

# Controlled trial of respiratory muscle training in chronic airflow limitation

G Guyatt, J Keller, J Singer, S Halcrow, M Newhouse

## Abstract

**Background** Whether respiratory muscle training is of benefit to patients with chronic airflow limitation is controversial. The objective of the study was to determine the effect of resistance breathing training on physiological and functional measures in patients with chronic airflow obstruction.

**Methods** The design was a randomised, double blind, controlled trial with a six month follow up. Eighty two patients with a forced expiratory volume in one second (FEV<sub>1</sub>) of less than 70% predicted, and an FEV<sub>1</sub>/vital capacity ratio of less than 0.7, were randomised to receive training for 10 minutes five times daily with progressively larger resistances through a resistive breathing device (PFLEX) as tolerated or to a sham device which gave minimal resistance. The main outcome measures, respiratory muscle strength and endurance, a progressive exercise test, a six minute walk test and physical and emotional function (chronic respiratory questionnaire) were assessed at monthly intervals. Patients in both groups were also randomised to wear or not wear nose clips during their training. **Results** No significant differences were observed between treatment and control groups, with or without nose clips, for any of the outcomes. Confidence intervals on the difference between treatments were narrow, excluding clinically important difference in any major outcome.

**Conclusion** This training regimen fails to strengthen respiratory muscles or improve exercise or functional capacity in patients with chronic airflow limitation.

It has been suggested that strengthening the respiratory muscles in patients with chronic airflow limitation may reduce the discomfort of daily activities and increase functional capacity. Some studies have reported improved respiratory muscle strength and endurance,<sup>1,2</sup> improved exercise capacity,<sup>3,4</sup> and improved functional capacity and reduced dyspnoea in day to day life following respiratory muscle training.<sup>5,6</sup> These studies have been limited, however, by inadequate controls,<sup>3</sup> lack of masking,<sup>1</sup> and small sample size.<sup>7-9</sup> In addition, most training regimens were conducted in hospital under medical supervision and may therefore have limited applicability in the community. The data have provided conflicting results with

some trials failing to show improvement in respiratory muscle strength and endurance,<sup>10</sup> exercise capacity,<sup>11,12</sup> or functional capacity.<sup>13</sup> We have conducted a controlled trial of one type of respiratory muscle training in patients with moderate to severe chronic airflow limitation.

## Methods

### RECRUITMENT

The protocol was approved by the local institutional review board. Informed consent was obtained from all patients. Patients were recruited from a registry of over 1000 patients with chronic airflow limitation (defined as a best forced expired volume in one second (FEV<sub>1</sub>) of less than 70% of predicted and an FEV<sub>1</sub>/vital capacity (VC) ratio of less than 0.7). Patients were included if their exertional dyspnoea was severe enough to limit three important and frequent activities of daily living. Patients were excluded for the following reasons: (1) clinical instability as judged by change in respiratory medication in the month before entry or admission to hospital in the two months before the study; (2) inability to report on their day to day function because of cognitive, emotional, or linguistic problems; (3) objection to the patient's participation by their respiratory or family physician for whatever reason; (4) involvement in a respiratory muscle training regimen within the previous year.

### STUDY DESIGN

#### Outline

The study began with a run-in training period, after which the patients were randomized in sequence to one of four groups: (1) an experimental group who trained using six increasing levels of resistance (using an inspiratory resistance device, PFLEX) with nostrils occluded by a nose clip; (2) an experimental group who trained with increasing levels of resistance but without a nose clip; (3) a control group who trained using a nose clip and with PFLEX devices in which the diaphragm had been removed so that the device provided minimal resistance only; and (4) a control group who trained using minimal resistance and without a nose clip. Patients were followed at monthly intervals for six months and spirometry, measures of respiratory muscle strength and endurance, exercise capacity, and quality of life were carried out on each visit. Training sessions with a respiratory muscle training nurse continued for three months after randomization.

Department of  
Clinical Epidemiology  
and Biostatistics

G Guyatt  
J Keller  
S Halcrow

Department of  
Medicine

G Guyatt  
M Newhouse

Department of Family  
Medicine

J Singer

McMaster University,  
Hamilton, Ontario,  
Canada L8N 3Z5

Reprint requests to:  
Dr Guyatt, Department of  
Clinical Epidemiology and  
Biostatistics, McMaster  
University Health Sciences  
Centre, Room 2C12, 1200  
Main Street West, Hamilton,  
Ontario, Canada L8N 3Z5

Accepted 1 March 1992

## STUDY PROTOCOL

Following a run-in period of two to four weeks in which subjects were taught the use of the respiratory muscle training circuit and practised completing the functional status questionnaires, patients visited the nurse. The nurse saw subjects in sequence as they completed the run-in period but had no part in their clinical care, nor in any aspect of the study apart from the training sessions. After randomization, subjects were asked to train for ten minutes five times a day using an inspiratory resistance device (PFLEX, Healthscan, Upper Montclair, New Jersey). Subjects were seen by the nurse for training purposes on entry, at weekly intervals for four visits, and then every two weeks for four visits. Efforts were made to ensure that subjects had completed the training sessions with the nurse by three months after randomization; if a visit was missed the interval between subsequent visits was shortened. At each visit subjects were given instruction in techniques of "diaphragmatic breathing" and training using the PFLEX. (The purpose of training in diaphragmatic breathing was to make it less likely that patients assigned to the control group (see below) would feel that they were gaining nothing from use of the PFLEX.) Subjects practised use of the PFLEX with the nurse for ten minutes at each session. Oxygen saturation was monitored by ear oximetry during supervised training. Each subject, whether assigned to progressive resistance training or to the control group, began at the lowest level of resistance (setting 1). If they were able to tolerate the increased resistance, training was done at one higher setting each week. Subjects were judged unable to train at a particular setting if they felt they could not complete a ten minute training session, if their oxygen saturation fell by more than 3% or to under 90%, or if their respiratory rate increased by more than five breaths per minute, or to a rate above 24 breaths per minute. The training sessions took approximately 20 minutes.

The nurse gave the appropriate type of the PFLEX device to the patient according to a randomization schedule and also gave instructions for training. Randomisation was blocked so that two of each consecutive group of eight patients were allocated to each of the four conditions.

Patients were told that the purpose of the study was to test the best method of training their breathing muscles, and were not provided with further information about the PFLEX device. Physicians and other study personnel were blind to allocation. Patients were repeatedly instructed not to mention their impressions of the training procedure to their physician or to anyone concerned with the study apart from the nurse.

## OUTCOME MEASURES

All outcome measures were obtained each month during the visit to the clinic. If patients were too ill to attend a scheduled visit, the visit was rearranged when they were better. The research assistant inquired about intercurrent

illness at each visit (and if so the nature of this) and whether there had been any changes in medication.

*Spirometry*

FEV<sub>1</sub> and VC were obtained from the best of two expirations (Collins water spirometer with a 420 microprocessor).

*Respiratory muscle strength*

Maximum inspiratory pressures were obtained as the best of three maximum efforts at functional residual capacity on a two channel recorder. The instantaneous peak pressure was recorded. A Marshall Town manometer was integrated into the circuit on the inspired side at the mouthpiece to check the pressures generated during the maximum pressure manoeuvre and during the session on the resistance circuit.

*Respiratory muscle endurance*

The patient sat in front of a respiratory muscle testing circuit and breathed through the inspiratory port. The circuit consisted of 1.5 inch tubing divided at three inch intervals by a layer of two standard sized paper tissues for the first ten levels and then one tissue for levels 11 to 13. Each segment had a five eighths inch hole on the inspiratory side with a rubber plug. The level of resistance could be determined by varying which hole was open. A pneumotachygraph and differential pressure transducer (Hewlett Packard 270 8005C) were used to measure inspiratory flow. There were 12 levels of resistance beginning at 12 cm/litre/second and increasing progressively to 112 cm/litre/second.

Respiratory muscle endurance was measured by asking patients to breathe for one minute at each level of resistance until they could not continue. The breathing pattern was standardized so the patient generated a one second inspiration at 0.5 litres/second and a three second expiration. A line was taped to the oscilloscope screen so the patient could target breathe the desired breathing pattern and flow rate. A test was terminated if patients felt unable to continue or if they could not target the line on the oscilloscope for three consecutive attempts. Patients were asked to rate how difficult it was to breathe on a modified Borg scale, in which 0 represents no dyspnoea and 10 represents a maximal effort.<sup>14</sup> Ratings were made every two minutes on the circuit and at the completion of the test.

A capnograph was connected to the circuit to measure end expiratory carbon dioxide tension (Pco<sub>2</sub>). Pco<sub>2</sub> tended to fall during the test, but never dropped below 25 mm Hg (3.5 kPa).

*Walk test*

The six minute walk test was administered in a quiet closed corridor 30 metres in length as previously described<sup>15</sup> with standardised encouragement. At the end of the test patients rated their maximum dyspnoea during the walk using a modified Borg scale. The walk test was conducted at least twice with each patient during the study run in period.

Table 1 Mean (SD) baseline characteristics

	Resistance (n = 43)	Control (n = 39)
Age	66.5 (8.3)	66.2 (6.8)
MIP (cmH <sub>2</sub> O)	52.5 (22.2)	57.4 (22.9)
FEV <sub>1</sub> (litres)	1.04 (0.33)	0.99 (0.35)
FVC (litres)	2.51 (0.59)	2.57 (0.66)
Walk test score (metres)	404.9 (86.1)	404.6 (93.8)
Endurance (seconds)	449.2 (204.7)	438.2 (163.7)
Exercise test time (seconds)	297.5 (132.1)	298.2 (91.2)
Sex (proportion male)	29/43 (67%)	29/39 (74%)

MIP—maximum inspiratory pressure; FEV<sub>1</sub>—forced expiratory volume in one second; FVC—forced vital capacity.

#### Cycle ergometer exercise test

A progressive exercise test using an electrically braked cycle ergometer was performed according to the protocol of Jones and Campbell.<sup>16</sup> Patients rated their dyspnoea using a modified Borg scale after each minute and at the end of the test and their leg fatigue using a modified Borg scale at the end of the test. All patients started to exercise at 100 kilopond metres. In patients whose initial walk test score was less than 400 metres or whose FEV<sub>1</sub> was less than 1 litre the work load was increased by 50 kilopond metres each minute; for the other patients the work load increased by 100 kilopond metres each minute.

#### Chronic Respiratory Disease Questionnaire

The Chronic Respiratory Disease Questionnaire (CRQ), a disease specific quality of life questionnaire which measures physical and emotional function and has proved reproducible, responsive and valid,<sup>17</sup> was administered at the end of each period. Physical function assessment includes asking patients to quantify their dyspnoea on five activities that are frequently performed and are important in their day to day lives, and four items relating to fatigue and energy level. Questions regarding emotional function include frustration, depression, anxiety, and fear and panic with dyspnoea. Patients are asked to rate their function on each item using an appropriate seven point scale, e.g. extremely short of breath; very short of breath; not at all short of breath. Higher scores represent better function.

#### Compliance

Patients were asked about the number of days they had not used the PFLEX, the number of days they had conducted fewer than five training sessions, and the number of training sessions they had undertaken during those days at each monthly visit. The questions were designed to encourage accurate reporting of PFLEX use.<sup>18,19</sup>

#### Statistical analysis

The primary analysis was an analysis of variance with three factors. Grouping factors were PFLEX (active versus placebo) and nose clips (use versus non-use); time was a repeated factor. Baseline scores on the variable of interest was used as a covariate. This analysis

was conducted on each major measure of outcome: maximum inspiratory pressure, respiratory muscle endurance, spirometry, lung volume, walk test score, cycle ergometer exercise capacity, and Chronic Respiratory Disease Questionnaire physical and emotional function. Six follow up visits were not achieved in all subjects. Results from at least four visits were available for each patient who completed the trial. In the primary analysis we included data from the first four visits for each patient. In a secondary analysis, we included only patients in whom data from all six visits were available. Since the results of this secondary analysis did not differ substantively from the primary analysis, the results of the latter are presented.

#### Results

We identified 847 potentially eligible patients of whom 133 were enrolled. Major reasons for patients not enrolling included an objection from the consultant or family doctor and patient refusal. Forty patients dropped out during the run in period, in most cases because they became ill or found the commitment too great. Of the eleven patients who dropped out after randomisation, seven were allocated to active treatment and four to control. The reasons for dropping out varied. All four patients who found the commitment too great were in the active treatment group whereas all four who dropped out because of non-compliance were in the control group.

The baseline characteristics of the 82 subjects who completed the trial are summarized in table 1. Subjects who did and did not receive resistance training were comparable with respect to all major variables. Although the total number of intercurrent illnesses and changes in medication were greater in the control group (79 and 87 respectively) than in the resistance group (69 and 57) the number of illnesses associated with an increase in bronchodilators, steroids, or oxygen therapy were identical (30 in both groups). Of the admissions to hospital three of eleven in the control group were for respiratory disease, as were four of eleven in the resistance group.

Blinding of patients and research staff appears to have been effective since only on one occasion did the research assistant deduce, on the basis of comments from the patient, that allocation was to the control group and in fact the deduction was incorrect.

When asked, patients said they had missed no training sessions during the previous month on 41% of occasions and on 59% of occasions they acknowledged missing some sessions—on 38% less than a third, on 50% one to two thirds, and on 12% more than two thirds. Non-compliance increased over the six months of the trial. During the first month patients said they had missed no training sessions during the previous month on 55% of occasions. By the sixth month the figure was 32%.

When patients were asked if any of the training sessions that they had undertaken were shorter than they should have been they said "no" on 53% of occasions. When some shor-

Table 2 Mean baseline and fourth follow up visit score with associated *p* values and confidence interval on difference in change between resistance and control groups

	Resistance		No resistance		<i>p</i> value*	Confidence interval†
	Baseline	4th visit	Baseline	4th visit		
Maximum inspiratory pressures (cm H <sub>2</sub> O)	53.5	53.6	57.2	58.1	0.60	-8.66, 4.98
Endurance time (seconds)	443	494	437	553	0.12	-144, 17.3
Exercise time (seconds)	309	294	308	301	0.64	-41, 26
Walk test score (metres)	406	416	409	429	0.19	-26, 5
CRQ physical	35.4	40.6	33.2	41.2	0.25	-5.5, 1.5
CRQ emotional	57.9	60.7	52.1	58.2	0.20	-6.1, 1.3

\*The *p* value is on the difference between the two groups in change from fourth visit to baseline

†This 95% confidence interval represents the plausible difference in changes between baseline and fourth visit in the two groups. Positive numbers favour resistance, negative numbers favour no resistance. For example, the resistance groups showed a mean improvement of 51 seconds in respiratory muscle endurance time while the control group improved by 116 seconds. The mean difference is -65 seconds, i.e. the 65 second difference favours the control group, and the plausible true difference lines between -144 and 17.3.

tening was acknowledged, 80% reported that it had not been more than 25%.

Whether patients were given nose clips or not did not influence the results. Nose clips did not cause a significant difference in any analysis, either as an independent factor or as part of an interaction with resistance, nor were there any appreciable trends according to whether patients were or were not given nose clips.

The primary outcomes on resistance training are presented in table 2. The results of each test were stable throughout the six months of the study. There were no major differences in the degree of change in patients receiving versus patients not receiving resistance training, although all outcomes showed a small, non-significant trend in favour of the group not receiving resistance training. The confidence intervals around the differences in change over the six months show that clinically important differences in favour of respiratory muscle training have been excluded.

### Discussion

The current study has a number of strengths. The study was randomised and double blind, which appears to have been effective, and both physiological and functional outcomes were measured carefully. The sample size is the largest of any controlled trial of respiratory muscle training yet undertaken, and this resulted in relatively narrow confidence intervals around the differences in improvement in the two groups, which allowed exclusion of important differences in favour of active treatment. Home training was tested so that the intervention (had it been effective) could have been applied widely. Home training, however, also implies the possibility of non-compliance.

Although our detailed inquiry concerning compliance suggested that most patients conducted their training sessions relatively regularly, patients did not keep a diary of PFLEX use, and definitive ascertainment of their compliance is not possible. The different reasons for dropping out between those allocated to treatment and the control group raises some concern; bias could be introduced if the reasons for dropping out were related to outcome. The number of patients who dropped out was small, however.

The most striking finding in our study was that training of the respiratory muscles was not achieved. One possibility is that respiratory muscle training regimens are in general ineffective. This would be true if, for instance, chronic airflow limitation imposes so severe an internal load on the respiratory muscles that they are fully trained for strength and endurance. If, however, respiratory muscles can be strengthened in patients with chronic airflow limitation, there must be other explanations for our negative results. Although patient non-compliance is a possible explanation, we believe that other explanations are more likely. It is possible that we selected patients less likely to respond to the intervention.<sup>17</sup> For instance, if enrolment had been restricted to patients with a low maximum inspiratory pressure, the results may have been positive. Given the heterogeneity of our population, and the lack of apparent trend in any subgroup, this seems unlikely.

An ability to tolerate increasing respiratory resistance can be achieved by changes in breathing pattern rather than by strengthening respiratory muscles, according to Belman and colleagues, who used the same PFLEX device as we used.<sup>18</sup> They found no improvement in resistance breathing performance or ventilatory muscle endurance with resistance breathing training with this device.

Findings in other studies can help decide the most likely explanation for our results. We have conducted a meta-analysis of all published and unpublished randomised trials of respiratory muscle training in patients with chronic airflow limitation,<sup>19</sup> meeting established criteria for a scientifically rigorous overview.<sup>20</sup> Of the 13 studies included in the meta-analysis, 11 had studied the effects of resistance training and two the effect of volume training. Of the 11 which studied the effects of resistance training, the flow rates (and thus the resistance) generated during training were controlled by the investigators in four. Outcomes examined included maximum inspiratory pressure, maximum voluntary ventilation, respiratory muscle endurance, laboratory exercise capacity, functional exercise capacity, and functional status. For most outcomes, there were small non-significant trends in favour of respiratory muscle training.

In a secondary analysis we compared resis-

tance studies in which the patient was required to target during training to achieve a specified flow rate with studies (such as the current one) in which there was no such requirement. There were substantial differences in effect size for respiratory muscle strength and endurance, functional exercise capacity, and functional capacity between the two types of studies; the effect sizes in the studies in which breathing pattern was controlled were clinically important.

This difference in effect between studies in which breathing pattern was and was not controlled is weakened by the fact that it relies on differences between (rather than within) studies.<sup>22</sup> The magnitude of the differences was modest and statistically significant for respiratory muscle strength and functional capacity, but not for respiratory muscle endurance, laboratory exercise capacity, and functional exercise capacity.

We believe that the most likely explanation for our failure to improve respiratory muscle strength and endurance is that flow rates were not controlled. Whether success in improving strength and endurance would have led to benefits in exercise capacity, functional capacity, or dyspnoea in daily living remains unknown.

We would like to acknowledge the following individuals for help in this study: for assistance with randomisation and supervision of training patients in the respiratory muscle training procedure, Ms Gerri Galassi; for constructing and helping to maintain the respiratory muscle endurance circuit, Mr Don McCormack; for supervision of data management, Ms Jenny Whyte; for assistance with data collection, Ms Sandi Harper; and for assistance with recruitment of patients, Drs Stewart Pugsley, Roger Haddon, Chris Allen, Allen McLellan, Serge Puksa, Helen Ramsdale, Frederick Hargreave, and John Morse.

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