TITLE: High-Flow Oxygen Therapy During Exercise Training in Patients With Chronic Obstructive Pulmonary Disease and Chronic Hypoxemia: A Multicenter Randomized Controlled Trial

RUNNING HEAD: HFOT Versus V-Mask During Exercise Training

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Objective. The study aimed to evaluate whether High-flow oxygen therapy (HFOT) during training was more effective than oxygen in improving exercise capacity in hypoxemic COPD.

Methods: One hundred seventy-one patients with COPD and chronic hypoxemia were consecutively recruited in 8 rehabilitation hospitals **in a** randomized controlled trial. Cycle-ergometer exercise training was used in 20 supervised sessions, at iso inspiratory oxygen fraction in both groups. Pre- and post-training endurance time (Tlim), 6 minutes walking distance (6MWD), respiratory and limb muscle strength, arterial blood gases, Barthel and Barthel Dyspnea Indices, COPD Assessment Test, MRF-26 questionnaire, and patient satisfaction were evaluated.

Results. Due to 15.4% and 24.1% dropout rates, 71 and 66 patients were analyzed in HFOT and V-mask groups, respectively. Exercise capacity significantly improved after training in both groups with similar patient satisfaction. Between-group difference in post training improvement in 6MWD (mean: 17.14 meters; 95% CI 0.87:33.43 meters) but not in Tlim (mean: 141.85 seconds; 95% CI -18.72:302.42 seconds) was significantly higher in HFOT. The minimal clinically important difference (MCID) of Tlim was reached by 47% of V-mask and 56% of HFOT patients, whereas the MCID of 6MWD was reached by 51% of V-mask and 69% of HFOT patients respectively.

Conclusion. In patients with hypoxemic COPD, exercise training is effective in improving exercise capacity.

Impact. Addition of HFOT during exercise training is not more effective than oxygen through V-mask in improving endurance time, the primary outcome, whereas it is more effective in improving the walking distance.

Pulmonary rehabilitation, including aerobic exercise training, has stronger evidence of effectiveness to improve exercise capacity, dyspnea, and health related quality of life (HRQL) than almost all other therapies in patients with chronic obstructive pulmonary diseases (COPD).[1-5] Oxygen supplementation[6] and non invasive ventilation during exercise may improve the effects of training.[7] However, the role of additional oxygen during training in patients with exercise induced desaturation is still discussed,[8-12] whereas non invasive ventilation is not tolerated by all patients, requires high expertise and is time-consuming for health professionals.[7]

High-flow oxygen therapy (HFOT) enhances ventilation and provides an extended range of oxygen concentrations. It can deliver up to 60 L/min of heated, humidified air via nasal cannula, with or without additional oxygen. Above a flow of 20 L/min, HFOT can generate a positive pressure in the upper airways[13]. In resting patients with COPD, HFOT increases alveolar ventilation, tidal end-expiratory lung volumes, gas exchange and reduces respiratory rate, tissue carbon dioxide and the work of breathing[14,15]. Compared to standard oxygen, HFOT and non invasive ventilation reduced the respiratory muscle load and the respiratory rate, while increasing the expiratory time[16]. Only 1 study showed that HFOT can increase exercise tolerance in stable patients with severe COPD,[17] and no clinical trial investigated the effects of HFOT in exercise training programs.

The aim of this randomized controlled study was to compare, in patients with COPD and chronic hypoxemia on long term oxygen therapy (LTOT), the effects on exercise capacity of adding HFOT to exercise training as compared to usual oxygenation by a Venturi mask (V-mask) at the same oxygen inspiratory fraction (FiO_2).

[H1]METHODS

[H2]Study patients

Patients were consecutively recruited between November 2017 and December 2018 in 8 Italian rehabilitation hospitals: Istituti Clinici Scientifici Maugeri (Lumezzane, Tradate, Pavia, Cassano Murge, and Veruno), Villa Pineta (Pavullo nel Frignano [Modena]), Don Gnocchi Foundation (Milano, Firenze).

The study protocol was defined according to the Consolidated Standard of Reporting Trials (CONSORT) guidelines[18], approved by the Ethics Committees of each center, (2109 CEC 20/04/2017) and registered at ClinicalTrials.gov ID NET03322787. Participants gave written informed consent. Details on methods have been published elsewhere.[19] During the study, patients continued their usual medications and LTOT.

Inclusion criteria were: a) age range 40 to 85 years; b) both sexes; c) diagnosis of COPD (post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 0.7)[1]; d) being on LTOT for at least 3 months; e) clinical stability (pH range: 7.38–7.42, without recent exacerbation for at least 30 days with any change in usual medications in the previous 7 days).

Exclusion criteria were: home non invasive ventilation, cognitive impairment (Mini-Mental State Examination score (MMSE) < 22)[20], clinical features of asthma and/or evidence of bronchodilator responsiveness, history of cardiovascular diseases, congestive heart failure, concomitant pulmonary fibrosis, overlap syndrome with obstructive sleep apnoea, lung cancer, active microbial infections, neuromuscular, orthopedic and/or medical diseases precluding exercise testing, pulmonary rehabilitation program within the last 6 months.

Eligible patients were individually randomized by means of a dedicated software program in fixed blocks of 4 (https://www.randomizer.org/) to either the intervention (HFOT) or control group (V-mask) (randomization ratio 1:1). This was a single-blind study: only the assessor of measurements was blind on group allocation; participants and care providers were not.

[H2]Protocol

[H3]Run-in phase. In order to define the amount of oxygen to administer during training, at the beginning of the program patients underwent a 30-min run-in phase on a cycle ergometer at an intensity corresponding to 50% of their maximal workload predicted according to the Luxton equation[21] from the baseline 6 minutes walking distance test (6MWD). Patients performed a preliminary session breathing through the V-mask: the FiO_2 able to maintain pulse oximetry (SpO_2) > 93% (range 94–98%) was registered and used for training sessions.

[H3]Exercise training program. All patients performed a cycle-ergometer exercise training consisting of 20 supervised sessions (5 sessions/week), lasting 30 min. After a warm-up phase at 0 watts, the initial workload was 50% of the theoretical maximal[19]. Increases or reductions by 10 watts in intensity were according to Maltais et al.[22]. The workload was increased when patients scored their dyspnea and/or leg fatigue less than 4 on a modified 10-point Borg scale[23]. The workload was unchanged if the Borg score was 4 or 5 and was reduced for scores above 5.[22] Patients had to maintain a cycling rate between 50 and 60 rpm.

[H3] Intervention (HFOT) group. Patients performed training while HFOT was administered through the AIRVO2® device (Fisher&Paykel, Auckland, New Zealand). This system generates up to 60 L/min of humidified, heated air (between 31 and 37 °C) by altering the FiO_2 within the system (FiO_2: 0.21-1)[24]. The air was administered with an open-circuit through an Optiflow™ nasal cannula (Fisher&Paykel, Auckland, New Zealand), delivering a gas flow directly into the nares. The cannula was connected to the machine by a tube with a breathable film inside to reduce condensate. The highest air flow tolerated was set starting from 60 L/min and was reduced in case of intolerance. The temperature was set at 37°C and reduced in the case of intolerance. Every change in flow and temperature was recorded**.** The FiO_2 was set according to the run-in phase. Figure 1 shows a representative patient during a training session with the HFOT system.

[H3]Control (V-mask) group. Patients performed sessions with oxygen through a V-Mask (Fiab SpA, ISO 13485, Firenze, Italy) with FiO_2 set according to the run-in session (see above).

[H2]Measurements

At baseline (T0), demographics, anthropometrics and clinical data, including comorbidities using the Cumulative illness rating scale (CIRS)[25], were recorded. Lung function was assessed after bronchodilation. Results were expressed as absolute and percent of the predicted values according to Quanjer[26].

Before (T0) and after training (T1) the following outcome measures were assessed:

On day 1 the following measures were assessed:

- Exercise capacity was assessed by the 6MWD[27], in patients breathing their usual O_2 supply (3.95 ± 2.63 L/min). Borg dyspnea and fatigue[23] and pulse oxymetry (SpO_2) were recorded before and at the end of the test. Performed distance in meters, as well as SpO_2 nadir and the SpO_2/heart rate (HR) ratio were recorded at the end of the test. The minimal clinical important difference (MCID) of the 6MWD following exercise training in COPD was recently reported to be a 30-meter increase[27].
- Respiratory muscle strength was assessed by the maximal inspiratory (MIP) and expiratory (MEP) pressures by means of an electronic manometer (Precision Medical, Northampton, PA, USA)[28].
- Quadriceps muscle strength was assessed by means of a manual dynamometer (Chatillon® X-3328 Series, Ametek Inc., Florida, USA)[29]. The maximal voluntary contraction (MVC) was expressed in kg.
- Dyspnea was evaluated by the Medical Research Council (MRC) scale[30] and the Barthel Dyspnea Index[31].
- The level of disability, was assessed by the Barthel Index[32], the Health Status by the COPD Assessment Test (CAT)[33] and Health-Related Quality of Life (HRQL) by the Maugeri Respiratory Failure questionnaire (MRF-26)[34] specifically designed for patients
- Arterial blood gases were assessed on blood samples from the radial artery while sitting patients breathed room air.

On day 2, exercise capacity was evaluated by the Constant Work Rate Exercise Test (CWRET) on a cycle ergometer in patients breathing their usual O_2 supply. The workload was set at 80% of the maximal workload predicted from the 6MWD performed at T0[21]. Under monitoring of pulse oximetry and 1-trace electrocardiogram (EKG), patients had to maintain a pedaling frequency of 60 to 65 rpm[35]. The test was stopped when the dyspnea and/or fatigue scale[36] was above 8 on the Borg scale, SpO_2 dropped below 80% or HR was above the maximal predicted or in presence of: a) ST segment depression on the EKG, b) signs or symptoms of angina pectoris, c) malignant arrhythmias. Arterial blood pressure, HR, SpO_2, SpO_2/HR ratio, dyspnea and fatigue Borg scale were recorded before and at the end of the test. Nadir SpO_2 was also recorded. The endurance time (Tlim) was recorded as the sum of the warm-up period and the test phase. The MCID of Tlim after exercise training is a 150-s increase[35].

After the training program patient satisfaction was rated on a 5-point Likert scale designed for the study (range 0–4, from the worst to the best) asking the following questions:

a) "How would you rate your feeling of comfort and well-being during training? "

b) "How would you rate your feeling of comfort and well-being using the oxygen delivery device used?"

Dropout reasons were defined as follows:

a) Unable to sustain at least 6 sessions/week; b) poor adherence due to psychological and personal issues during the training (self-discharge, personal commitment); c) relapse of COPD/pneumonia; d) Acute events with or without premature discharge from hospital; e) Device refuse

[H2]Statistical analysis

Statistical analysis was performed using STATA 11 (StataCorp LLC, TX USA) and R software (GPL, version 3.6.1, www.r-project.org). Continuous variables were expressed as mean

and standard deviation (SD). Binary and categorical outcomes were described as frequencies and percentage in each group. When statistical tests were performed, P value < .05 was considered statistically significant.

The Tlim was the primary outcome. The estimated sample size for a 2-sample comparison of means on the primary outcome [pre-to-post difference in Tlim] was 156 patients considering a mean 150s and 280s post-treatment increase in the control and treatment groups, respectively, with a SD of 250 s (alpha error 0.05, power 0.90) for both groups. The mean and SD estimated improvement in the control group was calculated according to the MCID of Tlim after rehabilitation (150s)[35]. The improvement in the treatment group was estimated by a preliminary internal pilot study in 10 patients. We estimated a drop-out rate of 10% of patients (n = 15) with a final sample size of 171 patients.

As primary analysis, a multivariate linear mixed-effects model was fitted in order to evaluate the presence of statistically significant variations in terms of the evaluated outcomes between T0 (baseline) and T1 (after training) and to assess the presence of statistically significant differences between groups accounting for potential differences between centres**.** To this aim, group and time (T0, T1) and the interaction between group and time were imposed as fixed terms, while patients' characteristics (to estimate the intra-individual variations between T0 and T1) and centres were used as random factors. More specifically, patients' characteristics were nested within centre (1|centre/characteristics) since each patient was referred to a single hospital. The inclusion of the centre as a fixed effect term did not alter the significance of the terms or their value. Multivariate linear mixed-effects models were fitted by the "lme" function implemented in the R package called "nlme."

As secondary analysis a linear regression model using the difference between values at T0 and T1 (T1–T0) as dependent variable was used, while values of outcomes at T0, groups and centre as covariates were also fitted using the "lm" function in the R (www.r-project.org) package "stats". Results were in line with those obtained by mixed-effect models.

In addition, in order to define the baseline characteristics related to the improvement in primary outcome and to the possibility of dropouts we performed a backward stepwise multiple logistic regression analysis to estimate the odds ratio (OR) of reaching the MCID in Tlim and 6MWT and to estimate the risk of dropouts, including each baseline variable. We included in the final equation all independent variables reaching the statistical significance ($P < .05$).

[H1]RESULTS

The study flow chart is shown in Figure 2. A total of 171 patients were enrolled (33 patients Lumezzane, 23 Pavia, 27 Tradate, 17 Cassano Murge, 18 Veruno, 21 Villa Pineta, 23 Milano, 9 Firenze), of which 34 dropped out. One hundred thirty-seven patients completed the study: 71 in the HFOT and 66 in the V-mask group, with a dropout rate of 15.4% and 24.1% in the HFOT and V-mask group, respectively ($p = .1581$). Causes of dropout are also described in Figure 2.

No cause of dropouts was statistically different between the 2 groups: the main reason of dropout was COPD relapse plus acute events (69.2% vs 47.6% for HFO and V-mask respectively $p = .217$), while the intolerance to the training protocol was 7.6% vs 19.0% ($p = .3608$). Only low Body Mass Index (BMI < 20 kg/m^2) predicted the risk of dropout from the program (OR 1.2123, SE 0.0478, 95% CI 0.1367:0.3299, $p < .001$). Table 1 shows the baseline characteristics of the patients.

[H2]Training

The exercise intensity started from 27.6 ± 2.2 and 26.5 ±1.9 watts ($p = .85$), the peak workloads were 37.9 ± 2.1 and 41.7 ± 2.5 watts, ($p = .34$) for V-mask and HFOT, respectively. The FiO_2 of V-mask group remained constant during training from 35.1 ±10.0 to 36.2 ± 9.2 % with 2 out of 66 patients needing increase of FiO_2.

[H2]Setting of the HFOT device

During the first training session, in the HFOT group the airflow was set at 47 ±13 L/min (range 20-60 L/min), temperature at 34 ± 3 °C (range: 30-37 °C), and FiO_2 at 36.5 ± 8.8 % remaining constant during all sessions (final FiO_2 36.1 ±10.5 % with 8 out of 71 patients needing increase of FiO_2). During the training program, the airflow was reduced 43 times in 22 patients, with a final value of 45 ± 12 L/min (range 10-60); temperature was reduced 30 times, in 18 patients, with a final value of 33 ±3 °C (30-37 °C).

[H2]Outcomes

Figure 3 shows the time course of training sessions. Workload, heart rate, dyspnea, fatigue perception, and SpO_2 improved significantly over time without statistical significance between groups.

Table 2 shows the distribution of outcomes by experimental group and time. No statistically significant difference in the evaluated outcomes was observed between groups at T0 ($p > .05$). For the primary outcome: Tlim increased significantly both in V-mask group (by 314.8 seconds, $p < .001$) and in HFOT group (by 456.6 seconds, $p < .001$). Further, no significant difference between groups was observed in changes in Tlim with patients under HFOT having a mean 141.8 (95%CI -18.72:302.42) seconds increase compared to V-mask (group x time interaction $p = .083$).

For the secondary outcomes: 6MWD increased significantly both in V-mask group [by 43.3 (95%CI 0.87:33.43) meters, $p < 0.001$] and in HFOT group (by 60.4 meters, $p < 0.001$). A statistically significant between groups difference was observed in changes in 6MWD, with HFOT group having a mean 17.14 meters increase compared to V-mask group (group x time interaction $p = .039$). No other outcome showed statistically significant between groups differences in changes from T0 to T1 (group x time interaction $p > .05$).

After training, arterial oxygen tension (PaO_2), dyspnea, and HRQL significantly improved in both groups, but not between groups. Respiratory muscle strength and leg fatigue improved slightly and significantly only in the HFOT group, without, however, any significant difference between

groups in pre-post changes. Arterial carbon dioxide tension and quadriceps MVC did not improve in either group.

[H2]Improvers

After training, Tlim improved from baseline by 104 ±133% in V-mask and 160 ±246% in HFOT (p = .100) while 6MWD improved by 19 ±25% in V-mask and 25 ±24% in HFOT (p = .199). The MCID of Tlim was reached in 47% of V-mask and in 56% of HFOT patients (p = .352) while the MCID of 6MWD was reached in 51% of V-mask and 69% of HFOT patients respectively (p = .036). **Figure 4** shows the percentage of improvers in tests of exercise capacity. Improvers were more prevalent in the HFOT group for 6MWD (p = .036) and for both tests (p = .026) whereas no significant between-group difference was found in prevalence of improvers only in Tlim (p = .350).

The stepwise multiple logistic regression analysis showed that only baseline Tlim was significantly able to predict improvement after training. A higher baseline value of Tlim was associated with a higher probability to improve above the MCID of 150 seconds (OR =1.14; SE = 0.0710; 95% CI 1.0180:1.2970). A lower baseline value of 6MWD and the belonging to HFOT group were associated with a higher probability to improve above the MCID of 30 meters (OR for 6MWD = 0.99; SE = 0.0020; 95% CI 0.9918:0.9997 and OR for HFOT group= 2.19; SE = 0.7966; 95% CI 1.0761:4.460).

[H2]Patient satisfaction

To the question, "How would you rate your feeling of comfort and well-being during training?" HFOT and V-mask patients, respectively, answered: "good" (24% vs. 23%), "very good" (52% vs. 45%) and excellent (24% vs. 22%) (p = .260) while to the question "How would you rate your feeling of comfort and well-being using the oxygen delivery device used" HFOT

patients and V-mask patients answered: “good” (41% vs 40%) “very good” (44% vs 40%) and excellent (6% vs 11%) respectively (p = .890).

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[H1]DISCUSSION

In severe patients with COPD and chronic hypoxemia on LTOT, HFOT during exercise training sessions, as compared to usual oxygen through V-mask, was not associated with a greater improvement in endurance time, the primary outcome, whereas the difference in improvement in 6MWD reached the statistical significance. Both groups achieved benefits from the exercise training program with significant improvements in exercise capacity, symptoms and HRQL. Although the p-value of primary analysis did not reach the statistical significance threshold, clinical benefits of HFOT were evident. We do not consider this study as negative simply based on p-value.

High-flow oxygen therapy has become widespread across different clinical settings. Its physiological effects in patients with acute respiratory failure are well established,[36] whereas the effects in stable patients with COPD with or without chronic hypoxemia are less clear. High-flow oxygen therapy enhances patient comfort and tolerance in comparison to traditional high-flow oxygenation systems, such as nasal prongs and non-rebreathing systems. Delivering higher flow rates, HFOT systems are less likely to allow entrainment of room air during inspiration. Combined with the expired air from the upper airway, these mechanisms ensure more reliable high FiO_2 levels. The flushing of upper airway dead space also improves ventilatory efficiency and reduces the work of breathing, generating a positive end-expiratory pressure (PEEP), which may counterbalance the intrinsic-PEEP, improve oxygenation, and provide back pressure to enhance airway patency during expiration, allowing more complete lung emptying.[15,37,38] One study showed that a 6-week

treatment with HFOT improved HRQL and reduced hypercapnia in patients with stable hypercapnic COPD [39]. In a previous study in severe patients with COPD with or without oxygen during exercise, 2 constant load exercise tests at 75% of maximum workload were randomly performed with and without HFOT, at the same FiO_2[17]. The endurance time significantly increased under HFOT. At iso-time, HFOT resulted in better oxygen saturation, lower dyspnea and leg fatigue [17].

In this study we compared the effects on exercise capacity of adding HFOT to exercise training as compared to usual oxygenation at the same FiO_2. Therefore potential differences would be ascribed to characteristics of HFOT different from FiO_2. Which mechanisms might be involved in the effects of HFOT on exercise training observed in our study is hard to say. Despite the modest post-training increase in MIP observed in the HFOT group, there was no significant between-group difference in post-training changes in all assessed outcomes other than 6MWD. The substantial lack of improvement in respiratory muscle strength is not surprising given that no specific in/expiratory muscle training was performed. Arterial oxygen tension significantly improved in both groups, without any difference either in SpO_2 nadir, SpO_2/HR ratio at end of exercise, or in quadriceps force.

The effect of additional oxygen as compared to air during exercise training in patients with COPD not needing LTOT is still discussed. Most studies reported no significant benefit in exercise capacity or HRQL[8-11], whereas only 1 study[12] reported an advantage in exercise capacity with the use of oxygen during exercise training in non hypoxaemic patients. However, our study confirms the benefits of exercise training also in more severe patients with hypoxemic COPD under LTOT [5]. In the present study, HFOT resulted in significantly greater improvement in 6MWD compared to V-mask. Although we can argue that the significant difference between groups in improvement in 6MWD seems unlikely to be clinically important, we must note that also the proportion of patients reaching the MCID was significantly higher in HFOT group.

Despite high variability, Tlim improved about 60% more with HFOT than with V-mask, however this difference did not reach the statistical significance. In contrast, in another study[40], in

patients with chronic hypoxemia and hypercapnia due to restrictive and obstructive diseases on long-term non invasive ventilation and LTOT, the addition of non invasive ventilation during exercise training significantly improved more Tlim, but not 6MWD compared to exercise training alone[40]. The discrepancy in results of 6MWD and endurance tests found in our study may not be surprising. Simple field tests like the 6MWD are used to assess the effects of pharmacological and non-pharmacological interventions, however in patients with COPD endurance tests are more responsive to pharmacological and non-pharmacological interventions than either the incremental or the 6MWD test [35]. Physiological conditions may be not the same in the tests we used [41,42], however, the modality of training is not likely to have influenced our results as our patients were trained on a cycle ergometer and the primary outcome measure of exercise capacity was evaluated by the endurance time assessed with a CWRET on a cycle ergometer whereas the secondary outcome measure was the walking test. Whether training by ground-based or treadmill walking (rather than cycling) would have differently affect endurance time, remains speculative. Therefore, our results with cycling training should not be generalized for others type of training (treadmill, ground-based walking, arm)**.** Furthermore, given the wide difference in favor of HFOT in mean values of post-training changes in Tlim, we cannot exclude a statistical effect, even though the sample size had been calculated on that outcome measure.

Dyspnea as assessed either by the MRC scale[30] or the Barthel Dyspnea Index[31] improved significantly in both groups, without significant differences between groups. These tools assess different components of the multifaced symptom.

Again, it is important to underline that the majority of patients of both groups defined the training protocol as comfortable or very comfortable and there was no significant difference in patients' satisfaction with the 2 devices, half of patients defining the devices as very comfortable or excellent. We cannot exclude that the humidification delivered via HFOT might have created a positive effect on the comfort and hence allow patients to exercise comfortably.

The dropout rate was higher than expected in both arms (Fig. 2). As a matter of fact, the

causes of dropouts were more associated to acute events than to training intolerance; intolerance to the training protocol was higher in the V-mask group. In a simulation study, exhaled air dispersion during HFOT and CPAP *via* different interfaces was limited by ensuring a good mask interface fitting[43]. Furthermore, HFOT can produce noise that can be reduced by attaching an intake filter[44].

[H2]Limitations of the study

Neither the patients nor the assessors were blind to the treatments. We did not measure respiratory mechanics, peripheral muscle oxygen delivery, or hemodynamics.

A comparison with the most popular tool to deliver oxygen during exercise (portable cylinder and nasal prongs) would have been more realistic, however we were aimed to compare the modalities at the same FiO_2, a target we got with the V-mask, although with the V-mask there was no measurement of the oxygen concentration by means of an oxygen analyzer, whereas the HFOT device regularly estimated the oxygen concentration.

Furthermore, an intention-to-treat analysis, as opposed to the per-protocol population analysis, would have been impossible to perform due to the high dropout rate.

Finally, the chosen intensity for the primary outcome (endurance time on a cycle ergometer) was derived from the 6MWD (based on the Luxton equation) and not an incremental cardiopulmonary exercise test. Previous studies have shown that this equation could be not very accurate[45] and this could explain at least in part why no difference was found in the primary outcome.

[H1]Conclusion

With the above limitations, we found that in patients with severe COPD and chronic hypoxemia on LTOT, exercise training resulted in benefits in exercise capacity and HRQL. The addition of HFOT during training sessions, as compared to usual oxygen through a V-mask, was not associated with a greater improvement in endurance time, the primary outcome, or in HRQL or

health status. However, a greater improvement in the 6MWD was observed in the HFOT group. Although the p-value of primary analysis did not reach statistical significance threshold of 0.05, the overall clinical benefits of HFOT were evident and we do not consider this study as negative simply based on p-value. This new modality may be a feasible and comfortable means to deliver oxygen to these patients during exercise training. Future studies should identify the physiological and clinical characteristics predicting patients more likely to respond to this treatment.

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Ethics Approval

The study protocol was defined according to the Consolidated Standard of Reporting Trials (CONSORT) guidelines and approved by the Ethics Committees of each center (2109 CEC 20/April/2017).

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Clinical Trial Registration

This study was registered at ClinicalTrials.gov (NET03322787).

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest related to the present manuscript.

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Table 1. Demographic, Physiological, and Clinical Characteristics of the Enrolled Patients.[a]

Measures	HFOT (n = 84)	V-mask (n = 87)
Males, %	73.8	68.9
Age, years	71.1 ± 7.8	71.8 ± 8.4
BMI, Kg/m^2	26.4 ± 6.3	25.7 ± 5.6
FEV_1,% pred	41.0 ± 15.6	42.6 ± 16.8
FVC,% pred	65.9 ± 17.5	68.4 ± 19.2
FEV_1/FVC, ratio	0.45 ± 0.17	0.46 ± 0.13
RV, % pred	170.1 ± 49.1	166.2 ± 44.2
MIP, cmH_2O	62.3 ± 18.4	67.8 ± 18.9
MEP, cmH_2O	69.0 (24.9)	71.4 (22.4)
CIRS, 1st item, score	1.70 ± 0.30	1.63 ± 0.25
CIRS, 2st item, score	2.93 ± 1.52	2.80 ± 1.43
PaO_2[b]**,** mmHg	58.4 ± 9.5	60.5 ± 8.6
$PaCO_2$[b]**,** mmHg	44.6 ± 7.6	43.6 ± 9.3
pH	7.43 ± 0.03	7.42 ± 0.03
6MWD, meters	293.4 ± 92.1	289.4 (91.3)
Tlim, seconds	321.3±203.2	349.2 ± 250.4
MRC, score	2.8 ± 1.1	2.9 ± 0.9
Barthel index, score	93.3 ± 9.4	93.7 ± 9.9
Barthel Dyspnea index, score	31.1 ± 19.1	34.9 ± 21.6

MVC, quadriceps, Kg[c]	20.5 ± 6.9	21.7 ± 7.1
MRF26, score	12.1 ± 6.2	12.9 ± 5.6
CAT, score	19.6 ± 6.9	19.9 ± 7.5

[a] (n = 171, mean ± SD). 6MWD = 6 minute walking distance; CAT= COPD Assessment Test; CIRS = Cumulative Illness Rating Scale; FEV_1 = Forced Expiratory Volume at 1 sec; FVC = Forced Vital Capacity; MRF26= Maugeri Respiratory Failure-26 Scale; MEP = Maximal Expiratory Pressure; MIP = Maximal Inspiratory Pressure; MRC= Medical Research Council score; MVC = maximal voluntary contraction; $PaCO_2$ = arterial carbon dioxide tension; PaO_2= arterial oxygen tension; pred = predicted; RV = Residual Volume; Tlim = Endurance time on CWRET.

[b] Breathing room air.

[c]Data available on 46 patients.

Table 2. Distribution of Outcomes by Experimental Group and Time in Patients Who Completed the Study[a]

Outcome	V-mask (n =66)			HFOT (n = 71)			Time-dependent variation	
	Time = 0	Time = 1		Time = 0	Time = 1		Group = 1 vs. Group = 0	
	Mean ± SD	Mean ± SD	*P*[b]	Mean ± SD	Mean ± SD	*P*[c]	Mean Delta (95% CI)	*P*[d]
Tlim, seconds	349.07 ± 272.9	663.87 ± 515.41	< .001 [e]	315.74 ± 202.59	772.39 ± 612.96	< .001	141.85 (-18.72:302.42)	0.083
6MWD, meters	284.88 ± 89.94	328.15 ± 86.01	< .001 [e]	289.25 ± 93.43	349.66 ± 97.22	< .001	17.14 (0.87:33.43)	0.039 [e]
PaO_2, mmHg	60.28 ± 9.37	62.86 ± 9.34	.013 [e]	58.62 ± 9.83	63.2 ± 9.07	< .001	2.01 (-0.77:4.78)	0.156
$PaCO_2$, mmHg	43.11 ± 8.56	43.23 ± 7.27	.878	44.3 ± 7.88	42.95 ± 6.26	.063	-1.47 (-3.57:0.63)	0.168
BORG fatigue at rest, score	0.56 ± 1.23	0.42 ± 0.97	.422	0.82 ± 1.62	0.53 ± 1.08	.079	-0.15 (-0.62:0.31)	0.518
MIP, cmH_2O	63.79 ± 19.12	65.19 ± 17.59	.345	61.98 ± 21.07	65.69 ± 20.87	.010	2.31 (-1.76:6.37)	0.263
MEP, cmH_2O	92.18 ± 32.57	93.6 ± 36.56	.582	94.45 ± 32.15	101.15 ± 32.75	.008	5.27 (-1.79:12.33)	0.142
MVC quadriceps, Kg	21.77 ± 7.53	20.71 ± 7.98	.239	21.17 ± 6.78	22.25 ± 7.22	.187	2.13 (-0.28:4.55)	0.081
MVC bicipities, kg	20.35 ± 8.02	20.35 ± 8.95	.999	19.46 ± 8.06	20.01 ± 9.75	.425	0.56 (-1.47:2.59)	0.585
MRC, score	3.02 ± 0.91	2.31 ± 0.95	< .001 [e]	2.8 ± 1.1	2.01 ± 0.96	< .001	-0.08 (-0.4:0.24)	0.615
CAT, score	20.58 ± 7.76	15.38 ± 7.42	< .001 [e]	19.56 ± 7.39	14.83 ± 7.35	< .001	0.47 (-1.27:2.21)	0.592
MRF26, score	13.36 ± 5.92	10.61 ± 5.59	< .001 [e]	12.34 ± 6.58	9.76 ± 6.18	< .001	0.18 (-1.13:1.49)	0.785
Barthel index, score	93.7 ± 10.14	93.73 ± 13.85	.984	93.38 ± 9.54	93.44 ± 13.11	.970	0.03 (-4.2:4.25)	0.990

[a]Outcome = analyzed outcome; Group = analyzed group; Time = measurement time; n = non-missing observations; Mean = mean value of the outcome's distribution; SD = standard deviation of the mean value of the outcome's distribution; Delta (95% CI) = adjusted mean time dependent variation in HFOT group vs. V-mask group0 as estimated

by multivariate linear mixed-effects models and 95% Confidence Interval (CI). CAT = COPD Assessment Test; MEP = Maximal Expiratory Pressure; MIP = Maximal Inspiratory Pressure; MRC = Medical Research Council score; MRF26 = Maugeri Respiratory Failure-26 Scale; MVC = maximal voluntary contraction; PaCO2 = arterial carbon dioxide tension; PaO2 = arterial oxygen tension; 6MWD = 6-minute walking distance; Tlim = Endurance time on CWRET.

[b]P-value from linear mixed-effects models for the paired difference between Time = 0 and Time = 1 in group = 0.

[c]P-value from linear mixed-effects models for the paired difference between Time = 0 and Time = 1 in group = 1.

[d]P-value from linear mixed-effects models for the interaction between time = 1 and group = 1; $P < .05$.

[e]Data available on 46 patients (24 for HFOT and 22 for V-mask).

LEGENDS TO FIGURES

Figure 1. A patient during the training session (with permission).

Figure 1

Figure 2. Flow chart of the study. Legend for Reasons: a = unable to sustain programs; b = poor adherence; c = acute events [COPD relapse + Other acute events]; d = device refuse.

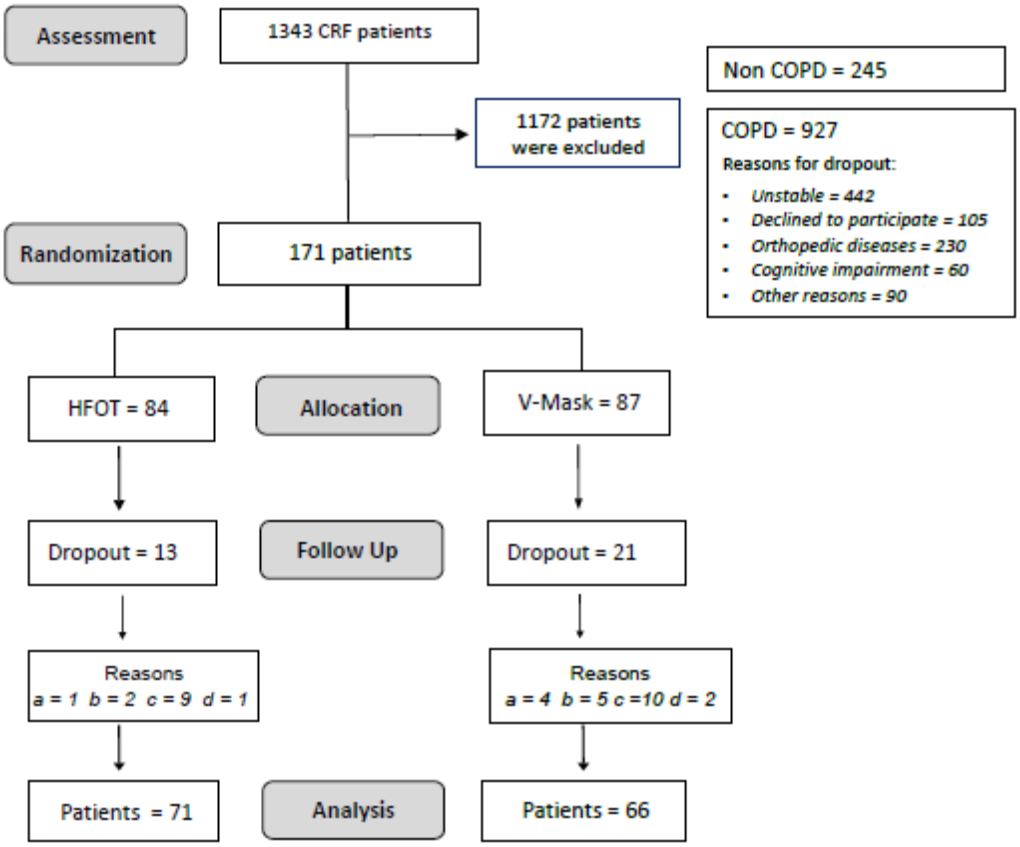

Figure 3. Time course of workload, heart rate, dyspnea, fatigue perception, and SpO_2. Data are presented as mean ± SD; p refers to changes over time. The non significant differences between groups are shown in the text.

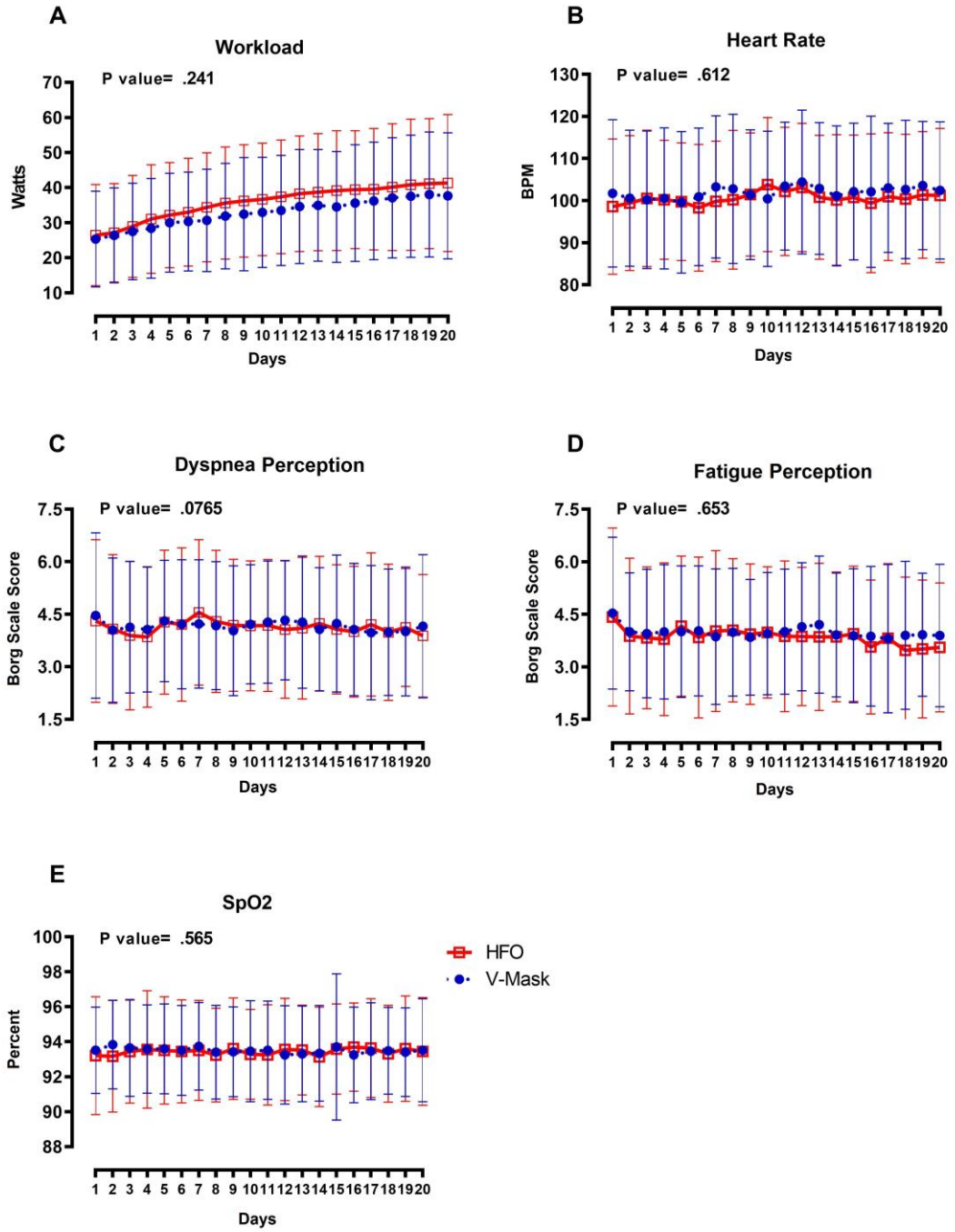

Figure 3

Figure 4. Prevalence of improvers (as defined as patients showing a change above the MCID) in each and in both outcome measures, in the overall study group and by treatment group.

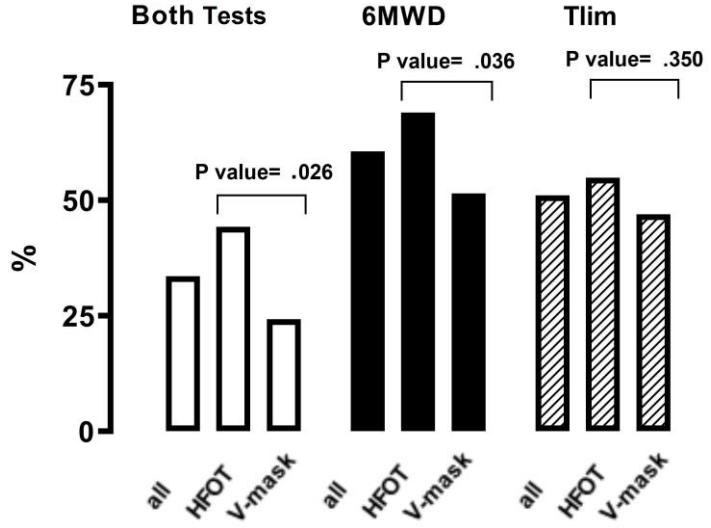

Figure 4