Respiratory Medicine (2007) **101**, 516–524

ELSEVIER

respiratoryMEDICINE

Clinical outcomes of expiratory muscle training in severe COPD patients☆

Susana Mota[a,b], Rosa Güell[a], Esther Barreiro[c], Ingrid Solanes[a], Alba Ramírez-Sarmiento[c], Mauricio Orozco-Levi[c], Pere Casan[a], Joaquim Gea[c,*], Joaquín Sanchis[a]

[a]*Departament de Pneumologia, Hospital de la Santa Creu i de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain*
[b]*Unitat de Pneumologia-Servei de Medicina Interna, Hospital Santa Caterina, Girona, Spain*
[c]*Servei de Pneumologia & Unitat de Recerca en Múscul i Aparell Respiratori (URMAR), Hospital del Mar—IMIM, Universitat Pompeu Fabra, 27, E 08003 Barcelona, Spain*

Received 28 December 2005; accepted 29 June 2006

KEYWORDS
Respiratory muscles;
Rehabilitation;
Breathing exercises;
Exercise;
Quality of life;
Dyspnoea

Summary
The most common symptoms in chronic obstructive pulmonary disease (COPD) patients are breathlessness and exercise limitation. Although both general and inspiratory muscle training have shown clinical benefits, the effects of specific expiratory muscle training remain controversial.
Objective: To investigate the effects of expiratory training on lung function, exercise tolerance, symptoms and health-related quality of life in severe COPD patients.
Methods: Sixteen patients (FEV_1, 28±8% pred.) were randomised to either expiratory muscle or sham training groups, both completing a 5-week programme (30 min sessions breathing through an expiratory threshold valve 3 times per week) (50% of their maximal expiratory pressure (MEP) vs. placebo, respectively). Lung function, exercise capacity (bicycle ergometry and walking test), and clinical outcomes (dyspnoea and quality of life (St. George Respiratory Questionnaire (SGRQ)) were evaluated both at baseline and following the training period.
Results: Although lung function remained roughly unchanged after training, exercise capacity, symptoms and quality of life significantly improved. The improvement in both walking distance and the SGRQ score significantly correlated with changes in MEP.

☆This study was supported, in part, by Spanish Grants from FUCAP, SEPAR, FIS (98/1143) and ISC III (RTIC C03/11), as well as by a Grant of the European Commission (BMH4-CT98-3406). Very preliminary results were presented at the European Respiratory Society Annual Congress, Stockholm 2002.

*Corresponding author. Tel.: +34 93 248 31 38; fax: +34 93 221 32 37.
E-mail address: jgea@imim.es (J. Gea).

doi:10.1016/j.rmed.2006.06.024

Conclusion: Our results confirm that a short outpatient programme of expiratory training can improve symptoms and quality of life in severe COPD patients. These effects could be partially explained by changes in expiratory muscle strength.

Introduction

The efficacy of pulmonary rehabilitation on chronic obstructive pulmonary disease (COPD) patients has been demonstrated in many studies.[1,2] Although pulmonary rehabilitation is a multi-dimensional therapy, muscle training appears to be its most effective component. This is not surprising since muscle dysfunction is common in COPD patients and, at least in part, appears to be the result of muscle deconditioning. General exercise, the training modality supported by the strongest evidence (level A) has been shown to improve exercise tolerance, dyspnoea and health-related quality of life.[2–4] Clinical benefits of specific ventilatory muscle training, however, have remained equivocal.[5] Nevertheless, different recent studies have shown that when training loads are well controlled, inspiratory training can induce specific improvements in the strength and endurance of inspiratory muscles, as well as a decrease in dyspnoea sensation both at rest and during exercise.[6–8] Therefore, it is currently accepted that inspiratory training is a meaningful addition to pulmonary rehabilitation programmes, mostly in those COPD patients with inspiratory muscle weakness.[7,9] However, the role of expiratory muscle training in COPD patients is much less well understood. On one hand, there is a relative paucity of data on expiratory muscle role in chronic respiratory conditions, on the other hand, the prevalence of expiratory muscle dysfunction and its impact in general clinical outcomes is unclear. Finally, the studies evaluating specific expiratory training programmes are rather scarce.

Expiratory muscles have been found to be active in COPD patients both at rest and during exercise, mostly at the end of expiration.[10,11] Moreover, these muscles are progressively recruited during bronchospasm and ventilatory loading.[12,13] Finally, they are essential for coughing and therefore, the clearance of the airways. However, these actions do not appear to result in significant muscle conditioning (training effect) in COPD patients. Although their maximal strength can be either only mildly decreased or relatively maintained,[14–17] COPD patients can actually suffer from progressive expiratory muscle dysfunction as expressed by a reduced endurance and early appearance of fatigue.[16] Moreover, even normal subjects can develop expiratory muscle fatigue during heavy ventilatory efforts.[18,19] Therefore, it is more likely that expiratory muscles of COPD patients, which persistently work under the overloads of increased airway resistance and decreased lung elastic recoil,[20] would develop muscle dysfunction. It should be recognised, however, that the intensity of expiratory muscle dysfunction appears to be relatively low if compared with weakness shown by COPD patients in peripheral or inspiratory muscles.[14–17]

Weiner et al.[17] recently reported that a 3-month programme of partially supervised expiratory muscle training using a threshold device was able to induce a significant increase in exercise capacity. These results were confirmed in a second study by the same authors.[21] However, the benefits of expiratory training programme were lower than those achieved with inspiratory training alone, and similar to those obtained by combining inspiratory plus expiratory components.[21] Nevertheless, the paucity of data does not allow for definitive conclusions. In addition, as previously demonstrated for inspiratory muscles, the intensity, frequency and duration of the loads, as well as the profile of the candidates, are determinant, and essential in the interpretation of data.[6,22,23]

The aim of the present study was to confirm the clinical benefits of a specific expiratory muscle training, and to provide new information about the effects of a relatively short training programme (only 5 weeks) on respiratory function, exercise capacity, dyspnoea and health-related quality of life in severely obstructed COPD patients. These outcomes can be considered as the main short-time targets in the treatment of these patients.

Methods

Patients

We studied patients with COPD in stages III (severe) or IV (very severe) according to GOLD classification[23] (FEV_1/FVC$<$70% and FEV_1 $<$50% pred.). Exclusion criteria were a positive bronchodilator response (FEV_1 increase $>$200 ml after 200 μg of inhaled salbutamol), chronic respiratory failure (PaO_2 lower than 60 Torr), abnormal body mass index (BMI) $>$30 or $<$20 kg/m^2, bronchial asthma, coronary disease, chronic metabolic or orthopaedic diseases, recent abdominal or thoracic surgery, and/or treatment with corticosteroids, hormones or chemotherapy. The patients were simultaneously participating in parallel studies aimed at investigating phenotypic changes induced by different training programs in respiratory muscles. All subjects gave their written informed consent prior to their participation in the study.

Study design

The protocol followed the World Medical Association guidelines for research on humans[24] and was approved by our institutional ethical committees. After a 4-week run-in period, during which their clinical stability was verified, the patients were randomised to either expiratory muscle training or sham training. Clinical and physiological measurements were performed before and at the end of the programme, and the research team was blind regarding the assigned training or sham groups.

Training programme

Training was done at the hospital under the supervision of an experienced physiotherapist. During the 1st week, patients received 3 sessions of general chest physiotherapy techniques (relaxation and postural drainage). From the 2nd to the 6th week both the control and the training groups had three 30-min sessions per week breathing through an expiratory threshold device.[25] The load in the training group was equivalent to around 50% of their maximal expiratory pressure (MEP) whereas no additional loads were used in the sham training group. Initially, repeated cycles of 3 min of work followed by 2 min of rest were conducted (total work-time 18 min). The length of work intervals was increased on a weekly basis while rest periods were shortened to obtain a total work time of 30 min in the last week of the programme. The valve opening pressure was continuously monitored at the mouthpiece to ensure the achievement of the target pressure. At the end of each session, 15 min of general abdominal muscle exercises were also used in the training group.

Lung function

Forced spirometry, as well as inspiratory capacity (IC), maximal voluntary ventilation, plethysmographic lung volumes, carbon monoxide transfer coefficient (DLco), arterial blood gases, and MEP were determined as described in previous articles,[6,16] and are expressed as percentages of appropriate reference values.[26–29]

Exercise tests

This included a 6-min walking test (6′WT), leg cycloergometry and arm cycloergometry. The 6′WT[30,31] was performed along a hospital corridor with continuous pulse oximetry monitoring. Both pre- and post-test dyspnoea (Borg scale) and distance walked were recorded. Each patient received instructions about the test and standardised encouragement to walk covering as much ground as possible. We performed 2 tests, with at least 30 min rest between them, and the highest distance obtained in the two tests was chosen. Incremental bicycle ergometry to volitional exhaustion was also performed for both upper and lower limbs using the classical protocol described by Jones and Campbell[32] Dyspnoea as well as limb symptoms were assessed (Borg scales) at baseline, every 2 min and at the end of the incremental limb exercise tests. Physiological variables were analysed at three different levels: maximal effort, 70% of pre-training peak O_2 uptake, and 60% of maximal voluntary ventilation.

Dyspnoea and health-related quality of life

Dyspnoea during daily activities was evaluated using a modified Medical Research Council (MRC) scale,[33] whereas quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) in its Spanish version.[34,35] The latter is an instrument, specific for COPD, which includes three different scales evaluating symptoms, activity and impact. The overall and each scale scores range from 0 to 100 (from no change to maximum change in quality of life, respectively).

Statistical analysis

Values are expressed as mean and standard error ($x \pm$ SEM). Baseline and post-training data were compared within groups using the Wilcoxon test for paired samples. The Mann–Whitney *U*-test was used to compare data and percentages of change between both groups. Correlations were studied by calculating the Spearman coefficient. A *P* value <0.05 was considered statistically significant.

Results

Eighteen male COPD patients were initially enroled (8 for the control group and 10 for the expiratory training group). However, two patients in the sham training group did not finish the study: one because of a COPD exacerbation and the other due to a gouty arthritis episode. The main baseline characteristics of all patients who finished the programme were similar in the 2 groups (Table 1). All patients had severe-to-very severe airway obstruction and most also had air trapping, decreased CO transfer coefficient, expiratory muscle dysfunction and mild-to-moderate hypoxaemia.

Respiratory function

Following expiratory training lung function remained essentially unchanged (Table 2 and Fig. 1a). However, MEP increased by 19%. No significant changes were observed in the sham group. When percentages of change following intervention were used to compare both groups, no differences were observed for respiratory function variables except for MEP. However, hyperinflation showed a slight tendency to be lower in those patients belonging to the

Table 1 Baseline characteristics of study subjects.

	Sham training ($n = 6$)	Expiratory training ($n = 10$)
Age, yr	66±3	62±2
Height, cm	167±3	168±2
Weight, kg	67±5	67±4
FEV_1, % pred.	28± 3	27±3
TLC, % pred.	115±1	131±6
MEP, % pred.	72±9	68±6
DLCO, % pred.	48±8	46±6
PaO_2, Torr	68±2	72±2
$PaCO_2$, Torr	46±3	44±2
$\dot{V}O_{2\,max}$, pred.	59±5	53±7
6′WT distance , m	430±47	421±34

Values are represented as x±SEM. Abbreviations: DLco, carbon monoxide diffusing coefficient; PaO_2 and $PaCO_2$, arterial blood partial pressures for oxygen and carbon dioxide, respectively; $\dot{V}O_{2\,max}$, maximal oxygen uptake (cycloergometry); 6′WT, 6-min walking test.

Table 2 Lung function data before (baseline) and after (end) training.

	Sham training ($n = 6$)		Expiratory muscle training ($n = 10$)	
	Baseline	End	Baseline	End
FVC, L	2.64 ± 0.19	2.88 ± 0.23	2.80 ± 0.13	2.96 ± 0.10
FEV_1, L	0.84 ± 0.07	0.91 ± 0.08	0.87 ± 0.08	0.86 ± 0.07
FEV_1/FVC, %	32 ± 4	32 ± 3	32 ± 2	29 ± 2
IC, L	1.72 ± 0.16	1.89 ± 0.14	1.47 ± 0.16	1.72 ± 0.08
FRC, L	5.08 ± 0.19	4.9 ± 0.25	6.42 ± 0.45	6.13 ± 0.39
RV, L	4.14 ± 0.21	3.90 ± 0.29	5.09 ± 0.49	4.81 ± 0.43
TLC, L	6.80 ± 0.32	6.79 ± 0.36	7.89 ± 0.48	7.77 ± 0.40
RV/TLC, %	61 ± 2	57 ± 3	63 ± 3	61 ± 3
MEP, cm H_2O	130 ± 10	131 ± 8	123 ± 12	147 ± 12*

For abbreviations see the text. *$P < 0.05$ in the comparison of pre- and post-training values.

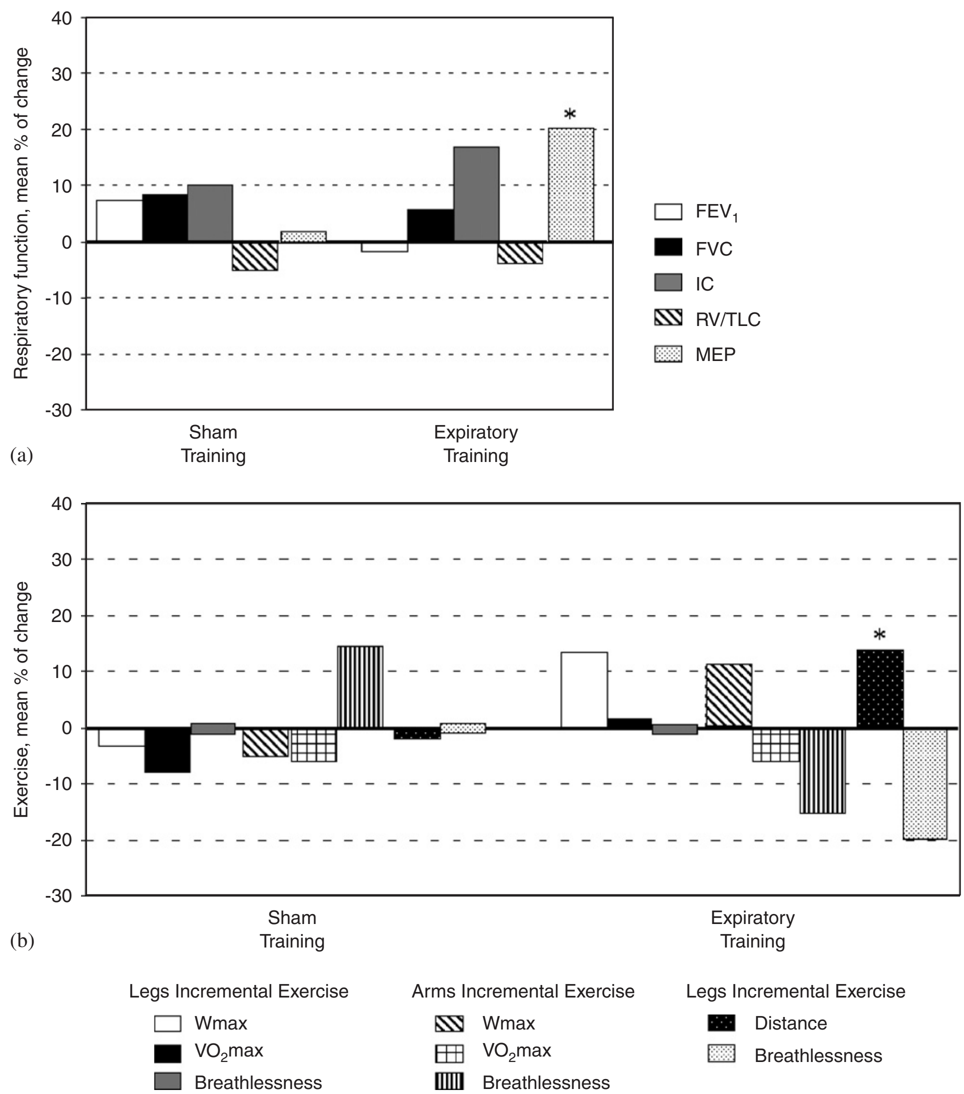

Figure 1 (a) Mean changes observed in representative variables of respiratory function following either sham training or expiratory muscle training. (b) Mean changes in exercise variables observed after training. From left to right, parameters corresponding to leg cycloergometry, arm cycloergometry and the 6 min walking test. *$P < 0.05$.

trained group (their increase in IC was 17% vs. only 9.8% in the control group, $P = 0.10$).

Exercise

The main variables obtained when exercising are shown in Table 3 and Fig. 1b. The distance walked during the 6′WT significantly improved after muscle training (13%), with no changes in the sham group. In addition, the change in the level of dyspnoea from baseline to the end of the walking test shown by trained patients was significantly better than that of controls (20 vs. 0%, respectively) Moreover, although no significant changes were observed in the incremental limb exercise tests in either trained or control patients, the analysis of the percentages of change in each group evidenced significant differences favouring trained patients in maximal workloads obtained in either leg or arm cycloergometries (12% and 11% vs. −3% and −5%, respectively, $P<0.05$ both). In addition, the improvement in exertional dyspnoea observed in trained patients for the latter test was significantly higher than that shown by the sham group ($P<0.05$) (Fig. 1b).

Dyspnoea at rest and health-related quality of life

The MRC scores showed that dyspnoea at rest improved in the training group (3±1 vs. 2±1, $P<0.01$) but not in the sham group (2±2 vs. 2±1). In addition, the former group showed a significant decrease in the SGRQ overall score, and specifically in symptoms and impact domains, after the programme (Fig. 2).

Correlations of changes induced by training

The increase in expiratory muscle strength observed in the trained group correlated with the improvements in both the distance walked, and the activity, impact and global scores obtained in the SGRQ (Fig. 3). Finally, a significant relationship was found between changes in exertional dyspnoea measured at the end point of the 6′WT and changes in the QoL assessment with global scale, $r = 0.634$, $P<0.05$).

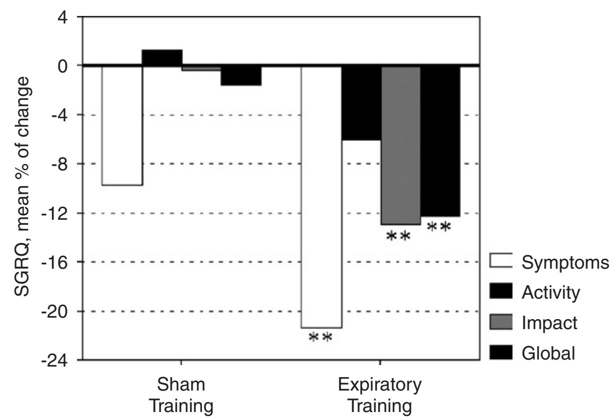

Figure 2 Mean changes in the St. George Respiratory Questionnaire (SGRQ) scores observed after the expiratory training programme. White bars correspond to the symptoms score; striped bars to the activity score; grey bars to the impact score; and black bars to the global SGRQ score. **$P<0.01$.

Table 3 Exercise variables before and after training.

	Sham training ($n = 6$)		Expiratory muscle training ($n = 10$)	
	Baseline	End	Baseline	End
Legs incremental exercise test				
W_{max}, Kpm/min	500±82	483±60	420±54	470±56
$\dot{V}O_{2\ max}$, L/min	0.96±0.10	0.88±0.09	0.93±0.10	0.94±0.08
$\dot{V}_E$, L/min	36±5	34±5	33±3	35±4
V_T, L	0.97±0.11	0.99±0.12	0.91±0.06	0.99±0.06
V_T/T_I, L/s	1.6±0.22	1.49±0.25	1.45±0.14	1.66±0.14*
Breathlessness, Borg	8±1	8±1	7±1	7±1
Arms incremental exercise test				
W_{max}, Kpm/min	200±43	190±30	185±26	205±32
$\dot{V}O_{2\ max}$, L/min	0.81±0.08	0.75±0.04	0.88±0.08	0.82±0.07
Breathlessness, Borg	7±1	8±0	7±1	6±1
Six-min walking test				
Distance, m	430±47	423±45	421±34	474±32**
Breathlessness, Borg	3±1	3±1	5±1	4±0

All data correspond to the maximal effort in each test. W_{max}, indicates maximal work rate; $\dot{V}O_{2\ max}$, maximal oxygen consumption; $\dot{V}_E$, minute ventilation; V_T, tidal volume; V_T/T_I, mean inspiratory flow. *$P\leqslant0.05$ and **$P<0.01$ in the comparison between pre- and post-training values.

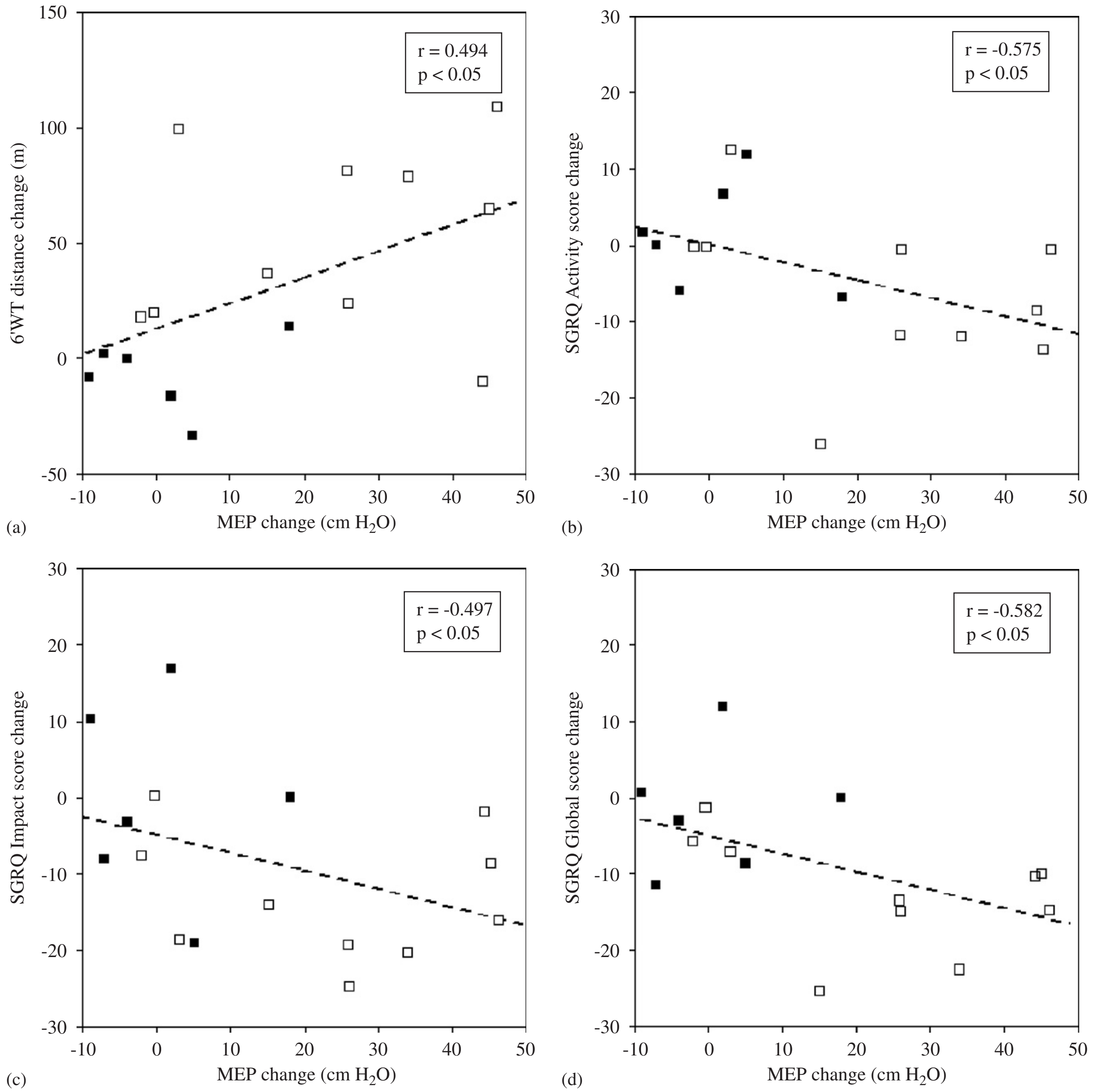

Figure 3 Relationships between changes in maximal expiratory pressure (MEP) following the training period on one hand, and modifications in (a) the distance obtained in the 6′WT, as well as in (b) the activity score, (c) the impact score and (d) the global score obtained in the SGRQ, on the other. Open squares represent trained patients while closed squares correspond to the control group.

Discussion

The main finding of the present study is the significant improvement in dyspnoea at rest, health-related quality of life, and timed walking distance in COPD patients following a short expiratory muscle training period. Most of these changes were proportional to the improvement in expiratory muscle strength. It should be noted that improvements in SGRQ scores and walking test distance were not only statistically significant but also should be considered clinically relevant.[34–36] The complementary analysis of differential changes in trained and control groups also revealed that improvements were greater in the former regarding maximal workloads obtained in either arm or leg cycloergometries, as well as in exertional dyspnoea in both the 6′WT and the upper limb exercise.

Although expiratory muscles have been little studied, it is known that in COPD patients these muscles can exhibit weakness, as evidenced by either mild reductions in maximal force and/or endurance.[15–17,20] Since muscle weakness might be improved through different mechanisms by training, we hypothesised that a specific expiratory training programme using an appropriate schedule would promote clinical benefits. This study was designed to respond to the relative lack of information about the impact of expiratory training on symptoms, quality of life and exercise in a clinical context, and the results observed confirm our initial hypothesis. The significant increase of expiratory muscle strength and its close correlation with the improvement in certain exercise and life-quality variables, strongly suggest a causative role for the former mechanism. Although MEP manoeuvre is volitional and therefore, can be biased by learning, the absence of changes in the control group strongly argues for an actual increase in expiratory muscle strength in trained patients. Our findings are also consistent with the results of Weiner et al.[17] regarding the benefits of expiratory training in exercise tolerance since submaximal exercise capacity (as measured by the walking test) increased significantly, and maximal work also tended to increase in both arm and leg incremental exercise tests.

The observation of an improvement in dyspnoea during activities of daily living as well as in health-related quality of life following expiratory training in severe COPD are probably the most relevant findings for the clinical practise. The perception of breathing difficulty during everyday tasks is modulated by physical, psychological and socio-cultural factors and it is known to be the main component of health-related quality of life in such patients.[34,35] When Suzuki et al.[37] studied the effects of specific expiratory training in healthy individuals, they were able to provide evidence of improved strength and reduced sensation of respiratory effort. Weiner et al.[17,21] however, found no significant changes in dyspnoea (measured by Mahler's baseline and transitional indices) after expiratory muscle training in a group of less severely obstructed COPD patients, who in any case had a more limited exercise capacity than ours. The differences between study populations, training protocols and instruments of measurement could explain the discrepancy, although it may also be attributable to insufficient statistical power.

In accordance with dyspnoea changes observed in the present study, health-related quality of life (not previously evaluated by Weiner et al.)[17,21] also improved significantly in our patients, both phenomena being statistically associated. This finding itself denotes the achievement of a capital goal for an integrated COPD treatment, since quality of life appears to have an independent prognostic value in the natural history of the disease, in terms of use of health resources, hospitalisation rates and survival.[38]

According to our results, four different possible mechanisms may have been implicated in the clinical improvement observed in COPD patients following expiratory training. First of all, a decrease in work-related oxygen consumption for the expiratory muscles. Since breathing pattern, ventilation, oxygen saturation, and heart rate during the exercise tests did not change following training, and peak oxygen uptake remained the same while maximal work tended to increase, clinical improvement could be a product of favourable changes in local expiratory muscle metabolism (i.e. a decrease in their oxygen consumption). Although the level of the stimulus delivered by the training programme used in the present study is theoretically able to induce aerobic adaptation within muscle fibres,[6] the methodological approach required to test this hypothesis necessarily would need further studies.

The second mechanism for clinical benefits observed following training in our COPD patients is a potential desensitisation to dyspnoea. The patients in our treatment group walked a statistically significant and clinically meaningful greater distance on the walking test, without an increase in Borg-rated dyspnoea. In fact, when analysing percentages of change in both trained and control patients, significant improvements favouring the former group were observed both in the walking test and arm cycloergometry in spite of increases in the workloads in both tests. Moreover, the perception of dyspnoea at maximal leg exercise did not change regardless of the greater improvement in workload reached by trained patients. All of this indicates an effective decrease in their task-related sensation of breathlessness. This perception is known to be a complex process in which the implicated factors are mainly those that promote increased output by respiratory system motoneurons[39–42]; and there is evidence that both inspiratory and expiratory muscle subsequent efforts play a role in generating the sensation of breathing effort.[40]

The third mechanism that would explain the clinical improvement observed in our patients is a reduction in lung volumes. We actually found that trained patients showed a mild tendency to have less air trapping (as expressed by different tendencies in FVC, inspiratory capacity, FRC and RV). However, one might have expected that increased expiratory strength would have favoured dynamic airway compression during exhalation. Nevertheless, expiratory muscle training may also act on the complex mechanisms involved in hyperinflation in two other different ways. For instance, by modifying the static equilibrium between the lung and the chest wall (improving abdominal muscle tone and elevating the diaphragm to diminish thoracic air trapping)[43]; and/or by increasing expiratory muscle activity to compensate for inspiratory muscle activity during expiration.[44] The absence of significant correlations between the clinical benefits of training and static lung volumes in our study, however, argues against a role for hyperinflation at rest. Although we did not investigate dynamic hyperinflation during exercise, our observation of an increased mean inspiratory flow at peak exercise in trained patients may reflect changes in inspiratory muscle activity as a by-product of mechanical modifications (such as a reduction in end-expiratory volume). However, it seems unlikely that a clinically relevant decrease in dynamic hyperinflation took place in patients who probably became flow-limited during exercise.[43]

Finally, the expiratory muscle training could have led to a more effective cough and therefore, a more efficient clearance of the airways. This was not assessed in our study. However, even if coughing capacity has been improved, it is unlikely that this would have a relevant role in our patients, who were clinically stable and non-bronchorrheic, with a daily sputum volume that was less than 30 mL according to our records.

General muscle training is probably the most widely used component in rehabilitation programs. Alone or combined with inspiratory muscle training, it has been clearly shown to induce clinical changes in COPD patients.[1–3,5,6] However, in keeping with some other recent reports,[17,21] our results clearly indicate that specific expiratory muscle training is also capable of inducing desired clinical benefits in severely obstructed COPD patients. In our experience this sort of training is easy to incorporate into clinical practise and has no adverse effects. Furthermore, its simplicity suggests that expiratory muscle training could probably also be performed at home, given a few supervised sessions to ensure correct procedure on the part of the patient. However, the actual feasibility of expiratory training home application should be evaluated in further studies. The efficacy of expiratory muscle training in comparison with the training of other muscle groups also warrants investigation. In this respect, as previously mentioned, Weiner and McConell[9] does not favour expiratory in front of inspiratory training, for two main reasons. In the first place, they reported greater improvement in the 6-min walked distance after inspiratory muscle training than after expiratory training, with no additional benefits resulting from the combination of both modalities.[21] In contrast, our group did not find significant changes in exercise capacity in a group of very obstructed COPD patients after a short inspiratory training programme structured in a similar way to the expiratory training used in the present study.[6] The second finding that caused Weiner and McConell[9] not to favour expiratory training over inspiratory training is that it was only after the latter that they found an improvement in dyspnoea at rest. We, however, did find an improvement after expiratory training. Discrepancies between their observations and ours remain an interesting question to explore but, as mentioned above, they are probably related to differences in protocols and patient profiles.

Our study has some limitations derived from the relatively small number of patients finally included. However, this is a restriction common to many other randomised placebo controlled studies and can be partially counterbalanced by comparison between percentages of change in different groups. On the other hand, although this limitation might seem to imply that our conclusions should be taken cautiously, the coincidence with findings obtained in previous studies strongly argues for their consistence.

To sum up, we confirm that specific expiratory muscle training improves functional exercise capacity as assessed by timed walking distance, and decreases dyspnoea during daily living activities, resulting in a better health-related quality of life in patients with severe COPD. Although our understanding of the physiological mechanisms underlying these benefits is not complete, our results suggest that they are directly related to changes occurring in expiratory muscle physiology.

Acknowledgements

We would like to thank Ms. Mercè Sangenís, Ms. Fátima Morante and Dr. Manuel Brufal for their important collaboration for the patients training and assistance, and to Mr. Juanjo Cuesta and Roger Marshall for their editing help.

References

1. 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**:1115–9.
2. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 1995;**122**:823–32.
3. ACCP/AACVPR pulmonary rehabilitation guidelines panel. Pulmonary rehabilitation. Joint ACCP/AACVPR evidence-based guidelines. *Chest* 1997;**112**:1363–96.
4. 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**:362–8.
5. Smith K, Cook D, Guyatt GH, Madhavan J, Oxman AD. Respiratory muscle training in chronic airflow limitation: a meta-analysis. *Am Rev Respir Dis* 1992;**145**:533–9.
6. Ramírez-Sarmiento A, Orozco-Levi M, Güell R, Barreiro E, Hernandez N, Mota S, et al. Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *Am J Respir Crit Care* 2002;**166**:1491–7.
7. Lötters F, Van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *Eur Respir J* 2002;**20**:570–6.
8. Geddes EL, Reid WD, Crowe J, O'Brien K, Brooks D. Inspiratory muscle training in adults with chronic obstructive pulmonary disease: a systematic review. *Respir Med* 2005;**99**:1158–440.
9. Weiner P, McConnell A. Respiratory muscle training in chronic obstructive pulmonary disease: inspiratory, expiratory, or both? *Curr Opin Pulm Med* 2005;**11**:140–4.
10. Ninane V, Rypens F, Yernault JC, et al. Abdominal muscle use during breathing in patients with chronic airflow obstruction. *Am Rev Respir Dis* 1992;**146**:16–21.
11. Ninane V, Yernault JC, De Troyer A. Intrinsic PEEP in patients with chronic obstructive pulmonary disease. Role of expiratory muscles. *Am Rev Respir Dis* 1993;**148**:1037–42.
12. Gorini M, Misuri G, Duranti R, et al. Abdominal muscle recruitment and PEEPi during bronchoconstriction in chronic obstructive pulmonary disease. *Thorax* 1997;**52**:355–61.
13. O'Donnell DE, Sanii R, Anthonisen R, et al. Expiratory resistive loading in patients with severe chronic airflow limitation. *Am Rev Respir Dis* 1987;**136**:102–7.
14. Man WD, Hopkinson NS, Harraf F, Nikoletou D, Polkey MI, Moxham J. Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease. *Thorax* 2005;**60**: 718–22.
15. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;**153**:976–80.
16. Ramirez- Sarmiento A, Orozco-Levi M, Barreiro E, Méndez R, Ferrer A, Broquetas J, et al. Expiratory muscle endurance in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:132–6.
17. Weiner P, Magadle R, Beckerman M, Weiner M, Berar-Yanay N. Specific expiratory training in COPD. *Chest* 2003;**124**:468–73.
18. Fuller D, Sullivan J, Fregosi RF. Expiratory muscle endurance performance after exhaustive submaximal exercise. *J Appl Physiol* 1996;**80**:1495–502.
19. Loke J, Mahler DA, Virgulto JA. Respiratory muscle fatigue after marathon running. *J Appl Physiol* 1982;**52**:821–4.
20. Whipp BJ, Pardy RL. Breathing during exercise. In: *Handbook of physiology. The respiratory system. Breathing during exercise*. Section 3, vol. III, pt. 2, chapter 34. Bethesda, MD: American Physiology Society; 1986. p. 605–29.
21. 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**: 1357–64.
22. Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. *Eur Respir J* 1997;**10**:2884–91.
23. www.goldcopd.com. Global initiative for obstructive lung disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *NHLBI/WHO workshop report*. Bethesda: National Heart, Lung and Blood Institute; Updated 2004.

24. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, as amended by the 52nd WMA Assembly, Edinburgh, Scotland, October 2000; Note of Clarification on Paragraph 29 added by the WMA General assembly. Washington, DC; 2002.
25. Orozco—Levi M, Gea J, Maldonado D. Proposal of a threshold pressure device to assess the endurance of expiratory muscles. *Lung* 2001;**179**:93–103.
26. Roca J, Sanchis J, Agustí-Vidal A, Rodríguez- Roisin R. Spirometric reference values for a Mediterranean population. *Bull Eur Physiopathol Respir* 1986;**22**:217–24.
27. Roca J, Burgos F, Barbera JA, Sunyer J, Rodriguez-Roisin R, Castellsague J, et al. Prediction equations for plethysmographic lung volumes. *Respir Med* 1998;**92**:454–60.
28. Roca J, Rodríguez-Roisin R, Cobo E, Burgos F, Pérez J, Clausen JL. Single-breath carbon monoxide diffusing capacity (DLCO) prediction equations for a Mediterranean population. *Am Rev Respir Dis* 1990;**141**:1026–32.
29. Morales P, Sanchis J, Cordero PJ, Díez J L. Maximum static respiratory pressures in adults. The reference values for a Mediterranean Caucasian population. *Arch Bronconeumol* 1997; **33**:213–9.
30. Butland RJ, Pang J, Gross ER, Woodkock AA, Geddes DM. Two, six, and 12 min walking tests in respiratory disease. *Br Med J* 1982;**284**:1607–8.
31. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, et al. Effect of encouragement on walking test performance. *Thorax* 1984;**39**:818–22.
32. Jones N, Campbell EJM. *Clinical exercise testing*. Philadelphia, PA: Saunders; 1988.
33. Mahler DA, Harver A. Measurement of symptoms: the benchmark of treatment. Minimizing the effects of dyspnea in COPD patients. *J Respir Dis* 1987;**8**:23–34.
34. Jones PW, Quirck FH, Baveystock CM. The St. George's Respiratory Questionnaire. *Respir Med* 1991;**85**(Suppl. B): 25–31.
35. Ferrer M, Alonso J, Prieto L, Plaza V, Monsó E, Marrades R, et al. Validity and reliability of the St. George's Respiratory Questionnaire after adaptation to a different language and culture: the Spanish example. *Eur Respir J* 1996;**9**:1160–6.
36. Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. *Am J Respir Crit Care Med* 1997;**155**:1278–82.
37. Suzuki S, Sato M, Okubo T. Expiratory muscle training and sensation of respiratory effort during exercise in normal subjects. *Thorax* 1995;**50**:366–70.
38. Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002; **166**:680–5.
39. Eltayara L, Becklake MR, Volta CA, Milic-Emili J. Relationship between chronic dyspnea and expiratory flow limitation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**154**:1726–34.
40. Kayser B, Sliwinski P, Yan S, Tobiasz M, Macklem PT. Respiratory effort sensation during exercise with induced expiratory-flow limitation in healthy humans. *J Appl Physiol* 1997;**83**: 936–47.
41. Marin JM, Montes de Oca M, Rassulo J, Celli BR. Ventilatory drive at rest and perception of exertional dyspnea in severe COPD. *Chest* 1999;**115**:1293–300.
42. American Thoracic Society. Dyspnea. Mechanisms, assessment and management: a consensus statement. *Am J Respir Crit Care Med* 1999;**159**:321–40.
43. Demedts M. Mechanisms and consequences of hyperinflation. *Eur Respir J* 1990;**3**:617–8.
44. Morris MJ, Madgwick RG, Lane DJ. Difference between functional residual capacity and elastic equilibrium volume in patients with chronic obstructive pulmonary disease. *Thorax* 1996;**51**:415–9.