6-MWD increased significantly during the 12-week rehabilitation period in both groups, whereas maximal exercise capacity (Wmax CPET) and SIPmax only increased in the control group. Borg score for dyspnea at iso-time 80% of endurance exercise significantly decreased in the RMET group. (table 3)

Table 1. Baseline demographic characteristics (test 1)

	RMET-group	**Control-group**	**P value** (between groups)
N	18	18	
age (yrs)	54.4 (7.7)	57.0 (8.5)	0.35
sex M/F	8/10	9/9	0.75
Smoking (packyears)	33.1 (21.8)	33.8 (16.2)	0.90
BMI (kg/m^2)	26.7 (5.0)	27.5 (3.3)	0.61
FEV1 (litres)	1.5 (0.4)	1.7 (0.5)	0.15
FEV1(%pred)	50 (14)	58 (15)	0.10
FEV1/IVC	46 (13)	50 (14)	0.47
RV (%pred)	137 (38)	127 (26)	0.36
Pimax kpa	6.9 (2.9)	7.2 (2.3)	0.69
Pimax (%pred)	89 (34)	93 (28)	0.73
HET ($minutes^{seconds}$)	8^{54} (5^{49})	6^{29} (4^{25})	0.17
SIPmax (kpa)	2.5 (0.9)	2.9 (1.2)	0.37
Wmax CPET (watt)	111 (33)	123 (35)	0.29
Wmax (%pred) CPET	65 (16)	67 (15)	0.66
VO2peak ml/min/kg	19.6 (4.5)	19.3 (4.0)	0.85
6-MWD (m)	519 (89)	550 (75)	0.27
6-MWD (%pred)	92 (15)	100 (12)	0.09
CLET ($minutes^{seconds}$)	17^{51} (10^{48})	16^{24} (15^{30})	0.75
CLET BORG dyspnea	8.4 (1.9)	8.3 (1.7)	0.78

Data are expressed as means (SD)

Legend to table 1:
BMI=body mass index
FEV_1= forced expiratory volume in 1 second
%pred=percentage of predicted value
IVC=inspiratory vital capacity
RV=residual volume
Pimax=maximal inspiratory mouth pressure
HET=hyperpnea endurance test
SIPmax= maximal sustainable inspiratory mouth pressure
Wmax CPET=maximal work load in watts during cardio-pulmonary exercise testing
VO2peak ml/min/kg=peak oxygen uptake in millilitres per minute per kilogram
6-MWD=6 minutes walking distance
CLET=constant load exercise test on cycle ergometer
CLET BORG dyspnea: Borg score for dyspnea during constant load exercise test at iso-time

Table 2: Demographics at start of rehabilitation (test 2)

	RMET-group	**Control-group**	**P value** (between groups)
Respiratory muscle function			
Pimax kpa	7.3 (2.8)	7.5 (3.0)	0.67
Pimax (%pred)	94 (32)	95 (35)	0.94
HET (minutes^{seconds})	13^{53} (5^{48})	5^{43} (4^{19})	<0.001
SIPmax (kpa)	3.1 (1.4)	2.6 (1.2)	0.23
Exercise performance			
Wmax CPET (watt)	120 (38)	126 (42)	0.64
Wmax (%pred) CPET	70 (18)	71 (25)	0.87
VO2peak ml/min/kg	19.9 (4.7)	19.9 (5.1)	0.97
6-MWD (meters)	535 (77)	544 (85)	0.76
CLET (minutes^{seconds})	28^{16} (14^{54})	16^{35} (14^{02})	0.02
CLET BORG dyspnea	5.4 (1.3)	7.2 (2.2)	0.01
Quality of life CRQ total	86.6 (18.4)	85.0 (15.0)	0.78

Data are expressed as means (SD)

Legend to table 2:
Pimax=maximal inspiratory mouth pressure
HET=hyperpnea endurance test
SIPmax= maximal sustainable inspiratory mouth pressure
Wmax CPET=maximal work load in watts during cardio-pulmonary exercise testing
VO2peak ml/min/kg=peak oxygen uptake in millilitres per minute per kilogram
6-MWD=6 minutes walking distance
CLET=constant load exercise test on cycle ergometer
CLET BORG dyspnea: Borg score for dyspnea during constant load exercise test at iso-time
CRQ=Chronic Respiratory Disease Questionnaire

Table 3: Changes in respiratory muscle performance and exercise capacity

	RMET		**Control**		**P-Delta** (between groups)
	pre-rehab test 1-2	rehab test 2-3	pre-rehab test 1-2	rehab test 2-3	test 1versus 3
Wmax CPET(watt)	+10(15)*	+4(14)	+2(13)	+11(17)*	0.45
$VO2_{peak}$ (ml/min)	+52(115)	+15(173)	17(260)	+51(196)	0.55
Pimax (kpa)	+0.7(1.6)	+1.0(1.6)	+1.1(3.9)	+1.1(1.0)	0.80
Pemax (kpa)	+0.8(3.8)	-0.1(4.3)	+2.3(4.6)	+1.2(4.3)	0.48
HET (minutes^{seconds})	$+4^{59}(3^{32})$‡	$+2^{30}(3^{11})$†	$-0^{46}(1^{33})$*	$+2^{00}(2^{35})$†	<0.001
SIPmax (kpa)	+0.6(0.8)*	+0.4(0.9)	-0.3(0.5)	+0.5(0.7)*	0.02
6-MWD (meters)	+23(31)†	+42(39)‡	-6(32)	+32(31)‡	0.02
CLET (minutes^{seconds})	$+10^{24}(6^{39})$‡	$+5^{19}(10^{49})$*	$+0^{11}(4^{10})$	$+7^{15}(8^{36})^{*}$	0.03
CLET BORG dyspnea	-3.0(2.1)‡	-1.0(1.4)†	-0.8(2.1)	-0.8(2.7)	0.01

Data are expressed as means (SD)

* p≤0.05 before versus after testing (within group)

† p≤0.01 before versus after testing (within group)

‡ p≤0.001 before versus after testing (within group)

Legend to table 3:

Wmax CPET=maximal work load in watts during cardio-pulmonary exercise testing
VO2peak ml/min=peak oxygen uptake in millilitres per minute
Pimax=maximal inspiratory mouth pressure
Pemax= maximal expiratory mouth pressure
HET=hyperpnea endurance test
SIPmax= maximal sustainable inspiratory mouth pressure
6-MWD=6 minutes walking distance
CLET=constant load exercise test on cycle ergometer
CLET BORG dyspnea: Borg score for dyspnea during constant load exercise test at iso-time
P-Delta: significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA

The extent of improvement during the 12-week rehabilitation-period (test 2 versus 3) did not significantly differ between both groups. However, the improvement over the whole study period (test 1 versus 3) was significantly higher in the RMET-group than in the control-group with respect to constant load exercise test, 6-MWD, HET, SIPmax and perception of dyspnea as measured by CLET BORG dyspnea. (figure 2, table 3)

Both groups showed a significant improvement in the CRQ, i.e. the total score and all domains separately improved, as well as dyspnea during daily activities (TDI). Improvements in CRQ and TDI during the 12-week rehabilitation period were not statistically significant between the groups. (table 4)

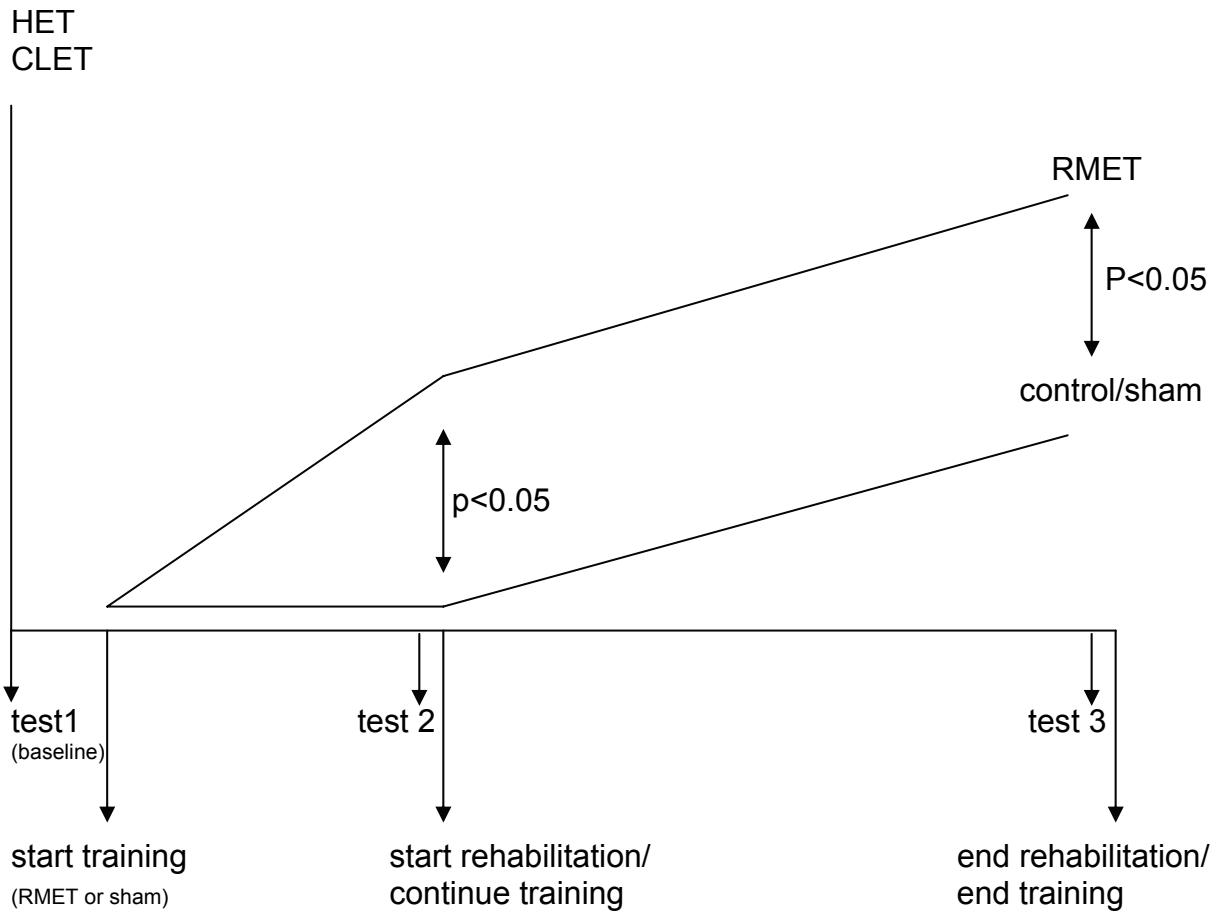
Table 4: Changes in health-related quality of life and dyspnea: CRQ and TDI

	RMET		**Control**		**P-Delta** (between groups)
	pre-rehab test 1-2	rehab test 2-3	pre-rehab test 1-2	rehab test 2-3	test 1 versus 3
CRQ total score	+7.9(8.8)‡	+ 18.4(13.8)‡	+2.6(8.5)	+ 18.6(11.8)‡	0.67
CRQ dyspnea	+2.8(3.9)†	+ 4.9(3.6)‡	+0.3(2.1)	+ 5.8(5.2)‡	0.84
CRQ mastery	+2.0(1.8)‡	+ 3.2(2.5)‡	+0.8(3.1)	+ 3.7(3.4)‡	0.96
CRQ emotional	+1.4(3.9)	+ 5.9(6.1)‡	+0.8(2.3)	+ 4.4(3.1)‡	0.38
CRQ fatigue	+1.7(3.1)*	+ 4.4(4.0)‡	+0.7(3.1)	+ 4.7(3.3)‡	0.91
Dyspnea TDI	+2.8(2.5)	+ 2.2(2.0)	-0.2(1.6)	+4.0(3.3)	0.39

Data are expressed as means (SD)
* p≤0.05 before versus after testing (within group)
† p≤0.01 before versus after testing (within group)
‡ p≤0.001 before versus after testing (within group)

CRQ=Chronic Respiratory Disease Questionnaire
TDI=Transition Dyspnea Index
P-Delta: significance of training induced changes (post- minus pre-training values: delta) between groups by ANCOVA

Figure 2: schematic view of changes over time with respect to HET and CLET



DISCUSSION

The results of this study in patients with moderate to severe COPD indicate that priming of the respiratory muscles by means of RMET before pulmonary rehabilitation leads to a significantly better outcome of a pulmonary rehabilitation program with regard to endurance exercise capacity, respiratory muscle endurance capacity and perception of dyspnea during exercise. No significant differences were found with respect to improvements in quality of life and in dyspnea during daily activities.

To our knowledge this is the first study showing that priming of the respiratory muscles before pulmonary rehabilitation leads to a better outcome of this program. So far some reports have been published on the effects of adding respiratory muscle training *during* a pulmonary rehabilitation program. These studies generally used strength training by means of inspiratory resistive training or threshold loading,[4-6] instead of endurance training, and showed results that considerably vary, i.e. from improvement of maximal exercise performance[5] and 12-minute walking distance,[4] to no effect on maximal and endurance exercise performance.[6] Only two studies have applied endurance respiratory muscle training by means of normocapnic hyperpnea during pulmonary rehabilitation in patients with COPD.[2;3] We found a statistically significant difference in improvement for endurance exercise capacity (CLET: +88%) and functional exercise capacity (6-MWD: +13%) between our study group and the control group, whereas Levine and co-workers did not show a significant difference in improvement between their study group and the control group for these parameters. In their COPD patients with an FEV_1 of about 1.5 litre the placebo training consisted of intermittent positive pressure ventilation during only one hour a day.[2] The second study that applied normocapnic hyperpnea in patients with COPD (FEV_1 1 litre) even found no statistically significant increase in the 12-Minute-walking-distance within the study group. The improvement of 65 meters in our study is not only statistically significant but also clinically relevant.[20] The difference in outcome likely results from the training protocol because the above mentioned studies started respiratory muscle training and general exercise training at the same time. Hence, the ventilatory muscles were not physiologically optimized before the start of the pulmonary rehabilitation. In summary, our study shows that RMET by means of tube-breathing applied before and during pulmonary rehabilitation, leads to an improvement in sub-

maximal endurance exercise capacity, which is a sensitive and valid method to asses changes in endurance exercise capacity.[23;24]

Notwithstanding the beneficial effects on endurance exercise capacity and dyspnea, priming of the respiratory muscles by means of RMET had no additional effects on quality of life and dyspnea during daily activities. Both increased significantly and clinically relevant within the RMET-group as well as the control-group, yet without a significant difference between the groups.

One of the limitations of our study is the fact that only patients with moderate and severe COPD were included. Especially patients with very severe COPD often have impaired respiratory muscle performance and/or a ventilatory limitation during exercise. Moreover, these patients often are eligible for participation in a pulmonary rehabilitation program. Given the positive effects of RMET before starting a rehabilitation program, we believe it of prime importance to further investigate this rehabilitation extension in patients with more severe COPD. However, RMET may be very hard to perform for this group of patients because their inspiratory capacity is often reduced as a result of (severe) hyperinflation.

As a result of our design, the time schedule of our study can be divided into two separate periods. The first period consists of home-based RMET before the start of rehabilitation (between test 1 and 2) These results have been described elsewhere. The second period, as described in this paper, covers the 12-week rehabilitation period (between test 2 and 3). At baseline (test 1, table 1) there were no differences between the two groups. However, after 5 weeks of home-based RMET, significant

differences had already occurred between both groups for respiratory muscle endurance, exercise endurance and perception of dyspnea (test 2, see table 2). In the ensuing 12 weeks of pulmonary rehabilitation, the extent of change that was achieved, with respect to respiratory and exercise endurance capacity and quality of life and dyspnea, did not differ significantly between both groups (table 3 and table 4). These observations are schematically reflected in figure 2 and have two major implications. First, home based RMET could partially replace rehabilitation, especially when the primary goal is to improve sub-maximal endurance exercise capacity. Secondly, priming of the respiratory muscles before the start of pulmonary rehabilitation leads to a better outcome of this program, because patients have a better starting-point after home-based RMET, which is *not* catched up by the control group after 12 weeks of rehabilitation.

The improvement in exercise capacity in our COPD patients can, in part, be explained by the improved respiratory muscle function.[25] HET and SIPmax significantly improved in our study group. In accordance with our results, previous studies using endurance respiratory muscle training as a training mode in patients with COPD also showed improvements in respiratory muscle function.[2;7;26] Adaptation to dyspnea, which originates in the central nervous system because of an imbalance between the motor neural output to the respiratory muscles and the magnitude of ventilation resulting from it, may be another explanation for the improved exercise capacity. During RMET, patients were enforced to increase their motor neural output daily, which may have led to an adaptation to this higher output, and thus a reduction in dyspnea. However, our study was not designed to answer this question. Nevertheless, our results show that an improved respiratory muscle

function leads to an increased exercise capacity. Whether adaptation to dyspnea sensation plays an important role in improvements in exercise capacity, needs further study.

The results of this study may have important clinical implications. Respiratory muscle training previously has been recommended as part of a pulmonary rehabilitation program, only in selected patients with decreased respiratory muscle strength and breathlessness.[1] Patients in our study were not selected because of respiratory muscle weakness or ventilatory limitation. Analysis of our data showed only a slightly lower Pimax compared to reference values.[14] Therefore, optimizing the respiratory muscles with endurance respiratory muscle training before the start of a pulmonary rehabilitation program, should be considered for all COPD patients, even those without impaired respiratory muscle function and it leads to a better outcome of a rehabilitation program.

In summary, we have shown that, optimizing the respiratory muscles by means of Respiratory Muscle Endurance Training in patients with moderate to severe COPD leads to a better outcome of a pulmonary rehabilitation program in terms of endurance exercise capacity, respiratory muscle performance and dyspnea perception during exercise. Many rehabilitation clinics have waiting lists up to several weeks before patients can be admitted. This study shows that such a period can be gainfully used by optimizing the respiratory muscles with home-based RMET by means of tube-breathing. This even results in a better outcome of the rehabilitation program.

REFERENCES

1. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. *Chest* 1997; 112:1363-1396.
2. Levine S, Weiser P, Gillen J. Evaluation of a ventilatory muscle endurance training program in the rehabilitation of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1986; 133:400-406.
3. Ries AL, Moser KM. Comparison of isocapnic hyperventilation and walking exercise training at home in pulmonary rehabilitation. *Chest* 1986; 90:285-289.
4. Dekhuijzen PN, Folgering HT, van Herwaarden CL. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. *Chest* 1991; 99:128-133.
5. Wanke T, Formanek D, Lahrmann H, et al. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *Eur Respir J* 1994; 7:2205-2211.
6. Larson JL, Covey MK, Wirtz SE, et al. Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160:500-507.
7. Scherer TA, Spengler CM, Owassapian D, et al. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. *Am J Respir Crit Care Med* 2000; 162:1709-1714.
8. Pauwels RA, Buist AS, Ma P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001; 46:798-825.
9. Rooyackers JM, Folgering HT. Cardio-respiratory load of exercise training in patients with severe COPD. *Int J Rehabil Res* 1998; 21:259-271.
10. Standardized lung function testing. Official statement of the European Respiratory Society. *Eur Respir J* Suppl 1993; 16:1-100.:1-100.
11. Martyn JB, Moreno RH, Pare PD, et al. Measurement of inspiratory muscle performance with incremental threshold loading. *Am Rev Respir Dis* 1987; 135:919-923.
12. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. *J Appl Physiol* 1982; 52:768-772.
13. Fiz JA, Montserrat JM, Picado C, et al. How many manoeuvres should be done to measure maximal inspiratory mouth pressure in patients with chronic airflow obstruction? *Thorax* 1989; 44:419-421.

14. Wilson SH, Cooke NT, Edwards RH, et al. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax* 1984; 39:535-538.

15. Guyatt GH, Berman LB, Townsend M, et al. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987; 42:773-778.

16. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988; 93:580-586.

17. Mahler DA, Tomlinson D, Olmstead EM, et al. Changes in dyspnea, health status, and lung function in chronic airway disease. *Am J Respir Crit Care Med* 1995; 151:61-65.

18. Folgering HThM, Doorn van P, Cox NJM. A prediction equation for Wmax in COPD-patients. *Eur Respir J* 1988; 1:67s.

19. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982; 14:377-381.

20. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166:111-117.

21 Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol* 1992; 64:145-152.

22. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin Chest Med* 1994; 15:305-326.

23. Van 't Hul HA, Gosselink R, Kwakkel G. Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD. *J Cardiopulm Rehabil* 2003; 23:143-150.

24. Covey MK, Larson JL, Wirtz S. Reliability of submaximal exercise tests in patients with COPD. Chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 1999; 31:1257-1264.

25. Pardy RL, Rivington RN, Despas PJ, et al. The effects of inspiratory muscle training on exercise performance in chronic airflow limitation. *Am Rev Respir Dis* 1981; 123:426-433.

26. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. *Am Rev Respir Dis* 1980; 121:273-280.

7

Summary and general discussion

SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is characterised by chronic airflow limitation that is not fully reversible. This airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Smoking cessation is the first step in the treatment of this disease. Inhalation therapy with bronchodilators is the most important pharmacological intervention to symptom management in COPD. Non-pharmacologic treatment includes rehabilitation, respiratory muscle training, ventilatory support, oxygen therapy and surgical interventions.

The studies presented in this thesis focussed on the effects of Respiratory Muscle Endurance Training (RMET), by means of normocapnic hyperventilation, in patients with COPD. Several reports have shown that RMET has beneficial effects, especially on endurance exercise performance in healthy volunteers, athletes and patients with COPD. However, the equipment used to remain normocapnic during a period of hyperpnea is very complicated and expensive, and therefore not available to a large population. The aim of this thesis was to asses whether RMET by means of tube-breathing, which is very easy and inexpensive, would be safe and feasible, and whether it would have beneficial effects on *endurance* exercise capacity, health-related quality of life and dyspnea in patients with moderate to severe COPD. Furthermore we wanted to test whether optimising the respiratory muscles of COPD patients *before* the start of a rehabilitation program, would lead to a better outcome of this program.

Chapter 1

Chapter 1 gives a survey of the various types of respiratory muscle training. Based on the physiologic principles of strength- and endurance-training two different methods of respiratory muscle training can be distinguished: strength-training by means of inspiratory resistive training and threshold loading *versus* endurance training based on normocapnic hyperpnea, which is also known as Respiratory Muscle Endurance Training (RMET). The effects of these training regimens on different outcome parameters, such as respiratory muscle performance, maximal and endurance exercise capacity, health-related quality of life and dyspnea are discussed. Furthermore the objectives of the studies are outlined.

Chapter 2

In this study we evaluated the feasibility and safety of Respiratory Muscle Endurance Training by means of tube-breathing in healthy volunteers. RMET is based on the principle of normocapnic hyperpnea. This technique is not applied on a large scale because complicated and expensive equipment is needed to maintain CO_2 homeostasis during hyperpnea. This CO_2 homeostasis can be preserved during a period of hyperpnea by enlarging the dead space of the ventilatory system. One of the possibilities to do so is to breathe through a tube. Thus, RMET by means of tube-breathing might be a new and inexpensive method to perform respiratory muscle training, possibly in a home-based setting. However, the safety (hypoxemia) and the effects of this kind of tube breathing on CO_2 homeostasis have never been evaluated. Therefore we performed a 10-minute run of tube-breathing in 20 healthy volunteers. The dead space of the ventilatory system was enlarged with 60% of the individuals Forced Vital Capacity. We measured oxygenation and $PaCO_2$. We also

determined perception of dyspnea (Borg-scores), respiratory muscle function and hypercapnic ventilatory responses. 14 out of 20 subjects became hypercapnic during tube breathing ($PaCO_2$>6.0 Kpa). No significant correlations were found between the different parameters. Subsequently, subjects were divided into two groups: normocapnic versus hypercapnic and mean values were compared. No significant differences were observed for change in oxygen saturation measured by oximetry (normocapnic –0.7% versus hypercapnic –0.2%, p=0.6), Borg score (normocapnic 4.3 versus hypercapnic 4.7, p=0.9) , respiratory muscle function nor hypercapnic ventilatory responses. Clinically relevant desaturations did not occur. We therefore concluded that tube breathing is well tolerated amongst healthy subjects. It may lead to hypercapnia, but seems a safe and feasible method in healthy subjects. When tube-breathing will be applied as respiratory muscle training modality, especially in patients with COPD, the potential development of hypercapnia must be considered.

Chapter 3

Chapter 3 describes the effects of tube breathing on CO2 homeostasis in COPD patients. The function of respiratory muscles can improve in response to training. Home-based endurance respiratory muscle training by means of tube-breathing is possibly a new training modality for respiratory muscles. The aim of this study was to investigate the effect of this tube-breathing on CO_2 homeostasis in patients with chronic obstructive pulmonary disease (COPD). We hypothesized that the ventilatory control system will stimulate ventilation during tube breathing, in order to preserve normocapnia.

Fourteen consecutive patients with moderate and severe COPD were included in the study. Pulmonary function test, hypercapnic ventilatory responses, endurance

capacity of the respiratory muscles and tube-breathing with dyspnea scores (Borg) were performed.

Strikingly, four patients became hypercapnic ($PaCO_2$>6.0 kpa) during tube-breathing. These hypercapnic patients had significantly more severe COPD, more hyperinflation, a worse capacity of their respiratory muscles and more dyspnea during tube-breathing compared to the normocapnic patients. No significant difference was found for the hypercapnic ventilatory response.

This study shows that impaired respiratory muscle capacity leads to hypercapnia and more dyspnea during tube-breathing in patients with moderate and severe COPD, whereas the ventilatory controlling system does not seem to play an important role.

Chapter 4

The effects of home-based RMET, by means of tube breathing, on endurance exercise capacity are described in this chapter. The aim of this study was to asses whether RMET improves exercise capacity and perception-of-dyspnea in patients with chronic obstructive pulmonary disease (COPD). We therefore randomised 36 patients with moderate to severe COPD to RMET (n=18) by means of tube-breathing or to sham training (control: n=18). Both groups trained twice daily for 15 minutes, 7 days per week, during 5 weeks. Endurance exercise performance on a cycle-ergometer showed a significant increase in the RMET-group: 1071±648 to 1696±894 seconds (mean±SD), p<0.001. 6-minutes-walking-distance and maximal exercise capacity also increased; 512±86 to 535±77 meters, p=0.007, and 111±33 to 120±38 watt, p=0.02 respectively. Perception-of-dyspnea (Borg-score) decreased from 8.4±1.9 to 5.4±1.3, p<0.001. Respiratory muscle endurance capacity also increased in the RMET-group: hyperpnea-endurance-time and sustainable inspiratory pressure

increased from 534±349 to 833±348 seconds, p<0.001 and from 2.5±0.9 to 3.1±1.4 kpa, p=0.005 respectively. The control-group showed no significant changes.

Ventilatory parameters were also analysed during the constant-load exercise test on a cycle ergometer at iso-time. This provides effort-independent information regarding training effects. In the RMET group, minute ventilation at iso-time (80% of the first test) decreased from 43 to 40 litres, p=0.03, respiratory rate decreased from 37 to 30 breaths/minute, p<0.001, tidal volume increased from 1.2 to 1.4 litres, p=0.04 and BORG-score decreased from 8 to 5, p<0.001. The control-group showed no significant changes. In conclusion, home-based RMET by means of tube-breathing leads to an improvement of endurance exercise capacity, a reduction in perception-of-dyspnea, and an improvement of respiratory muscle performance in patients with moderate to severe COPD.

Chapter 5

Not only physiologic parameters in terms of exercise capacity are important in the evaluation of COPD patients. Parameters as dyspnea and health status are at least as important. In this chapter we described the effects of home-based RMET on dyspnea and health-related quality of life in the same study subjects as described in the previous chapter. 36 patients with COPD, GOLD II and III were randomised into two groups: RMET by means of tube-breathing (n=18) and sham training with an incentive spirometer (control: n=18). Patients in both groups trained twice daily, 15 minutes, 7 days a week during 5 weeks. Pulmonary function tests and respiratory muscle performance was measured. Dyspnea scores were determined by means of Mahler's Baseline Dyspnea Index and Transition Dyspnea Index (BDI and TDI). Health status was evaluated by the Chronic Respiratory Disease Questionnaire

(CRQ). Patients in the RMET-group showed significant improvement of respiratory muscle endurance capacity. There was also a significant improvement in dyspnea and quality of life in the RMET-group: TDI-focal score increased by 2.8±2.5 points [mean±SD], p=0.001, CRQ-total score increased from 78.7±20.6 to 86.6±18.4, p=0.001. The control group showed no significant changes. These data confirm the hypothesis that RMET by means of tube-breathing leads to a reduction in dyspnea and an improvement in quality of life. Furthermore, RMET can interrupt a negative loop that originates in many patients with COPD. Respiratory muscle deconditioning contributes to dyspnea, which influences quality of life and mastery in a negative way. Dyspnea itself, leads to a decrease in physical activities, which acts negatively upon quality of life. A decline in physical activity leads to further deconditioning of the organism as a whole and the respiratory muscles in detail. Both aspects lead to a further decline in health status.

The results of chapter 4 and chapter 5 might have implications for the future non-pharmacologic management of moderate and severe COPD patients. With the knowledge that RMET by means of tube breathing is not very expensive and easy applicable, and therefore available to almost all chest physicians, it can be speculated that this mode of ventilatory muscle training should not be reserved for combination along with a pulmonary rehabilitation program. RMET might even, in part, replace pulmonary rehabilitation when this form of therapy is not available.

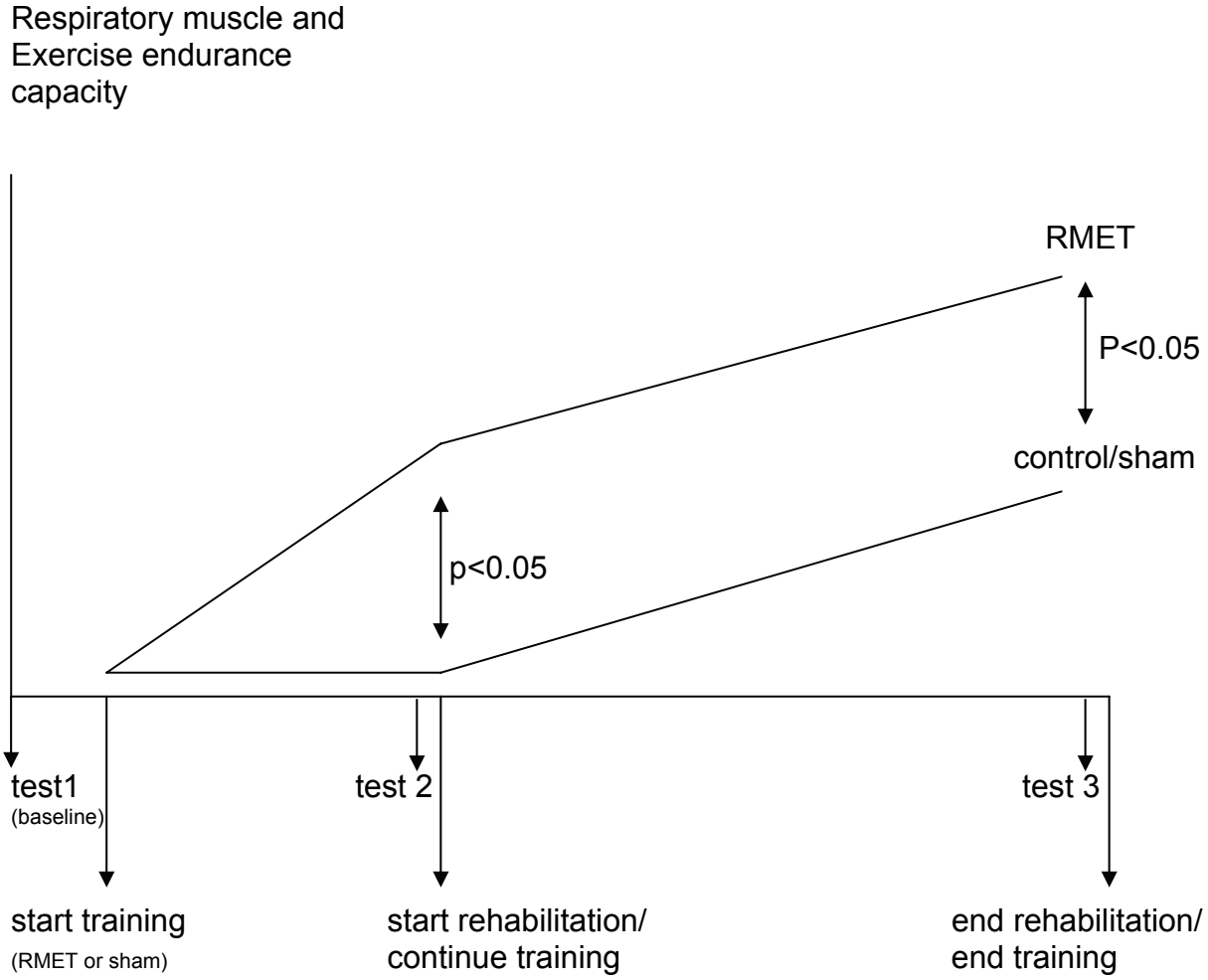
Chapter 6

In this chapter we describe the effects of Respiratory Muscle Endurance Training on the outcomes of a pulmonary rehabilitation program. Respiratory Muscle Endurance Training leads to an improvement of exercise capacity and to a reduction in the

perception of dyspnea. We therefore hypothesized, that optimizing the condition of the respiratory muscles by means of RMET, *before* the start of a rehabilitation program might lead to a better outcome of such a program. Endurance exercise capacity and perception of dyspnea were primary outcome parameters. We also looked at the effects of this intervention on quality of life and dyspnea during daily activities. The same patients as described in chapter 4 and chapter 5 continued after 5 weeks of home-based training with either RMET or sham training, during the subsequent rehabilitation program. Patients had moderate and severe COPD and they had already (randomly) been divided into Respiratory Muscle Endurance Training (RMET: n=18) by means of tube-breathing or to sham training (control: n=18) with an incentive flowmeter. As was mentioned before, both groups trained two times a day for 15 minutes, during 17 weeks. Training started 5 weeks *prior* to the start of pulmonary rehabilitation and was continued until the end of the rehabilitation program. *During* rehabilitation, improvements in respiratory muscle endurance capacity and exercise endurance performance were not statistically different between both groups. Quality of life and dyspnea during daily activities also improved to the same, statistically and clinical relevant, extent. However, due to the 5 weeks of isolated home-based RMET, patients in the RMET-group achieved significantly better improvements during the *entire* training-period (preceding home-based RMET and subsequent pulmonary rehabilitation) as compared to the control group for the following variables: Respiratory muscle endurance capacity, $p<0.001$; endurance exercise capacity, $p=0.03$ (see figure 1) and perception of dyspnea (Borg-score), $p=0.01$. We therefore concluded that RMET by means of tube-breathing leads to a better outcome of a pulmonary rehabilitation program in terms of respiratory muscle

performance and exercise endurance capacity with less dyspnea in patients with moderate and severe COPD.

Figure 1: schematic view of changes over time with respect to respiratory muscle endurance capacity and exercise endurance capacity



GENERAL DISCUSSION

Respiratory muscle training has been applied since several decades in order to improve not only respiratory muscle function, but also exercise capacity. This respiratory muscle training was mostly performed by means of inspiratory resistive training and threshold loading. These training modalities are mainly based on the physiological principals of strength training. Inspiratory manoeuvres against a resistance are performed with low frequencies and high power. The studies performed with this respiratory muscle *strength* training, showed improvements in respiratory muscle function. However, the results with regard to exercise capacity showed some inconsistencies. This may partly be due to the different training frequencies and intensities, different duration of training and different patient selection that was used. Furthermore some studies applied this training in conjunction with general exercise training, which is an important part of a pulmonary rehabilitation program. This led to the recommendation that respiratory muscle training can be applied as part of a pulmonary rehabilitation program, only for selected patients with decreased respiratory muscle strength and breathlessness.[1]

Literature from sports medicine,[2;3] healthy sedentary subjects[4;5] and patients with COPD[6] and cystic fibrosis[4] shows that respiratory muscle training that is mainly based on endurance principles is a very promising technique, because it leads to improvement in ventilatory muscle endurance capacity and endurance exercise capacity. In this kind of respiratory muscle *endurance* training subjects perform unloaded breathing with high frequencies and large tidal volumes. This method of respiratory muscle training is based on normocapnic hyperpnea. From a physiological point of view, this type of training is much closer related to daily life situations, which means that this *endurance* training is much more specific when

compared to strength training. Only one study looked at the effects of home-based RMET in patients with COPD.[7] A complicated and very expensive device was used for home-based training. This study showed improvements in respiratory muscle endurance capacity, 6-MWD and Vo2-peak. However, no difference was found between the study group and the control group, in endurance exercise capacity and dyspnea during daily activities.

In view of the above mentioned, we investigated whether home-based RMET could be performed by tube-breathing, which is easy to perform and inexpensive and therefore available to many patients. We have shown that that tube breathing is a safe and simple method to perform RMET. Furthermore in our studies RMET led to improvement in respiratory muscle endurance capacity, improvement in endurance exercise performance and reduction in dyspnea on exertion. Moreover dyspnea during daily activities improved, as well as health related quality of life. We also looked at effects of training and optimizing the respiratory muscles by means of RMET via tube-breathing *before* the start of a pulmonary rehabilitation program. In the RMET group, endurance exercise capacity, respiratory muscle endurance capacity as well as perception of dyspnea showed a significant better improvement during this period as compared to a control group. No difference was found for dyspnea and quality of life.

In view of the above mentioned it can be concluded that respiratory muscles can be trained in several ways. Strength training and endurance training have been investigated since several decades. However, endurance training did not gain much interest for clinical use because it involved practical problems in terms of expensive and complicated equipment. This led to a decreased interest for this technique and

consequently less clinical studies. On the other hand commercially available threshold loaders and incentive spirometers for respiratory muscle *strength* training were developed. Since then a lot of studies have been performed with these devices and they are widely used in daily practice. However, when looking at daily-life situations and at the specificity of training, endurance respiratory muscle training may be much better. The results with this technique are promising and with new equipment, that enables home-based training, more studies can be performed and routine clinical use becomes available.

REFERENCES

1. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest 1997; 112(5):1363-1396.
2. Holm P, Sattler A, Fregosi RF. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. BMC Physiol 2004; 4(1):9.
3. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol 1992; 65(4):347-353.
4. Keens TG, Krastins IR, Wannamaker EM, Levison H, Crozier DN, Bryan AC. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. Am Rev Respir Dis 1977; 116(5):853-860.
5. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152.
6. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280.
7. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000; 162(5):1709-1714.

8

Samenvatting en discussie

SAMENVATTING

Chronisch Obstructief Longlijden (COPD) wordt gekenmerkt door een chronische luchtwegvernauwing welke niet volledig reversibel is. Deze luchtwegvernauwing is meestal progressief en gaat gepaard met een abnormale inflammatoire reactie van de luchtwegen en longen, op giftige deeltjes of gassen. De eerste stap in de behandeling van COPD betreft het stoppen met roken. Inhalatie therapie met luchtwegverwijders is de belangrijkste farmacologische interventie, met name gericht op symptoombestrijding. Non-farmacologische behandelingen bestaan uit longrevalidatie, ademspiertraining, non-invasieve ademhalingsondersteuning, zuurstoftoediening en chirurgische interventies.

De studies in dit proefschrift beschrijven de effecten van ademspier-duurtraining (Respiratory Muscle Endurance Training; RMET), door middel van normocapnische hyperpnoe, bij patiënten met COPD. Meerdere publicaties hebben laten zien dat RMET gunstige effecten heeft, met name op het inspannings-duurvermogen, bij gezonde vrijwilligers, atleten en patiënten met COPD. Echter de apparatuur, die noodzakelijk is om tijdens een periode van hyperpnoe, normocapnisch te blijven, is erg duur en gecompliceerd. Dientengevolge is deze trainingsmethode niet voor een grote populatie beschikbaar. Het doel van dit proefschrift was te onderzoeken of ademspier-duurtraining op een veilige manier verricht kan worden door middel van het ademen met een opgelegde frequentie, door een slangensysteem, waardoor de dode ruimte fors vergroot wordt: tube-breathing. Voorts werd onderzocht of tube-breathing gunstige effecten heeft op het inspannings-duurvermogen, op dyspnoe en op de kwaliteit van leven bij patiënten met matig en ernstig COPD. Bovendien werd onderzocht of het optimaliseren van de ademspieren, voorafgaand aan een longrevalidatie programma, leidt tot een betere uitkomst van een dergelijk

programma. Hierbij dient opgemerkt te worden dat tube-breathing een eenvoudige en goedkope trainingsmethode is .

Hoofdstuk 1

Hoofdstuk 1 geeft een overzicht van de verschillende methoden van ademspiertraining. Twee verschillende vormen van ademspiertraining kunnen onderscheiden worden op basis van fysiologische trainingsprincipes: enerzijds kracht-training door middel van inspiratoire weerstandstraining en threshold loading, anderzijds duur-training door middel van normocapnische hyperpnoe. Deze laatste techniek wordt ook wel 'respiratory muscle endurance training' (RMET) genoemd. De effecten van bovengenoemde trainingsmodaliteiten op verschillende uitkomstparameters, zoals ademspierfunctie, maximaal- en duur-inspanningsvermogen, kwaliteit van leven en dyspnoe worden besproken. Bovendien worden de studiedoelen besproken.

Hoofdstuk 2

In hoofdstuk 2 wordt de haalbaarheid en de veiligheid (ten aanzien van hypoxie) van RMET door middel van tube-breathing bij gezonde vrijwilligers beschreven. RMET is gebaseerd op het principe van normocapnische hyperpnoe. Normocapnische hyperpnoe wordt niet op grote schaal toegepast omdat gecompliceerde en dure apparatuur nodig is om CO2-homeostase te behouden tijdens een periode van hyperpnoe. Deze CO2-homeostase kan bewerkstelligd worden door de dode ruimte van het respiratoire systeem te vergroten. Een van de mogelijkheden om dat te doen is door middel van het ademen via de grote dode ruimte van een slangensysteem: tube-breathing. RMET door middel van tube-breathing zou een nieuwe en goedkope

manier kunnen zijn om ademspiertraining toe te passen, eventueel zelfs in de thuissituatie. Echter de veiligheid en de effecten van deze manier van tube-breathing op CO2-homeostase zijn nooit onderzocht.

Derhalve verrichtten 20 gezonde vrijwilligers een 10 minuten durende tube-breathing sessie. De dode ruimte van het ventilatoire systeem werd met 60% van de individuele geforceerde vitale capaciteit vergroot. Oxygenatie en koolzuurspanning werden bepaald, evenals dyspnoe perceptie (Borg-score), ademspierfunctie en de hypercapnische ventilatoire respons. Bij 14 van de 20 vrijwilligers ontstond hypercapnie tijdens tube-breathing (PaCO2>6,0 Kpa). Er werden geen significante correlaties gevonden tussen de verschillende parameters. Vervolgens werden de proefpersonen op grond van hun CO2 gehalte verdeeld in twee groepen: normocapnisch versus hypercapnisch, waarbij de gemiddelde waardes vergeleken werden. Er werden geen significante verschillen gevonden ten aanzien van: verandering in oxygenatie, gemeten door middel van oxymetrie (normocapnisch –0,7% versus hypercapnisch –0,2%, p=0,6), Borg-score (normocapnisch 4,3 versus hypercapnisch 4,7, p=0,9), ademspierfunctie of hypercapnische ventilatoire respons. Er traden geen klinisch relevante desaturaties op. Deze studie laat zien dat RMET door middel van tube-breathing kan leiden tot hypercapnie, echter het wordt goed verdragen en leidt niet tot significante bijwerkingen. Derhalve lijkt RMET een veilige en haalbare methode voor ademspiertraining bij gezonde personen.

Hoofdstuk 3

In dit hoofdstuk worden de effecten van tube-breathing op CO2-homeostase, bij patiënten met COPD, beschreven. De functie van de ademhalingsspieren kan verbeteren ten gevolge van training. RMET door middel van tube-breathing,

toegepast in de thuissituatie zou een nieuwe trainingsmodaliteit voor de ademhalingsspieren kunnen zijn.

Het doel van deze studie was te onderzoeken wat het effect van tube-breathing op CO2-homeostase is bij patiënten met COPD. De hypothese luidde dat het respiratoire regelmechanisme de ademhaling zodanig zou stimuleren tijdens tube-breathing, dat normocapnie zou blijven bestaan. Veertien opeenvolgende patiënten met matig en ernstig COPD werden geincludeerd in de studie. Patiënten ondergingen longfunctie testen, een hypercapnische ventilatoire respons, een ademspierduurtest en een tube-breathing sessie met dyspnoe-score (Borg). Tijdens tube-breathing werden 4 patiënten hypercapnisch (PaCO2>6,0 kpa). Deze hypercapnische patiënten hadden een significant ernstiger COPD, meer hyperinflatie, een slechtere ademspierfunctie en hogere dyspnoe scores tijdens tube-breathing in vergelijking met de normocapnische patiënten. Er werd geen significant verschil gevonden ten aanzien van de hypercapnische ventilatoire respons. Ook werd geen klinisch relevante desaturatie gevonden bij deze COPD-patienten tijdens tube-breathing.

Deze studie toont dat met name een verminderde ademspierfunctie leidt tot hypercapnie en meer dyspnoe tijdens tube-breathing in patiënten met matig en ernstig COPD. Het respiratoire regelmechanisme lijkt geen belangrijke rol te spelen in deze.

Hoofdstuk 4

In dit hoofdstuk worden de effecten van RMET, door middel van tube-breathing, op het inspannings-duurvermogen beschreven. Het doel van deze studie was te onderzoeken of RMET leidt tot een verbetering van het inspanningsvermogen en een

afname van dyspnoe-sensaties bij patiënten met matig en ernstig COPD. Hiertoe werden 36 patiënten gerandomiseerd in twee groepen: RMET door middel van tube-breathing in de thuissituatie (n=18) of placebo-training (controle n=18). Beide groepen trainden twee maal daags gedurende 15 minuten, 7 dagen per week gedurende 5 weken. Het inspannings-duurvermogen, dat gemeten werd op een fietsergometer op 50% van het individueel behaalde maximale wattage, toonde een significante toename in de RMET-groep: van 17 minuten 51 seconden naar 28 minuten en 16 seconden, p<0,001. De 6-minuten loopafstand en het maximale inspanningsvermogen namen ook toe: van 512 naar 535 meter, p=0,007 en van 111 naar 120 watt, p=0,02 respectievelijk. De dyspnoe-sensatie (Borg-score) nam af van 8,4 naar 5,4, p<0,001. Ook het ademspier-duurvermogen verbeterde in de RMET-groep. Hyperpnoe-endurance-time nam toe van 534 naar 833 seconden, p<0,001 en sustainable inspiratory pressure nam toe van 2,5 naar 3,1 kpa, p=0,005. De controle-groep toonde geen significante veranderingen.

Behalve bovengenoemde uitkomsten werden ook ventilatoire parameters op gelijke tijdstippen tijdens de inspanningduurtest vergeleken tussen de eerste en de tweede test: iso-time vergelijking. Parameters werden vergeleken op 80% van de tijd welke behaald was bij de eerste inspanningsduurtest. Een dergelijke vergelijking geeft inspanningsonafhankelijke informatie met betrekking tot eventueel behaalde trainingseffecten. In de RMET-groep daalde het ademminuut volume van 43 naar 40 liter, p=0.03. De ademhalingsfrequentie daalde van 37 naar 30 teugen per minuut, p<0,001 en het teugvolume steeg van 1,2 naar 1,4 liter, p=0,04. De Borg-score daalde van 8 naar 5, p<0,001. De controle groep toonde geen significante verschillen. Derhalve werd geconcludeerd dat RMET door middel van tube-breathing leidt tot een verbetering van het inspanningsduurvermogen, een afname van

dyspnoe sensatie en een verbetering van de ademspierfunctie bij patiënten met matig en ernstig COPD.

Hoofdstuk 5

Bij het evalueren van COPD patiënten zijn niet alleen fysiologische parameters van belang. Steeds meer belang wordt gehecht aan parameters als dyspnoe en kwaliteit van leven. In dit hoofdstuk worden de effecten van RMET op dyspnoe en kwaliteit van leven beschreven in dezelfde populatie als beschreven in het vorige hoofdstuk. 36 patiënten met matig en ernstig COPD werden gerandomiseerd over twee groepen: RMET door middel van tube-breathing (n=18) en placebo-training met een incentive spirometer (controle n=18). Alle patiënten trainden twee maal daags gedurende 15 minuten, 7 dagen per week gedurende 5 weken. Longfunctie onderzoek en ademspiertesten werden verricht. Dyspnoe werd gemeten met behulp van Mahler's Baseline Dyspnea Index en Transition Dyspnea Index (BDI en TDI). Kwaliteit van leven werd gemeten door middel van de Chronic Respiratory Disease Questionnaire (CRQ). Patiënten in de RMET-groep toonden een significante verbetering van het ademspier-duurvermogen. Ook dyspnoe en kwaliteit van leven verbeterden significant in de RMET-groep: TDI toonde een toename van 2,8 punten, p=0,001 en CRQ nam toe van 78,7 naar 86,6, p=0,001. De controle groep toonde geen significante veranderingen. Deze data bevestigen de hypothese dat RMET door middel van tube-breathing leidt tot een afname van dyspnoe en een verbetering van de kwaliteit van leven. Bovendien blijkt dat RMET de neerwaartse spiraal met betrekking tot verslechtering van dyspnoe en kwaliteit van leven, die bij vele patiënten met COPD ontstaat, kan doorbreken. Deconditionering van de ademhalingsspieren draagt bij aan dyspnoe, hetgeen de kwaliteit van leven negatief

beïnvloedt. Dyspnoe leidt tot een afname van fysieke activiteiten, hetgeen ook weer negatief werkt op kwaliteit van leven. Een afname van fysieke activiteiten leidt tot een verdere deconditionering van het gehele organisme, en daarmee gepaard gaande een verdere achteruitgang van de respiratoire spieren. Beide aspecten leiden tot een verslechtering van de kwaliteit van leven.

De resultaten van hoofdstuk 4 en 5 zouden consequenties kunnen hebben voor de niet-farmacologische behandeling van patiënten met matig en ernstig COPD. Met de wetenschap dat RMET door middel van tube-breathing een goedkope en makkelijk toepasbare trainingsmethodiek is, kan gespeculeerd worden over de plaatsbepaling in de behandeling van COPD. Men zou kunnen stellen dat deze trainingsvorm, die op deze manier voor bijna iedereen beschikbaar is, niet alleen gereserveerd zou moeten worden voor toepassing in een revalidatieprogramma. RMET zou zelfs, indien revalidatie of inspanningstraining niet beschikbaar is, een goed alternatief kunnen zijn.

Hoofdstuk 6

In dit hoofdstuk worden de effecten van RMET op de uitkomsten van een revalidatie programma beschreven. RMET leidt tot een verbetering van het inspanningsvermogen en tot een afname van dyspnoe sensatie. Derhalve werd de volgende hypothese opgesteld: het optimaliseren van de ademhalingsspieren door middel van RMET, *vóór* de start van een revalidatie programma, leidt tot een betere uitkomst van een dergelijk programma. Primaire uitkomst parameters waren inspannings-duur-vermogen en dyspnoe sensatie. De effecten van deze interventie op kwaliteit van leven en dyspnoe tijdens activiteiten van het dagelijks leven werden ook gemeten. De patiënten, beschreven in hoofdstuk 4 en 5, starten na 5 weken

thuistraining met het revalidatie programma. Tijdens deze revalidatie periode continueerden zij hun eigen ademspiertraining (hetzij RMET, hetzij placebo-training). De patiënten hadden matig tot ernstig COPD, en zij waren reeds (at random) verdeeld in 2 groepen: Respiratory Muscle Endurance Training (RMET: n=18) door middel van tube-breathing of placebo training (controle: n=18) met een incentive flowmeter. Beide groepen trainden 2 maal per dag 15 minuten, gedurende 17 weken. De ademspiertraining startte 5 weken voor de start van de longrevalidatie en werd gecontinueerd tot het einde van de revalidatie. *Tijdens* de revalidatie periode was er geen statistisch significant verschil tussen beide groepen met betrekking tot de verbetering van het ademspierduurvermogen en inspanningsduurvermogen. Kwaliteit ven leven en dyspnoe tijdens activiteiten van het dagelijks leven verbeterden ook, statistisch en klinisch relevant, in gelijke mate. Echter, ten gevolge van de 5 weken RMET in de thuissituatie *voorafgaand* aan de revalidatie, bereikten patiënten in de RMET-groep significant betere toename tijdens de *gehele* trainingsperiode (ademspiertraining thuis *en* daarop volgende longrevalidatie) in vergelijking met de controle-groep ten aanzien van de volgende variabelen: ademspierduurvermogen, $p<0,001$; inspanningsduurvermogen, $p=0,03$; en dyspnoe sensatie (Borg-score), $p=0,01$. Derhalve luidt de conclusie dat RMET door middel van tube-breathing leidt tot een beter resultaat van een longrevalidatie programma met betrekking tot ademspierfunctie en inspanningsduurvermogen en een afname van dyspnoe bij patiënten met matig en ernstig COPD.

DISCUSSIE

Ademspiertraining wordt sinds enkele decennia toegepast, met als doel verbetering van ademspierfunctie en inspanningsvermogen. Deze ademspiertraining werd meestal verricht door middel van inspiratoire weerstands-training en threshold loading. Deze beide trainingsmethodieken zijn met name gebaseerd op de fysiologische principes van krachttraining. Inspiratoire manoeuvres tegen een bepaalde weerstand worden gedaan in een lage frequentie en met een hoge kracht. De studies waarin ademspier-kracht-training werd toegepast, toonden een verbetering van de ademspierfunctie. Echter de resultaten met betrekking tot inspanningscapaciteit waren niet altijd even eenduidig. Dit is gedeeltelijk toe te schrijven aan het feit dat verschillende trainingsschema's gebruikt werden. Ook werden verschillende patiënten groepen geincludeerd. Bovendien pasten verschillende studies ademspiertraining toe, tegelijkertijd met algemene inspanningstraining. Dit laatste is een belangrijk onderdeel van een longrevalidatie programma. Al met al leidden deze observaties tot de aanbeveling dat ademspiertraining toegepast kan worden als een onderdeel van een longrevalidatie programma, met name voor patiënten met afgenomen ademspierkracht en kortademigheid.[1] Literatuur uit de sportgeneeskunde[2;3] studies verricht bij gezonde vrijwilligers,[4;5] patiënten met COPD,[6] en cystic fibrose,[4] tonen dat ademspiertraining die met name gebaseerd is op duurprincipes (in plaats van kracht) een veelbelovende vorm van training is, vanwege het feit dat zowel ademspierduurvermogen als ook inspanningsduurvermogen verbeteren. Deze vorm van ademspierduurtraining is gebaseerd op ademen zonder weerstand met een hoge frequentie en met grote teugvolumes: normocapnische hyperpnoe. Vanuit fysiologisch oogpunt gezien is deze vorm van training veel meer gericht op de

situatie in het dagelijks leven; deze duur-training is veel specifieker in vergelijking met krachttraining. Slechts één studie heeft RMET in de thuissituatie toegepast bij patiënten met COPD.[7] Een duur en gecompliceerd apparaat werd gebruikt voor training in de thuissituatie. Deze studie toonde een verbetering van het ademspierduurvermogen, de 6-minuten looptest en de maximale zuurstof opname (VO2-peak). Er werd echter geen verschil gevonden in inspanningsduurvermogen en dyspnoe tijdens activiteiten van het dagelijks leven, tussen de studiegroep en de controle-groep.

Met bovenstaande gegevens als basis, hebben wij onderzocht of RMET in de thuissituatie verricht zou kunnen worden door middel van tube-breathing, hetgeen een gemakkelijk toepasbare en goedkope techniek is en dientengevolge voor vele patiënten beschikbaar is. We hebben aangetoond dat tube-breathing een veilige en eenvoudige methode is om RMET toe te passen. Bovendien toonden onze studies een verbetering van ademspierduurvermogen, een verbetering van inspanningsduurvermogen en een afname van dyspnoe sensatie tijdens inspanning ten gevolge van RMET. Voorts nam de dyspnoe tijdens activiteiten van het dagelijks leven af en verbeterde de kwaliteit van leven. De effecten van training en optimalisatie van de ademhalingsspieren door middel van RMET via tube-breathing *voorafgaand* aan een long revalidatieprogramma werden ook geëvalueerd. Zowel inspanningsduurvermogen alsook ademspierduurvermogen toonden een significante grotere toename gedurende deze periode in de RMET groep, in vergelijking met de controle groep. De perceptie van dyspnoe nam significant sterker af in de RMET groep in vergelijking met de controle groep. Er werd overigens geen verschil gevonden met betrekking tot dyspnoe en kwaliteit van leven.

Gezien bovenstaande gegevens kan geconcludeerd worden dat ademhalingsspieren op meerdere manieren getraind kunnen worden. Zowel kracht-training, alsook duur-training zijn in dit kader onderzocht. Echter duur-training heeft slechts een beperkte interesse gewekt, met name ten aanzien van het gebruik in de dagelijkse praktijk. Dit was mede het gevolg van praktische problemen in de zin van dure en gecompliceerde apparatuur, welke nodig was om deze vorm van training uit te kunnen voeren. Dit heeft geleid tot een afname van de interesse voor deze techniek en dientengevolge weinig klinische studies. Daarentegen werden threshold loaders en incentive spirometers ontwikkeld voor kracht-training en door de commerciële industrie op de markt gebracht. Sindsdien zijn vele studies met deze apparaten verricht en worden zij veelvuldig gebruikt in de dagelijkse praktijk. Echter wanneer we kijken naar de situatie in het dagelijkse leven en naar de specificiteit van de training dan sluit ademspier-duur-training hier veel beter bij aan. De resultaten van deze techniek zijn veelbelovend en met eenvoudige en goedkope uitrusting (± €35,-) welke training in de thuissituatie mogelijk maakt kunnen nieuwe studies verricht worden en kan routinematig klinisch gebruik van deze techniek geïmplementeerd worden.

REFERENCES

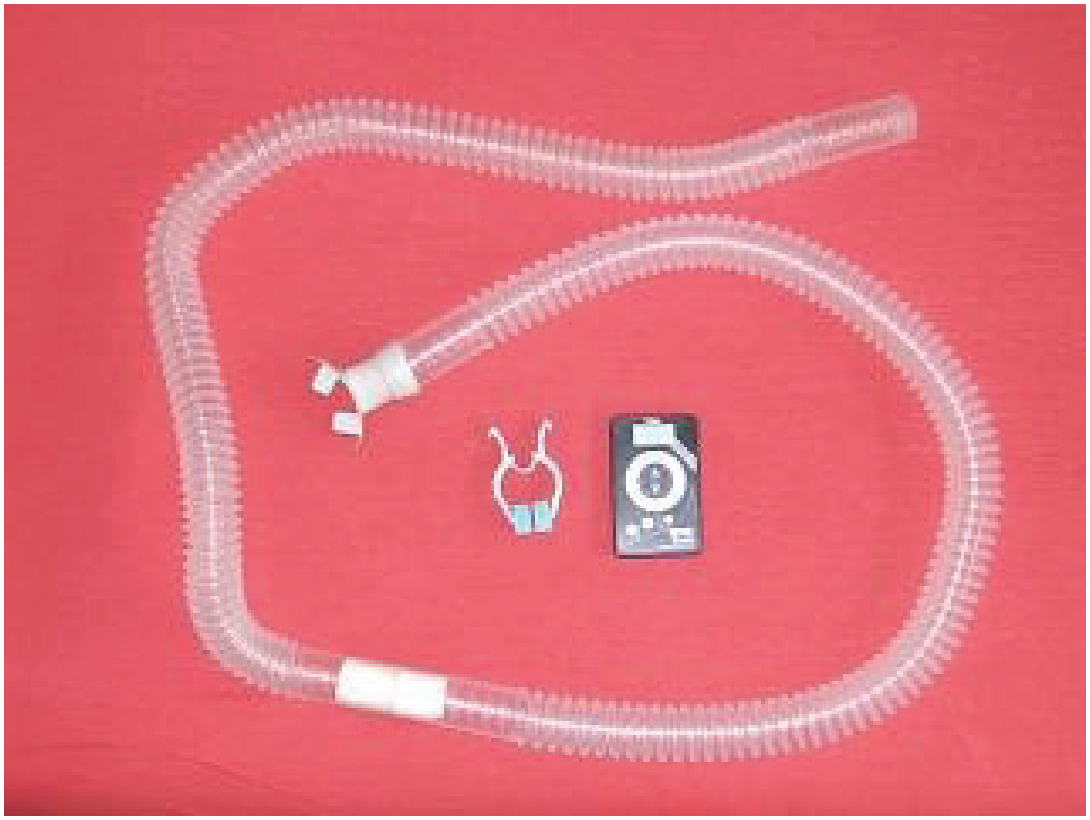
1. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonary Rehabilitation. Chest 1997; 112(5):1363-1396.
2. Holm P, Sattler A, Fregosi RF. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. BMC Physiol 2004; 4(1):9.
3. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. Eur J Appl Physiol 1992; 65(4):347-353.
4. Keens TG, Krastins IR, Wannamaker EM, Levison H, Crozier DN, Bryan AC. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. Am Rev Respir Dis 1977; 116(5):853-860.

5. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. Eur J Appl Physiol 1992; 64(2):145-152.

6. Belman MJ, Mittman C. Ventilatory muscle training improves exercise capacity in chronic obstructive pulmonary disease patients. Am Rev Respir Dis 1980; 121(2):273-280.

7. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic obstructive pulmonary disease. Impact On exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med 2000; 162(5):1709-1714.

Equipment



Dankwoord

Training en ademspier-duurtraining in het bijzonder, vergt een behoorlijke inspanning, motivatie en doorzettingsvermogen. Het verrichten van wetenschappelijk onderzoek doet daar niet voor onder. Derhalve kan promoveren als een trainingsprogramma worden gezien. Er is echter een belangrijk verschil: ademspier-duurtraining betreft een individuele training, daar waar promoveren het karakter van een groepstraining heeft. Gaarne wil ik mijn dank betuigen aan de hele groep, die met mij dit trainingsprogramma heeft doorlopen:

- Alle patiënten en vrijwilligers die vele inspannende en benauwende trainingen hebben moeten doorstaan.
- Het Nederlands Astma Fonds voor het ter beschikking stellen van de subsidie.
- Professor Dr. Folgering, beste Hans, 5 jaar geleden heb je mij enthousiast gemaakt voor het verrichten van wetenschappelijk onderzoek. Mede dankzij jou heb ik dit traject met veel plezier doorlopen. Naast het feit dat je op elk moment tijd voor mij vrij maakte en de afgelopen 2 jaren bij nacht en ontij mailtjes en telefoontjes beantwoordde ben ik je met name dankbaar voor het vertrouwen dat je in me gesteld hebt. Toen ik 3 jaar geleden naar Leeuwarden vertrok heb je misschien wel eens je bedenkingen gehad over de afloop van het project, je hebt dit echter nooit laten blijken en altijd een positieve houding aangenomen. Voorts waardeer ik je interesse in mijn leven naast het onderzoek!

- Dr. Vos, beste Petra, jouw kritische blik en positieve instelling waren (en zijn nog steeds) altijd zeer welkom. Onze samenwerking heb ik altijd als buitengewoon plezierig ervaren.

- Dr. Festen, beste Jan, dank voor de inspanningen die je verricht hebt om het onderzoek in te passen in het laatste jaar van mijn opleiding.

- Machteld Jongmans. Ook ik heb mogen profiteren van jouw organisatorische kwaliteiten. Dank voor de samenwerking.

- Afdeling Longfunctie Dekkerswald. Andre, Ger, Kees, Agnes, Petra, Oda, Christel, Thea, Irma, Vicky; Dank voor jullie hulp bij de planning en de metingen. Ik heb met veel plezier op jullie afdeling gewerkt.

- Afdeling Longrevalidatie Dekkerswald. Het is goed toeven op een afdeling met een prima sfeer. Met veel plezier heb ik mijn onderzoek op jullie afdeling uitgevoerd.

- Dr. Boot, lieve Cecile, dank voor alles!!!

- Friese maatschap Longziekten, beste maten, werken vanuit een goede organisatie en een plezierige sfeer geeft ruimte voor persoonlijke ontplooiing.

- Mijn ouders, lieve pap en mam, dank voor jullie interesse, vertrouwen en onvoorwaardelijke steun. Hopelijk kan ik nog lang van jullie wijsheden gebruik maken.

- Gijs en Pien, ik vind het prachtig om mijn leven nogmaals te (be-) leven.

- Helene, samen met jou is alles veel leuker.

Curriculum Vitae

Ralph Koppers werd op 30 november 1967 geboren in Venlo. In 1986 behaalde hij zijn VWO diploma aan het Sint Thomascollege te Venlo. De studie Geneeskunde werd gevolgd aan de Rijksuniversiteit te Maastricht, waar hij in 1990 zijn doctoraalexamen behaalde. Tijdens de doctoraalfase verrichte hij wetenschappelijk onderzoek als student-assistent op de afdeling Radiodiagnostiek van het Rikshospitalet te Oslo, Noorwegen. In 1993 behaalde hij zijn artsexamen. Vervolgens vervulde hij de militaire dienstplicht als arts van de 41-ste Afdeling Veldartillerie te Seedorf, Duitsland. In 1994 begon hij als arts-assistent op de afdeling longziekten van het Sint Maartens Gasthuis te Venlo. De opleiding tot longarts werd gestart in 1997 en afgerond in 2003. De vooropleiding werd gevolgd op de afdeling interne geneeskunde in het Rijnstate Ziekenhuis te Arnhem (opleider Dr. Verschoor) en de opleiding tot longarts in het Universitair Longcentrum Dekkerswald/Universitair Medisch Centrum Nijmegen, Sint Radboud (opleider Prof. Dr. C.L.A. van Herwaarden en Prof. Dr. P.N.R. Dekhuijzen). In 2001 startte hij, in deeltijdfunctie, met wetenschappelijk onderzoek naar de effecten van ademspier-duur-training op inspanningsvermogen en kwaliteit van leven bij patiënten met COPD, hetgeen geresulteerd heeft in het voorliggende proefschrift. Sinds februari 2003 is hij werkzaam als longarts in het Medisch Centrum Leeuwarden. Hij is getrouwd met Helene Høyset en vader van twee kinderen, Gijs (1998) en Pien (2000).