



Osteopathic manipulative treatment effectiveness in severe chronic obstructive pulmonary disease: A pilot study

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KEYWORDS

Chronic obstructive pulmonary disease (COPD); Pulmonary rehabilitation; Osteopathic manipulative treatment

Summary

Objectives: Few and contrastingly data are available about use of osteopathic manipulative treatment (OMT) in patients with chronic obstructive pulmonary disease (COPD).

Design: Comparing the effects of the combination of pulmonary rehabilitation and OMT compared with pulmonary rehabilitation (PR) in patients with severely impaired COPD.

Setting: Rehabilitative pulmonary department.

Interventions: Patients underwent exercise training, OMT, educational support and nutritional and psychological counselling.

Main outcomes measures: Exercise capacity through 6 min walk test (6MWT – primary outcome) and pulmonary function test (secondary outcomes) were evaluated at the beginning and at the end of the training. Patients were randomly assigned to receive PR + soft manipulation (G1) or OMT + PR (G2) for 5 days/week for 4 weeks.

Results: 20 stable COPD patients (5 female – mean age, 63.8 ± 5.1 years; FEV1 $26.9 \pm 6.3\%$ of predicted) referred for in-patient pulmonary rehabilitation were evaluated. Respect to the baseline, 6 MWT statistically improved in both group. In particular, G2 group gained 72.5 ± 7.5 m ($p = 0.01$) and G1 group 23.7 ± 9.7 m. Between group comparison showed a difference of 48.8 m (95% CI: 17 to 80.6 m, $p = 0.04$). Moreover, in G2 group we showed a decrease in residual volume (RV – from 4.4 ± 1.5 l to 3.9 ± 1.5 l, $p = 0.05$). Between group comparison showed an important difference (-0.44 l; 95% CI: -0.26 to -0.62 l, $p = 0.001$). Furthermore, only in G2 group we showed an increase in FEV1.

Conclusions: This study suggests that OMT + PR may improve exercise capacity and reduce RV in severely impaired COPD patients with respect to PR alone.

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Introduction

The term complementary and alternative medicine (CAM) covers a diverse range of therapies. The main manipulative therapies generally considered to be complementary medicine are acupuncture, chiropractic and osteopathy.¹ National surveys suggest that CAM is popular throughout the industrialized world.²

CAM has been used in patients with chronic obstructive pulmonary disease (COPD). In 2004 a cross sectional study³ showed that 41% of 173 patients with COPD claimed to be using some form of CAM. More recently, another study⁴ showed that 43.2% of 155 patients with COPD had used some type of CAM.

Osteopathy belongs to CAM.¹ However, few and contrastingly data are available about its use in patients with COPD. In 1975 Howell et al.⁵ showed a statistical significant improvements in oxygen tension, pulse oxymetry, total lung capacity and residual volume in patients with COPD who underwent osteopathic manipulative treatment (OMT). Conversely, Noll et al.⁶ more recently showed that OMT worsened air trapping in patients with COPD. Furthermore, OMT seems not to influence quality of life and exercise capacity.⁷

We therefore decided to perform OMT in a population of patients with COPD. COPD is defined⁸ as a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. It is characterized by chronic airflow limitation and by weight loss, nutritional abnormalities and skeletal muscle dysfunction. In Table 1 diagnostic classification, assessment

of severity and pharmacological treatment of COPD are summarized.

OMT is defined as the therapeutic application of manually guided forces by an osteopathic practitioner to improve physiologic function and/or support homeostasis that has been altered by somatic dysfunction (see below for the definition). First aim of this study was to evaluate the effect on exercise capacity, as measured by 6 min walk test (6MWT); second aim was to evaluate possible changes in pulmonary function.

Material and methods

Study subjects

The study population included COPD patients consecutively admitted to our Operative Unit and to the Respiratory Rehabilitation Unit of Pio Albergo Trivulzio in Milan from January to May 2008.

20 patients affected by COPD were enrolled. Diagnosis of COPD was made according to the guidelines of the global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD).⁸ We selected only stable COPD, who did not show signs of exacerbation from at least 3 months. In according with OMT practitioners, we choose to enrol patients with stage III, severe COPD because of their limited exercise capacity and their low body mass index, to facilitate OMT manoeuvres. Exclusion criteria were the occurrence of acute exacerbation during the period of the study or history of diseases

Table 1 Diagnostic classification, assessment of severity and therapy of COPD.⁸

Stage	Spirometric cutpoints	Symptoms	Pharmacologic treatment
1, Mild	FEV1/FVC < 0.70 FEV1 > 80% prd	Chronic cough and sputum (not always)	- Short acting bronchodilator (when needed)
2, Moderate	FEV1/FVC < 0.70 50% < FEV1 < 80% prd	Shortness of breath on exertion plus cough and sputum (sometimes)	- One or more long acting bronchodilators - Rehabilitation - Short acting bronchodilator (when needed)
3, Severe	FEV1/FVC < 0.70 30% < FEV1 < 50% prd	Greater shortness of breath, reduced exercise capacity, fatigue	- One or more long acting bronchodilators - Rehabilitation - Inhaled glucocorticosteroids (if repeated exacerbations) - Short acting bronchodilator (when needed)
4, Very severe	FEV1/FVC < 0.70 50% < FEV1 < 80% prd plus chronic respiratory failure	Quality of life very appreciable impaired; life threatening exacerbations.	- One or more long acting bronchodilators - Rehabilitation - Inhaled glucocorticosteroids (if repeated exacerbations) - Long term oxygen if needed - Short acting bronchodilator (when needed)

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Respiratory failure: arterial partial pressure of oxygen less than 60 mm Hg with or without arterial partial pressure of CO₂ greater than 50 mm Hg while breathing air at sea level.

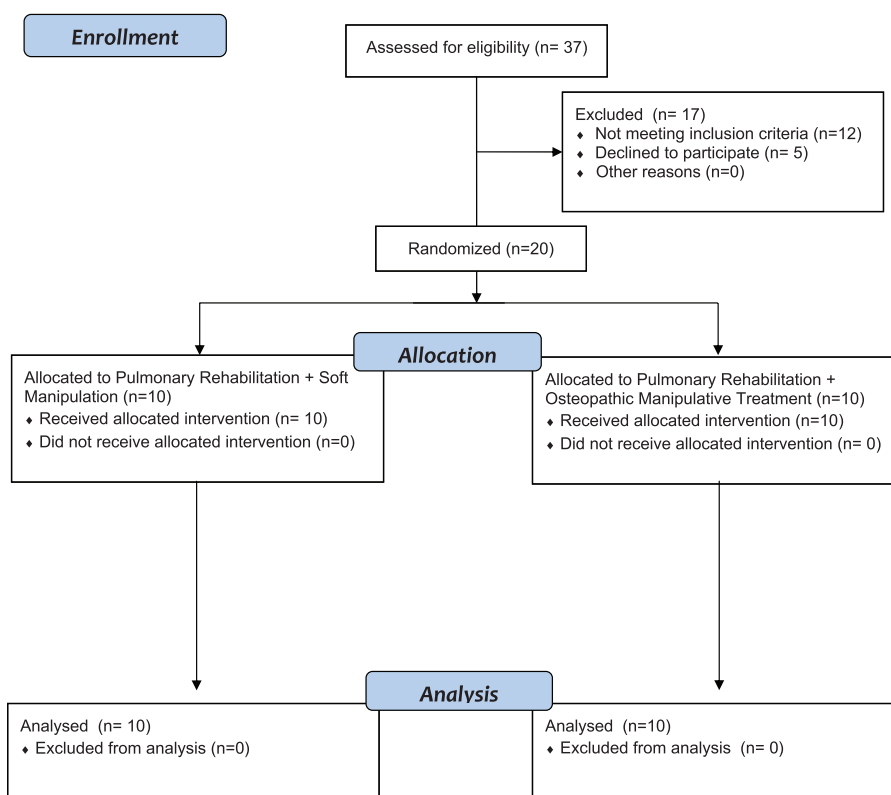


Figure 1 Diagram showing the flow of participants through each stage of the randomized trial.

other than COPD, in particular neurological diseases or joint degenerative disease leading to spinal or body rigidity.

Each patient was informed about the aim of the study and about the concept and the type of treatment. Each patient read and signed an informed consent.

Our Institutional Ethical Committee approved the study.

All patients received regular treatment with inhaled bronchodilators according to current guidelines for their disease stage. This treatment did not change during the study.

For allocation of the participants, a prior randomization list was drawn based on computer-generated list of random numbers. We used a random number generator through <http://stattrek.com/Tables/Random.aspx#tableques>. The list was obtained before the study commenced. Numbers were randomly selected within the range of 1–20. Duplicate numbers were not allowed. Participants were randomly assigned following simple randomization procedures to 1 of 2 treatment groups (see below). Random number list and the allocation sequence were respectively downloaded, sealed and concealed by an investigator with no clinical involvement in the trial (C.B.). She had the assignment schedule in a safe and locked room, sequentially assigned each patient to the treatment, and resumed and collected data only when study was ended. The data collector were blinded to the intervention assignments throughout the study. Patients were treated with OMT or with soft manipulation (sham osteopathic treatment). Since they were not in contact with each other, they remained blinded to the randomization and they were not able to compare the type of treatment.

Patients were divided in two groups: G1 and G2; G1 (10 patients; 2 female) received pulmonary rehabilitation

program (PR) plus soft manipulation (sham osteopathy treatment) and G2 (10 patients; 3 female) received OMT + PR. The attending physician, the technician of respiratory laboratory (who performed spirometry) and the respiratory therapist (who performed 6MWT) were blinded to group assignments.

A diagram showing the flow of participants through each stage of our randomized trial is shown in Fig. 1.

Study design

In this longitudinal study, pulmonary function and exercise capacity were assessed at baseline and at the end of the treatment.

Methods

Lung function was recorded using a spirometer (Master scope body; Jaeger; Wurzburg, Germany) and a calibrated pneumotachograph. Both dynamic (VC, FVC, FEV1) and static (RV) volumes were recorded before and after 200 mcg of inhaled salbutamol.

6 min-walk test (6MWT) was performed following the American Thoracic Society guidelines.⁹ Subjects were instructed to walk in a corridor from one end to the other of 20 m, while trying to cover as much ground as possible in the given 6 min. If necessary, subjects were allowed to stop and rest during test, but they were taught to recommence walking as soon as they felt able to do so. At the beginning and at the end of exercise patients were asked to

grade their level of breathing and fatigue according to the modified Borg scale.¹⁰

Pulmonary rehabilitation program

Patients underwent a comprehensive PR program consisting of exercise training, educational support, psychological counselling and nutritional intervention.

Both lower and upper extremity training was performed, using a cyclette (Corival V3; Lode BV; Groningen; The Netherlands) and an arm cycle ergometer (Monark 881; Monark; Stockholm; Sweden) respectively. Working load was determined in two steps: firstly, the patient cycled at zero watt for 5 min; secondly, load was gradually increased every minute until a score of 5 ± 1 to the Borg scale or 80% of predicted maximal heart frequency were reached. Rehabilitation training consisted of one session on cyclette and one on cycle ergometer for 5 days/week for 4 weeks, for a total of 40 sessions. Length of each session was 30 min.

Osteopathic manipulative treatment

The examination was performed by osteopathic practitioners with emphasis on the neuromusculoskeletal system including palpatory diagnosis for somatic dysfunction and viscerosomatic change, in the context of total patient care. The examination was concerned with range of motion of all parts of the body, performed with the patient in multiple positions to provide static and dynamic evaluation.

All osteopathic practitioners adopted the same examination form. Examination was done according to the following scheme: anamnesis; physical examination of thoracic outlet, spine, rib cage, thoracic and pelvic diaphragm and tentorium cerebelli; and cranio-sacral evaluation. This latter allowed to check possible restrictions among cranium bones and/or between sacrum and iliac bones joint mobility using a thorough palpation to disclose the occurrence of tension of intracranial membranes. Furthermore, quality of kinetic of primary respiratory mechanism was evaluated.

The treatment was done once a week for 4 weeks for a total of 4 sessions. Each session lasted 45 min.

Both PR and OMT were completely tailored to suit the needs of the individual.

Statistical analysis

We assumed to conduce the analysis on all randomized patients irrespective of their completion of treatment (intention to treat analysis); however, all patients completed the entire clinical trial and therefore all patients were counted towards the final results (per – protocol analysis).

Analysis of the study was performed using a statistical software package (StatSoft version 5.5; Tulsa, OK, USA). Data are presented as mean \pm SD. Primary study outcome, i.e. values at rest and at the end of 6MWD, and secondary outcomes, i.e. change in forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), vital capacity (VC) and residual volume (RV) were compared

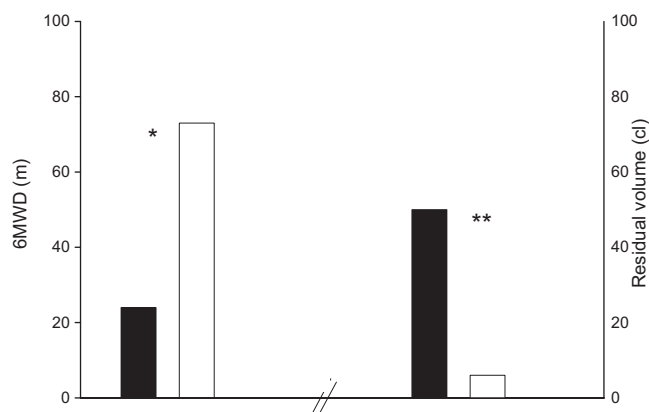


Figure 2 Change in 6MWD (expressed in meters) and in residual volume (expressed in centilitres) at entry and completion of the study. Black bar: between G1 group difference; white bar: between G2 group difference; * p 0.001, ** p 0.04.

using Student's paired t -test. Threshold for statistical significance was set at $p < 0.05$.

Results

The sample for the analysis consisted of 20 patients, of whom 5 (25%) were female. Patients were in the 60-year age group and, on average, with a low body mass index. According to the GOLD definition,⁸ all our patients were in stage III (severe COPD), showing severe airflow limitation, great shortness of breath and reduced exercise capacity.

Between group comparison of mean baseline characteristics are shown in Table 2.

There were no adverse effects or side-effects. Both PR and OMT were well tolerated.

Functional results

The primary study outcome was the mean change of 6MWT from entry to week 4. Within groups analysis showed that both group reached an appreciable increase in 6MWD. In particular, G1 group gained 23.7 ± 9.7 m. Adding OMT to PR led to a further gain in 6MWD of 72.5 ± 7.5 m ($p = 0.01$). The difference between G1 and G2 group at the end of the study (48.8 m; 95% CI from 17 to 80.6 m) was significant ($p = 0.04$).

Concerning secondary outcomes, i.e. possible change in pulmonary function, we did not show any significant difference in G1 group, while combination of PR and OMT led to a considerable ($p = 0.05$) reduction in RV, which decreased of about 11%: in this case we showed a substantial ($p = 0.001$) difference between group (-0.44 l; 95% CI from -0.26 to -0.62 l). Furthermore, G2 group showed a noteworthy change in FEV1, which at the entry was 0.99 ± 0.4 l and improved of about 14% (1.13 ± 0.4 l). However, we were not able to show between group difference regarding FEV1.

Functional results are summarized in Table 3 and Fig. 2.

Osteopathic results

Somatic dysfunction was found at the level of occiput-C1-C2, C3-C4, T2-T9 and T12-L1 vertebrae. Rib dysfunction during

Table 2 Baseline characteristics (mean value \pm SD) of the two groups of patients. G1, pulmonary rehabilitation + soft manipulation; G2, osteopathic manipulative treatment + pulmonary rehabilitation.

	G1	G2	p-Value
Age, years	63.5 \pm 4.7	64.2 \pm 5.5	0.87
BMI, kg/m ²	18.2 \pm 2.5	17.9 \pm 3.1	0.29
FEV1, % predicted	26.5 \pm 6.2	27.4 \pm 6.4	0.85
VC, % predicted	74.9 \pm 7.5	72.6 \pm 8.2	0.86
FVC, % predicted	73.3 \pm 4.6	69.5 \pm 6.1	0.91
RV, % predicted	189.9 \pm 37.6	191.4 \pm 36.4	0.85
6MWT, m	281.2 \pm 97.4	279.4 \pm 87.8	0.72

Data are expressed as mean \pm SD.

BMI, body mass index; FEV1, forced expiratory volume in the first second; VC, vital capacity; FVC, forced vital capacity; RV, residual volume; 6MWT, 6 min walk test.

inhalation was found. In particular, an abnormally elevated first rib was found. Sternum was characterized by increase of tissue density and by a motion decrease. Scalenes, trapezius and sternocleidomastoid showed an augmented muscle tension. The anatomic connection between the occiput and the sacrum by the spinal dura mater (the so called cranio-sacral mechanism) revealed a "compressive" dysfunction of both cranium and sacrum. The examination of the four diaphragms showed a motion barrier during the inhalation phase.

After the treatment, examination showed a diminished tissue resistance, an increased joint motion and a better, reciprocal function of the diaphragms.

Discussion

This study showed that OMT may further improve exercise capacity in comparison to PR alone in patients with severe COPD; moreover, patients treated with OMT showed a significant decrease of residual volume.

It is well known that exercise training is the best available means of improving exercise tolerance in patients with COPD.¹¹ In our study all the patients underwent exercise training focused on both lower and upper extremities, the latter being useful both in stable¹¹ and in critically ill¹² patients with COPD. As expected, PR was able to improve exercise capacity in patients with COPD. Adding OMT to PR we found a further increase of 6MWD. This led to a noteworthy difference between the two groups. A first, important consideration is that adding OMT to PR is able to permit a gain in distance walked that is over the gain threshold for clinical significance.^{9,13–15} In other words, while PR, as expected, allowed to reach the so called minimal important difference (MID) which in patients with COPD is approximately 25 m,¹⁶ OMT + PR largely overcome MID.

The further gain in 6MWT due to OMT is difficult to explain, at least looking at the results from a conventional point of view. In other words, both group of patients underwent the same pharmacologic therapy and the same training exercises, but patients treated with OMT + PR showed a considerable improvement in 6MWT respect to patients treated with PR alone. May this be a consequence of OMT itself? And if so, how OMT can do it? We hypothesized that the decrease of RV could play a role in improving 6MWT. So far, effects of

OMT on pulmonary function are uncertain. Noll et al.⁶ measured the immediate effect of one OMT session on pulmonary function in elderly subjects with COPD showing a significant increase in RV. Therefore, to explain the decrease in RV we achieved, we hypothesized that performing more than one OMT treatment could reasonably lead to a decrease in airway resistance. Doctors of Osteopathic Medicine RM Engel and SR Vemulpad¹⁷ approached patients with COPD through a series of manual treatment sessions during a 4-to-6-week period; they believe that gradually increasing the intensity of the same treatment technique over successive treatment sessions is likely to circumvent the immediate adverse effects on airway obstruction reported by Noll et al. Another possible mechanism explaining the influence of OMT on RV could be its effect on chest wall mobility. At the end of the study practitioners referred a diminished tissue resistance. Moreover, patients treated with OMT reported subjective improvement in their breathing. This could mean that OMT improved chest wall mobility, as it has been already shown with exercises to stretch respiratory muscles in patients with COPD.¹⁸ Regardless of the mechanism, decrease of RV may explain the better exercise capacity. Indeed, the correlation between dynamic lung hyperinflation and exercise performance is well known.¹⁹ Any intervention that reduces lung hyperinflation improves exercise capacity.²⁰ Diaphragmatic mobility is the parameter that could provide information on respiratory mechanics and functional capacity in patients with COPD.²¹ Patients with reduced diaphragmatic mobility showed poorer 6MWD performance and greater RV.²⁰ Therefore, if OMT may reduce RV, this may explain the gain in 6MWT achieved by patients treated with OMT + PR.

Several limitation should be considered when interpreting the results of our study. First of all, it must be pointed out that we are not osteopathic practitioners nor operators. This study was thought and drawn starting from a curiosity point of view. The Salvatore Maugeri Foundation is the largest Italian institution devoted to Rehabilitation. In its Respiratory Units common protocol for PR are applied. The majority of patients admitted to the Respiratory Unit to perform Rehabilitation is affected by COPD. COPD patients at all stages of disease appear to benefit from exercise training programs.⁸ Ideally, pulmonary rehabilitation should involve several types of health professionals. So we decided to add OMT to common pulmonary rehabilitation. This was possible thank to the availability of three students of the

Table 3 Functional results in group of patients treated with pulmonary rehabilitation (G1) and in group of patients treated with pulmonary rehabilitation and osteopathic manipulative treatment (G2).

Measure	PR		Group (G1)		Post-pre difference (95% CI)		PR + OMT		Group (G2)		Post-pre difference (95% CI)		Between group difference (95% CI)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
VC, l	1.88 ± 0.8	1.86 ± 1.0	1.86 ± 1.0	1.86 ± 1.0	0.02 (-0.19 to 0.23)	0.02 (-0.19 to 0.23)	1.76 ± 0.4	1.87 ± 0.3	1.76 ± 0.4	1.87 ± 0.3	0.11 (-0.15 to 0.37)	0.11 (-0.15 to 0.37)	0.09 (-0.71 to 0.89)	0.09 (-0.71 to 0.89)
FEV1, l	0.89 ± 0.4	0.90 ± 0.4	0.90 ± 0.4	0.90 ± 0.4	0.01 (-0.12 to 0.14)	0.01 (-0.12 to 0.14)	0.99 ± 0.4	1.13 ± 0.4	0.99 ± 0.4	1.13 ± 0.4	0.14 (0 to 0.26)	0.14 (0 to 0.26)	0.13 (-0.66 to 0.9)	0.13 (-0.66 to 0.9)
FVC, l	1.75 ± 0.7	1.79 ± 0.8	1.79 ± 0.8	1.79 ± 0.8	0.04 (-0.07 to 0.15)	0.04 (-0.07 to 0.15)	1.96 ± 0.7	2.05 ± 0.6	1.96 ± 0.7	2.05 ± 0.6	0.09 (-0.49 to 0.33)	0.09 (-0.49 to 0.33)	0.05 (-0.01 to 0.11)	0.05 (-0.01 to 0.11)
RV, l	4.29 ± 1.5	4.23 ± 1.4	4.23 ± 1.4	4.23 ± 1.4	-0.06 (-0.11 to 0.01)	-0.06 (-0.11 to 0.01)	4.4 ± 1.5	3.9 ± 1.7**	4.4 ± 1.5	3.9 ± 1.7**	-0.5 (-1 to 0)	-0.5 (-1 to 0)	-0.44 (-0.26 to -0.62)§	-0.44 (-0.26 to -0.62)§
6MWT, m	281.0 ± 97.4	304.7 ± 96.6	304.7 ± 96.6	304.7 ± 96.6	23.7 (-3.5 to 50.9)	23.7 (-3.5 to 50.9)	297.0 ± 59.3	369.5 ± 80.0*	297.0 ± 59.3	369.5 ± 80.0*	72.5 (33.9 to 111.1)	72.5 (33.9 to 111.1)	48.8 (17 to 80.6)**	48.8 (17 to 80.6)**

Results are expressed as mean ± SD.
 VC, vital capacity; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; 6MWT, 6 min walk test; 95% CI, 95% confidence interval.
 * p 0.01.
 ** p 0.04.
 *** p 0.05.
 § p 0.001.

School of Osteopathic Manipulation (A.M. – A.C. – S.R.) who were near the degree to and who were qualified to perform OMT. The Authors’ (E.Z. – P.B. – C.F.) lack of familiarity with the treatment may account for the unexpected, surprising results we found and, contemporarily, for the poor design we initially draw. Indeed, we did not consider airway resistance nor respiratory muscle pressures, data that could better explain the results we found. Furthermore, we did not consider quality of life, another very important outcome in patients with COPD. Moreover, we acknowledge that the small size of the study seriously limits any conclusion. Undoubtedly, further studies are needed to evaluate the effects of OMT in patients with COPD. However, we believe any effort should be done to try to ameliorate prognosis of a disease that is a major public health problem, that is projected to rank fifth in 2020 in burden of diseases caused worldwide and that is still relatively unknown or ignored by the public as well as public health and government officials.⁸

In conclusion, adding OMT to PR could increase exercise capacity in patients with COPD, probably through the decrease of their residual volume, by means a reduction in airway resistance or through an increased chest wall mobility.

Conflict of interest

None declared.

References

- Xue CCL, Zhang AL, Vivian Lin, Ray Myers, Barbara Polus, Story DF. Acupuncture, chiropractic and osteopathy use in Australia: a national population survey. *BMC Public Health* 2008;**8**:105–12.
- Goldbeck-Wood S, Dorozynski A, Lie LG. Complementary medicine is booming worldwide. *BMJ* 1996;**313**:131–3.
- George J, Ioannides-Demos LL, Santamaria NM, Kong DC, Stewart K. Use of complementary and alternative medicines by patients with chronic obstructive pulmonary disease. *Med J Aust* 2004;**6**(181):248–51.
- Abadoglu, Cakmak E, Kuzucu Demir S. The view of patients with asthma or chronic obstructive pulmonary disease (COPD) on complementary and alternative medicine. *Allergol Immunopathol* 2008;**36**:21–5.
- Howell RR, Allen TW, Kappler RE. The influence of osteopathic manipulative therapy in the management of patients with chronic obstructive lung disease. *J Am Osteopath Assoc* 1975;**74**:757–60.
- Noll RD, Degenhardt BF, Johnson JC, Burt SA. Immediate effects of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease. *J Am Osteopath Assoc* 2008;**108**:251–9.
- Pickett C, Stoll ST, Crusier D, Cipher DJ. Chronic obstructive pulmonary disease (COPD): immediate effects of osteopathic manipulative treatment on exercise tolerance and dyspnea. *J Am Osteopath Assoc* 2006;**106**:485.
- Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532–55.
- American Thoracic Society statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–7.

10. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. *Scand J Work Environ Health* 1990;16(Suppl. 1):55–8.
11. American Thoracic Society/European Respiratory Society. Statement on Pulmonary Rehabilitation. *Am J Respir Crit Care Med* 2006;173:1390–413.
12. Porta R, Vitacca M, Gilè LS, Clini E, Bianchi L, Zanotti E, et al. Supported arm training in patients recently weaned from mechanical ventilation. *Chest* 2005;128:2511–20.
13. Wise RA, Brown CD. Minimal clinically important differences in the six-minute walk test and the incremental shuttle walk test. *COPD* 2005;2:125–9.
14. Patel SA, Sciruba FC. Emerging concepts in outcome assessment for COPD clinical trials. *Semin Respir Crit Care Med* 2005;26:253–62.
15. Puhan MA, Mador MJ, Held U, Goldstein R, Guyatt GH, Schunemann HJ. Interpretation of treatment changes in 6 min walk distance in patients with COPD. *Eur Respir J* 2008;32:637–43.
16. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF. Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010;91:221–5.
17. Engel RM, Vemulpad SR. Immediate effects of osteopathic manipulative treatment in elderly patients with chronic obstructive pulmonary disease. *J Am Osteopath Assoc* 2008;108:541–2.
18. Kakizaki F, Shibuya M, Yamazaki T. Preliminary report on the effects of respiratory muscle stretch gymnastics on chest wall mobility in patients with COPD. *Respir Care* 1999;44:409–14.
19. O'Donnell DE, Laveneziana P. Dyspnea and activity limitation in COPD: mechanical factors. *COPD* 2007;4:225–36.
20. O'Donnell DE. Hyperinflation, dyspnea and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006;3:180–4.
21. Paulin E, Yamaguti WPS, Chammas MC, Shibao S, Stelmach R, Cukier A, et al. Influence of diaphragmatic mobility on exercise tolerance and dyspnea in patients with COPD. *Respir Med* 2007;101:2113–8.