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Randomized trial of non-invasive ventilation combined with exercise training in patients with chronic hypercapnic failure due to chronic obstructive pulmonary disease

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Summary
Background: Non-invasive ventilation and exercise training might prove beneficial in the management of COPD patients.
Objetive: to compare the combined use of exercise training and non-invasive ventilation with the two interventions separately in chronic respiratory failure due to chronic obstructive pulmonary disease. As primary objective exercise capacity and secondary objectives gas exchange, peripheral muscle strength, BODE index, quality of life and systemic inflammatory response.
Methods: Forty-five patients with severe chronic obstructive pulmonary disease were randomized into three groups for an intervention of 12 weeks: exercise training alone, ventilation alone and combined treatment. We assessed exercise capacity, pulmonary function, BODE index, perception of dyspnoea, quality of life and several biomarkers.
Results: All exercise capacity parameters improved after training and the combined treatment. In addition, peripheral muscle strength and six-minute walk distance increased after ventilation. We found differences between the combined group and the ventilation group in submaximal effort and in oxygen consumption. Changes in respiratory function were observed in blood gases that improved after ventilation and the combined treatment, with differences between these groups. BODE index, perception of dyspnoea and quality of life improved in all three groups without differences between groups. Levels of interleukin 8 and tumour necrosis

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factor α decreased after ventilation, and interleukin 8, C-reactive protein and surfactant protein D decreased after training, while all four of these markers fell after the combined treatment. No differences between groups were found.
Conclusions: The combination of ventilation and exercise training had greater benefits than the separate treatments: improvements were observed in both blood gases and the levels of more biomarkers decreased. In addition, submaximal exercise capacity increased in all groups. The improvements seen in BODE index, perception of dyspnoea and quality of life were similar in all groups.

Background

One type of treatment that is helpful for improving the quality of life in COPD is pulmonary rehabilitation. In addition to increasing exercise capacity, training improves patient symptoms by relieving dyspnoea and reduces use of health resources [1].

Studies evaluating the effectiveness of home non-invasive ventilation (NIV) in long term in stable COPD patients have produced variable results and controversial conclusions, though there is evidence that selected patients may benefit from this therapeutic approach [2]. In particular, NIV may usefully contribute to improving muscle strength and decreasing the number of hospital admissions, and consequently improve quality of life in these patients [3].

It seems reasonable that the combination of the two therapeutic approaches, NIV and exercise training might prove beneficial in the management of these patients. Some studies have made a partial evaluation of the combined use of these treatments with small numbers of patients [4—7]. However, only two types of groups have been evaluated: patients undergoing training and patients receiving both training and ventilation (that is, no comparison has been made to a group receiving ventilation only).

Given this, we believed it would be interesting to design an exercise training programme for COPD patients combined with ventilatory support at night, and explore whether there were benefits compared to the use of each treatment in isolation.

Accordingly, the primary objective of this study was to test whether there was a beneficial effect on exercise capacity as time in submaximal exercise test from training combined with NIV, compared to each of the treatments alone in patients with COPD. As secondary objectives, we compared the impact of combined treatment on gas exchange, peripheral muscle strength, BODE index, quality of life and systemic inflammatory response.

Methods

Study participants

This was an interventional study in which 45 patients were prospectively recruited from May 2007 to September 2011 and randomized via a computer-generated randomisation sequence into one of three groups of 15 patients: ventilation group, training group, and training and ventilation group. Inclusion criteria were: being an adult patient with a diagnosis of COPD, as defined by the GOLD criteria [8]; having been clinically stable for at least the previous three months; airflow obstruction with forced expiratory volume in the first second of expiration (FEV_1) <50%; and chronic respiratory failure with hypoxaemia (arterial oxygen pressure, $PaO_2 < 60$ mmHg) and hypercapnia (arterial carbon dioxide pressure, $PaCO_2 > 45$ mmHg). According to the GOLD guideline available at the moment of the trial, patients under this condition were classified into GOLD stage 4. These are the actual indications for home mechanical ventilation in COPD [9]. Patients selected for NIV were those randomized to receive it. Our Clinical Research Ethics Committee approved the study protocol, and the study was registered on ClinicalTrials.gov (ID NCT01377818). Written informed consent was obtained from subjects prior to their inclusion.

All patients were receiving adequate treatment for their disease including inhaled medications (basically long-acting muscarinic antagonist and the combination of a long-acting beta2 agonist with an inhaled corticosteroid) and long-term oxygen therapy according to current indications [10].

Additional details of the methods are provided in the Online Supporting Information.

Training programme

Training sessions were carried out on three non-consecutive days every week for 12 weeks. The programme was structured as reported previously [11], and consisted of a combination of resistance and strength training [12—14].

Ventilation programme

NIV was administered using a bilevel positive airway pressure system administered by a nasal mask (Respironics). The system was initially programmed to provide: 10 cmH_2O inspiratory positive airway pressure (IPAP), and 4 cmH_2O expiratory positive airway pressure (EPAP), using the ST mode. The IPAP was increased progressively to a maximum of 20 cmH_2O, depending on patient tolerance, clinical response and arterial oxygen saturation (as assessed by continuous pulseoximetry).

Patients received continuous ventilatory support during the night hours (for 6—8 h per night).