

Comparison of oxygen uptake during cycle ergometry with and without functional electrical stimulation in patients with COPD: protocol for a randomised, single-blind, placebo-controlled, cross-over trial

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) has systemic repercussions that can lead to peripheral muscle dysfunction. Muscle atrophy reduces aerobic capacity, greatly limiting activities of daily living and quality of life. Pulmonary rehabilitation is the gold standard treatment for these patients, however, patients may not be able to reach sufficient training intensities for benefits to occur. Technologies such as functional electrical stimulation (FES) are currently being adapted and tested to enhance exercise training. We hypothesise that FES coupled with cycling (FES-cycling) will improve maximal uptake of oxygen (VO₂) and aerobic capacity more than endurance training with placebo stimulation.

Methods: A randomised, single-blind, placebo-controlled crossover trial will be carried out to evaluate the effects of FES-cycling on VO₂ during endurance exercise on a cycle ergometer in patients with COPD. 25 patients with COPD will carry out two 30 min sessions at a constant load; one session with active and one with placebo FES. The primary outcome is oxygen uptake recorded with a metabolic measurement system. Secondary outcomes include ventilation equivalent for oxygen, ventilation equivalent for carbon dioxide, cardiac output, lactate values, perceived dyspnoea and perceived muscle fatigue.

Results and conclusions: Approval has been granted by our Institutional Review Board (Comité de Protection des Personnes Nord-Ouest 3). The results of the trial will be presented at national and international meetings and published in peer-reviewed journals.

Trial registration number: NCT02594722.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disabling condition with a

KEY MESSAGES

- ▶ Can a new concept of neuromuscular electrical stimulation (FES-cycling) improve metabolic and cardiovascular responses during endurance exercise in patients with chronic obstructive pulmonary disease (COPD)?
- ▶ To perform a preliminary study to evaluate cardiovascular and metabolic adaptations during FES-cycling endurance training in patients with COPD prior to evaluating the effects of a long-term programme.
- ▶ This study is the first to evaluate FES-cycling in COPD, which could become a new tool for pulmonary rehabilitation.

prevalence of 4–10% in the worldwide adult population.^{1 2} COPD is associated with systemic complications and peripheral muscle dysfunction, and is known to affect vital prognosis.³ Moreover, muscle fatigue occurs quickly and patients lack exercise tolerance, thus their quality of life is reduced.^{4 5} Multidisciplinary programmes combining cardiovascular training and patient education have been developed to reduce sedentariness and deconditioning.⁶

The effects of cardiovascular training depend on its intensity.^{7–9} Unfortunately, because of exertional dyspnoea and a limited exercise capacity, patients with COPD, and particularly those with severe COPD, may not be able to reach a high enough intensity for training to be beneficial. Maltais *et al*¹⁰ reported that the majority of patients included in their rehabilitation programme were unable to maintain a high intensity of training. Current training strategies thus



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focus on increasing muscle work while avoiding increasing dyspnoea.⁷

Neuromuscular electrical stimulation may be a useful compromise for patients with high levels of dyspnoea,^{11–14} however, despite some advantages, the contractions produced are not very functional.^{15–16} Functional electrical stimulation coupled with peddling, termed ‘functional electrical stimulation cycling’ (FES-cycling), was developed at the end of the 1980s. Since then, it has been used increasingly in patients with neurological disorders.^{17–18} The principle of FES-cycling is to electrically stimulate one or several muscle groups during an active or passive peddling task synchronised by a computer.¹⁹ It has been proposed as an alternative or complement to voluntary exercise for patients with neurological disorders, and has been shown to optimise training, and improve muscle strength and cardiovascular capacity.^{20–21} Mutton *et al*²² showed a 10% increase in aerobic capacity in patients with spinal cord injury following a programme of FES-cycling. Increases in muscle volume have also been found in patients with spinal cord injury, using this technique.²³

A recent study evaluated the effect of FES-cycling on the metabolic and cardiovascular responses of healthy patients.²⁴ Oxygen uptake (VO_2) increased during the FES-cycling, as did cardiac frequency and lactate. These physiological results suggest that FES-cycling can improve cardiovascular and metabolic responses to exertion.

To the best of our knowledge, no studies have evaluated the potential benefits of FES-cycling in patients with COPD. Prior to evaluating the effects of a long-term programme, we propose to carry out a randomised, single-blind, placebo-controlled, cross-over trial to evaluate cardiovascular and metabolic adaptations during FES-cycling endurance training in patients with COPD.

OBJECTIVE

Primary objective

To evaluate the effect of FES-cycling on exertional VO_2 compared with usual endurance training coupled with placebo-FES.

Secondary objectives

To evaluate the effect of FES-cycling on the respiratory equivalent for oxygen (ventilation/ VO_2), the respiratory equivalent for carbon dioxide (ventilation/ VCO_2), the ventilation/ VCO_2 slope, cardiac output, lactate, perceived dyspnoea and perceived muscle fatigue.

METHOD

Study design

A single centre, randomised, single-blind, placebo-controlled, cross-over trial comparing VO_2 during cycle-ergometer endurance exercise with active and placebo FES in patients with COPD. The study will be carried out in the functional exploration department of the Havre Hospital Group. The patients will carry out

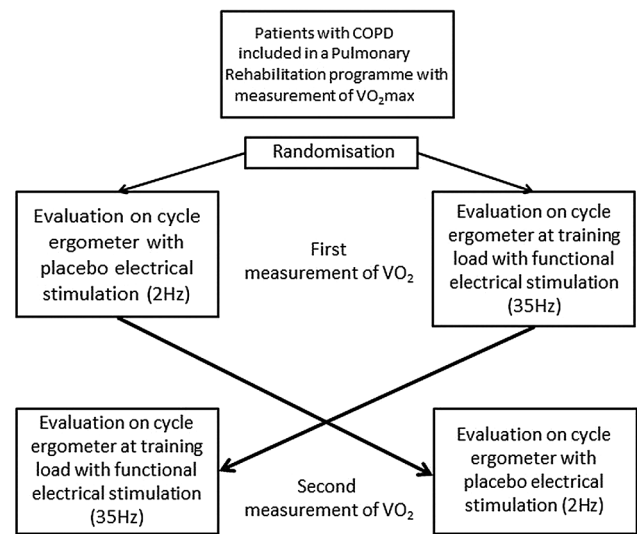


Figure 1 Study design. COPD, chronic obstructive pulmonary disease; VO_2 , maximal oxygen uptake.

two consecutive 30 min constant-load endurance sessions on a cycle ergometer with FES of the quadriceps muscle (FES-cycling session) and with placebo electrical stimulation (Control session). The order of the sessions will be randomised (figure 1).

Participants

Inclusion criteria

Patients with GOLD stage 2, 3 or 4 COPD participating in a respiratory rehabilitation programme. Patients with no changes to β -blocker treatment in the past 3 months. Patients who agree to participate voluntarily and who sign the informed consent form.

Exclusion criteria

- ▶ Patients with a pacemaker.
- ▶ Patients who have had an exacerbation within the past 4 weeks.
- ▶ Patients with other conditions that may affect their participation in rehabilitation (osteoarticular or neuromuscular disorders or severe psychiatric disorders, patients with severe anaemia (<8 g/dL).
- ▶ Patients with central neurological pathology.
- ▶ Patients on non-invasive night-time mechanical ventilation.
- ▶ Patients who are unable to carry out 30 min of exercise.

Recruitment

Prior to participating in the respiratory rehabilitation programme at the Havre Hospital Group, patients will undergo an initial exercise test including measurements of VO_2 max, the 6 min walk test (6MWT) and a cardio-respiratory assessment to screen for contraindications to exercise. VO_2 max will be evaluated during a triangular effort test with increasing load, on an ergometer. Following a 2 min warm-up, the intensity will be

increased by 10 W every minute. The test will be carried out under the surveillance of a pulmonologist and a cardiologist. As is customary in our training programmes, the load for the endurance session will be set as the load at which ventilatory threshold was reached during the exercise test.

Patients who fulfil the inclusion criteria will be informed of the protocol. Those who wish to participate will receive all the necessary information. The date of the evaluation will be determined at least 4 weeks after the signing of the informed consent form, and a maximum of 6 weeks after the initial exercise test.

Randomisation

The order of the tests will be randomised using independent methods. Randomisation will be carried out by the Clinical Research Unit via computer software. The investigator will receive the randomly generated treatment allocation in a sealed envelope just before the endurance session.

Intervention

VO₂ will be measured during 30 min of endurance exercise with functional electrical stimulation using the Reha Stim device. Two RehaMove electrodes (5×9 cm) will be positioned at each extremity of both quadriceps muscles to stimulate both muscles. A rectangular, intermittent, bidirectional current with no ramp will be used and the intensity will be modulated to obtain a palpable muscle contraction. The other electrical stimulation parameters will be identical for all patients (length: 300 μs, frequency: 35 Hz. These settings are based on usual electrostimulation protocols¹⁵).

During the ergometric cycling, the stimulator will be controlled by a personal computer. The software will ensure that muscle contractions are induced at the appropriate pedal angles during knee extension.

Following a 2 min warm-up, the load will be increased to reach the training load determined during the initial exercise test. The patients will peddle at a frequency of 50–60 rotations per minute for 30 min.¹²

At the end of the session, a capillary measurement of lactate will be taken using 'lactatepro II'. The patient will be asked to evaluate his/her dyspnoea on the Borg scale and muscle fatigue on a visual analogue scale.

Control

VO₂ will be measured during 30 min of endurance exercise with placebo electrotherapy that does not influence ventilation (length 300 μs, frequency 2 Hz).²⁵ The intensity will be low, so as not to produce any muscle contraction.

Conditions will be identical for both endurance sessions and patients will have a 30 min rest between each. The training load will be identical for both endurance sessions.

Blinding

The use of placebo electrotherapy means that patients can be blind to their group. The therapist who sets up the equipment will not be blind; however, both the pulmonologists carrying out the data analysis will be blind to the allocations.

DATA COLLECTION

Oxygen uptake

The primary outcome will be oxygen uptake (VO₂) throughout the test. VO₂ will be continuously measured using a metabolic measurement system (Vmax Spectra 29) that carries out a breath-by-breath gas analysis. The mean is calculated every 30 s. A pulmonologist (BL) and a physiotherapist (either CM, GP, ARQ or YC) will review all test results.

Ventilation equivalent for oxygen

The ventilation equivalent for oxygen (ventilation/VO₂ ratio) will be used to determine the number of litres of air required to obtain 1 L of oxygen.

Ventilation equivalent for carbon dioxide

The ventilation equivalent for carbon dioxide (ventilation/VCO₂ ratio) will be used to determine the number of litres of air required to eliminate 1 L of carbon dioxide.

Cardiac output

The linear relationship between the adjustment of cardiac output and the increase in oxygen consumption will be used to estimate cardiac output (L/min). The following equation will be used to estimate cardiac output during the endurance session: $5.5 \times \text{VO}_2 \text{ (L/min)} + 5$.^{26 27}

Lactate

Capillary blood lactate values will be measured at the end of each endurance session. The Lactate Pro II device will be used. With this device, the measurement takes only 15 s and requires only 0.3 μL of blood.²⁸

Dyspnoea

Perceived dyspnoea will be measured using the Borg scale, at the end of each endurance session.

Muscle fatigue

Perceived muscle fatigue will be measured using a visual analogue scale at the end of each endurance session.

POWER CALCULATION AND SAMPLE SIZE

VO₂ will be measured using an infrared gas analyser. Based on the results of previous studies,²⁹ 22 pairs of patients should be included to detect a difference in mean VO₂ between groups of 200 mL and to reject the null hypothesis with a power of 90%.³⁰ The associated type I probability error is 0.05. We plan to include 10% more participants, thus 25 patients in total.

STATISTICAL ANALYSIS

Normally distributed data will be expressed as means (\pm SDs) and non-normally distributed data will be expressed as medians (and IQRs).

The values of VO_2 , VCO_2 and VE will be collected breath-by-breath and means will be calculated every 5 min. Within-group data will be analysed using paired t tests or Wilcoxon signed rank tests. Analysis of variance will be used to compare changes during the sessions between groups. A Bonferroni t test will be used post hoc. The level of significance will be set at ≤ 0.05 .

STRENGTHS AND LIMITATIONS

This study is the first to evaluate the effects of FES in patients with COPD.

The use of a placebo will reduce the risk of interpretation bias.

There are two main limitations in this study. First, it is single centre. Second, the evaluation of a single session does not provide information regarding long-term clinical effectiveness; however, the results will provide a basis for such a study.

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Contributors CM, GP, OC and BL were responsible for trial concept and design. CM, GP, ARQ, YC and BL were responsible for acquisition of data. DB and JQ analysis and interpretation of data and drafting the article. CM, DB, OC and BL revising it critically for important intellectual content and final approval of the version to be published. CM had full access to all trial data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests None declared.

Ethics approval CPP Nord-Ouest 3.

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Ethics and dissemination The study has been approved by our Institutional Review Board (Comité de Protection des Personnes Nord-Ouest 3). In conformity with the Declaration of Helsinki, all participants will be recruited to participate voluntarily and they will sign a written informed consent form. The results of the trial will be presented at national and international meetings and published in peer-reviewed journals. Results will be registered with ClinicalTrials.gov. We will also disseminate the main results in a letter to all participants. The study has been registered with ClinicalTrials.gov (NCT02594722).

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