

Official title: EVALUATION OF A RESPIRATORY MUSCLE TRAINING PROGRAM RESTRICTING NASAL BREATHING WITH FEELBREATHE® DEVICE IN COPD PATIENTS

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Background

The benefits of pulmonary rehabilitation programs (RP) in chronic obstructive pulmonary disease (COPD) patients have been shown and are recognized as an effective tool for improving dyspnea, exercise tolerance and quality of life in all the guidelines(1)(2)(3).

Inspiratory muscles training (IMT) has been used as a complement added to the supervised pulmonary RP and some studies have shown an improvement in the inspiratory muscles strength, tolerance to exercise (Oxygen uptake efficiency slope), dyspnea and distance walked in the six minutes walking test (6MWT) after a inspiratory muscles training program in patients with COPD (4).

The Feelbreathe® device, tested in our study can be used in static and dynamic situations (5) and is a nasal ventilatory flow restriction device made by a strip of hypoallergenic material (3M Spain, S.A. Medical Specialties / O.E.M.) that is placed and adhered under the nostrils impairing the free pass of air through the nose by producing resistance to flow. The Feelbreathe® device (FB) has been authorized by the Spanish Agency for Medicines and Health Products for application on COPD patients (Expedient 521/15/EC. AEMPS-Madrid-Spain-Patent N°: P200902402).

Previous studies have shown that an increased airflow resistance while breathing nasally, during exercise, increases the breathing effort (6) which may potentially improve the exercise tolerance (7) and energy efficiency (8). In healthy subjects FB has shown changes in lung ventilation, gas exchange and heart rate during exercise with improvements on ventilatory efficiency (9).

So, the objective of this study was to assess the effects of a nasal restriction device for inspiratory muscle training adding to a rehabilitation program on exercise capacity (Oxygen uptake efficiency slope), quality of life, dyspnea and inspiratory muscle strength in stable COPD patients.

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Participants

Subjects were recruited from the Pneumology outpatient of the University Hospital Puerta del Mar in Cádiz (Spain). Consecutive patients were screened by reviewing their charts and by interview. Inclusion criteria were diagnosis of COPD according to guidelines criteria (1) (10) with moderate or severe airflow obstruction (GOLD 2 or 3)(10), dyspnea grade 2 or greater by mMRC scale and a stable clinical condition for at least 2 months. Exclusion criteria were poor compliance, treatment with oxygen therapy or non-invasive mechanical ventilation, CO₂ retention, medical conditions that can produce or increase dyspnea on exercise in addition to COPD (cardiovascular, metabolic or other respiratory diseases) or osteoarticular or neuromuscular diseases that may limit the correct performance of the 6MWT. A total of 36 patients were included in this study.

Written informed consent was obtained from all patients before starting the study. This clinical trial received ethical approval from the Ethics Committee University Hospital Puerta del Mar and met the requirements of the Declaration of Helsinki.

Design

Participants were randomly assigned according to a computer-generated randomization table to three groups: 1) those who participated in the supervised RP using the Feelbreathe® device (FB group), 2) those who participated in the supervised RP with oronasal breathing without Feelbreathe® device (ONB group) and, 3) those included in the control group (CG) which received standard medical recommendation for patients with COPD.

Demographic and clinical data were recorded. Dyspnea was assessed by the modified Medical Research Council (mMRC) dyspnea questionnaire (11) and quality of life by the COPD Assessment Test (CAT) questionnaire (12). Spirometry was performed according to American Thoracic Society criteria (13)(14) {Formatting Citation} (Spirometer CPX, Cardinal Health, Hoechberg, Germany). Then, they performed a resting electrocardiogram (QRS Universal ECG, QRS, Plymouth, MN, USA). P_{Imax} was measured during a maximal, static inspiratory effort measured at the mouth (Micro RPM, Micro Medical Ltd., Chatham, Kent, UK). P_{Imax} was recorded as the highest value averaged over 1s from three maneuvers that varied by less than 10% and was measured based on three maximal reproducible respiratory efforts. Then, an incremental test on treadmill (Technogym Run Race 1400HC, Gambettola, Italy) was performed to determine the $\text{VO}_{2\text{peak}}$ (Circuit Spirometry Vmax 29C, Sensormedics, USA). While performing the tests, the cardiac response was measured every 10s (JECG 12 Canal, Friedberg, Alemania). Blood oxygen saturation percentage (Ear oximeter, Hewlett-Packard 47201A, Corvallis, EEUU) and respiratory gas exchange were measured every 5 sand breath by breath respectively, throughout the test. Finally, one week apart, the patients performed the 6MWT according to the ATS guideline (15).

All tests were performed according to a standardized protocol before starting the training and 2 days after its completion.

Training program

Participants carried out a supervised RP for 8 weeks, 3 days per week. The training sessions lasted 60 minutes and included a warming up phase, a main phase and a recovery phase. After each session, Borg's perceived exertion was measured. The RP included aerobic exercise on cycle ergometer and on treadmill (progressing since 10' to 30' and since 40 to 75% of the reserve heart rate (RHR) or 6-7 score based on Borg's perceived exertion), strengthening of lower and upper limb muscles groups, breathing exercises (pursed lip breathing, diaphragmatic and abdominal breathing and diaphragmatic mobility) and finally stretching exercises.

In the FB group, for restricted nasal breathing, at the beginning of the training program, the small size device was used (4 mm). The size of the device was progressively increasing according to the patient adaptation to the 5 or 6 mm device,

depending on the score on Borg's perceived exertion scale. If the patient has a score under 4 after the RP sessions the size of the FB device was increased.

FB was placed under the nostrils, using sterile gloves and assessing the patient did not have mucus or injuries. The device was used during the RP and patients were invited to have a physiological breathing by nasal inspirations and mouth expirations.

Statistical Analysis

Descriptive data of the participants are expressed as mean \pm standard deviation or number and percentage for continuous and categorical variables respectively. Percentage of change (%Change) for each variable was calculated as:

$$\%Change = (\text{mean(Post-test value)} - \text{mean(Pre-test value)}) / \text{mean(Pre-test value)} * 100$$

Differences among RP (between differences) and between pre- and post RP tests within each breathing condition (within differences) were analysed using a Bayesian hierarchical model. 6MWT distance, P_{Imax} and CAT were considered as continuous variables while mMRC dyspnea was treated as an ordinal variable. To analyse differences at baseline only a categorical variable indicating the RP (GC, ONB or FB) was introduced in the model as predictor. However, to analyse both between and within differences RP, time (pre- or post-PR) and their interaction were introduced as predictor variables. Due to the sample size in our study we choose to analyse our data using Bayesian inference since it has proven to be a proper method of statistical inference for small sample size (16)(17). Inference was performed based on the 95% credible interval (95% CrI) which contains a range of values where we can be 95% certain that the true value lie given the data at hand and the model fitted. The Bayesian hierarchical model was fitted using the package *brms* for the R programming language for statistical computing and graphics (18). All parameters estimated showed a good convergence with values of $\hat{R} = 1$ and number of effective sample size > 1000 . Further analysis can be found in the supplemental file while the code and the dataset to replicate it are stored in https://github.com/JorgeDelro/COPD_2_1.

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