

This is the peer reviewed version of the following article:

High flow oxygen therapy during exercise training in COPD patients with chronic respiratory failure: a multicenter randomised trial / Vitacca, Michele; Paneroni, Mara; Zampogna, Elisabetta; Visca, Dina; Carlucci, Annalisa; Cirio, Serena; Banfi, Paolo; Pappacoda, Gabriele; Trianni, Ludovico; Brogneri, Antonio; Belli, Stefano; Paracchini, Elena; Aliani, Maria; Spinelli, Vito; Gigliotti, Francesco; Lanini, Barbara; Lazzeri, Marta; Clini, Enrico; Ambrosino, Nicolino. - In: PHYSICAL THERAPY. - ISSN 0031-9023. - 100:8(2020), pp. 1249-1259. [10.1093/ptj/pzaa076]

*Terms of use:*

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

27/04/2026 04:33

(Article begins on next page)

**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

**TOC CATEGORY:** Cardiovascular/Pulmonary

**ARTICLE TYPE:** Original Research

**AUTHOR BYLINE:** Michele Vitacca, Mara Paneroni, Elisabetta Zampogna, Dina Visca, Annalisa Carlucci, Serena Cirio, Paolo Banfi, Gabriele Pappacoda, Ludovico Trianni, Antonio Brogneri, Stefano Belli, Elena Paracchini, Maria Aliani, Vito Spinelli, Francesco Gigliotti, Barbara Lanini, Marta Lazzeri, Enrico M. Clini, Alberto Malovini, Nicolino Ambrosino on behalf of Associazione Italiana Riabilitatori Insufficienza Respiratoria and Associazione Italiana Pneumologi Ospedalieri rehabilitation group.

© The Author(s) 2020. Published by Oxford University Press on behalf of the American Physical Therapy Association. All rights reserved. For permissions, please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com)

## **AUTHOR INFORMATION:**

M. Vitacca, MD, Respiratory Rehabilitation Department, Istituti Clinici Scientifici Maugeri IRCCS, Via Salvatore Maugeri, 4 - 27100 Pavia, Italy. Address all correspondence to Dr Vitacca at: [michele.vitacca@icsmaugeri.it](mailto:michele.vitacca@icsmaugeri.it).

M. Paneroni, PT, Respiratory Rehabilitation of the Institute of Lumezzane, Istituti Clinici Scientifici Maugeri IRCCS, Brescia, Italy.

E. Zampogna, PT, Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Varese, Italy.

A. Carlucci, MD, Respiratory Rehabilitation of the Institute of Pavia, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.

P. Banfi, MD, Respiratory Rehabilitation of the Institute of Milano, IRCCS Fondazione Don Gnocchi, Milano, Italy

A. Brogneri, PT, Respiratory Rehabilitation of Villa Pineta, Pavullo nel Frignano, Modena, Italy.

S. Belli, PT, Respiratory Rehabilitation of the Institute of Veruno, Istituti Clinici Scientifici Maugeri IRCCS, Novara, Italy.

M. Aliani, MD, Respiratory Rehabilitation of the Institute of Cassano delle Murge, Istituti Clinici Scientifici Maugeri IRCCS, Bari, Italy.

B. Lanini, MD, Respiratory Rehabilitation of the Institute of Firenze, IRCCS Fondazione Don Gnocchi, Firenze, Italy.

M. Lazzeri, PT, Ospedale Niguarda Ca' Granda, Milano, Italy.

E.M. Clini, MD, Department of Medical and Surgical Sciences, Università degli Studi Modena e Reggio Emilia, Modena, Italy.

A. Malovini, PhD, Laboratory of Informatics and Systems Engineering for Clinical Research of the Institute of Pavia, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy.

N. Ambrosino, MD, Respiratory Rehabilitation of the Institute of Montescano, Istituti Clinici Scientifici Maugeri IRCCS, Montescano, Pavia, Italy.

D. Visca, MD, Respiratory Rehabilitation of the Institute of Tradate, Istituti Clinici Scientifici Maugeri IRCCS, Varese, Italy

S. Cirio, PT, Respiratory Rehabilitation of the Institute of Pavia, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy

G. Pappacoda, PT, Respiratory Rehabilitation of the Institute of Milano, IRCCS Fondazione Don Gnocchi, Milano, Italy

L. Trianni, MD, Respiratory Rehabilitation of Villa Pineta, Pavullo nel Frignano, Modena, Italy.

E. Paracchini, PT, Respiratory Rehabilitation of the Institute of Veruno, Istituti Clinici Scientifici Maugeri IRCCS, Novara, Italy

V. Spinelli, PT, Respiratory Rehabilitation of the Institute of Cassano delle Murge, Istituti Clinici Scientifici Maugeri IRCCS, Bari, Italy

F. Gigliotti, MD, Respiratory Rehabilitation of the Institute of Firenze, IRCCS Fondazione Don Gnocchi, Firenze, Italy.

**KEYWORDS:** Pulmonary Rehabilitation, Exercise Tolerance, Oxygen Therapy

**ACCEPTED:** February 5, 2020

**SUBMITTED:** August 7, 2019

**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).<sup>1-5</sup> Oxygen supplementation<sup>6</sup> and non invasive ventilation during exercise may improve the effects of training.<sup>7</sup> However, the role of additional oxygen during training in patients with exercise induced desaturation is still discussed,<sup>8-12</sup> whereas non invasive ventilation is not tolerated by all patients, requires high expertise and is time-consuming for health professionals.<sup>7</sup>

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<sup>13</sup>. 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<sup>14,15</sup>. Compared to standard oxygen, HFOT and non invasive ventilation reduced the respiratory muscle load and the respiratory rate, while increasing the expiratory time<sup>16</sup>. Only 1 study showed that HFOT can increase exercise tolerance in stable patients with severe COPD,<sup>17</sup> 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<sub>2</sub>).

## **[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<sup>18</sup>, 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.<sup>19</sup> 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<sub>1</sub>)/forced vital capacity (FVC) < 0.7)<sup>1</sup>; 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)<sup>20</sup>, 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<sup>21</sup> from the baseline 6 minutes walking distance test (6MWD). Patients performed a preliminary session breathing through the V-mask: the FiO<sub>2</sub> able to maintain pulse oximetry (SpO<sub>2</sub>) > 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<sup>19</sup>. Increases or reductions by 10 watts in intensity were according to Maltais et al.<sup>22</sup>. The workload was increased when patients scored their dyspnea and/or leg fatigue less than 4 on a modified 10-point Borg scale<sup>23</sup>. The workload was unchanged if the Borg score was 4 or 5 and was reduced for scores above 5<sup>22</sup>. 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<sub>2</sub> within the system (FiO<sub>2</sub>: 0.21-1)<sup>24</sup>. 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<sub>2</sub> 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<sub>2</sub> 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)<sup>25</sup>, were recorded. Lung function was assessed after bronchodilation. Results were expressed as absolute and percent of the predicted values according to Quanjer<sup>26</sup>.

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<sup>27</sup>, in patients breathing their usual O<sub>2</sub> supply ( $3.95 \pm 2.63$  L/min). Borg dyspnea and fatigue<sup>23</sup> and pulse oxymetry (SpO<sub>2</sub>) were recorded before and at the end of the test. Performed distance in meters, as well as SpO<sub>2</sub> nadir and the SpO<sub>2</sub>/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<sup>27</sup>.
- 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)<sup>28</sup>.
- Quadriceps muscle strength was assessed by means of a manual dynamometer (Chatillon® X-3328 Series, Ametek Inc., Florida, USA)<sup>29</sup>. The maximal voluntary contraction (MVC) was expressed in kg.
- Dyspnea was evaluated by the Medical Research Council (MRC) scale<sup>30</sup> and the Barthel Dyspnea Index<sup>31</sup>.
- The level of disability, was assessed by the Barthel Index<sup>32</sup>, the Health Status by the COPD Assessment Test (CAT)<sup>33</sup> and Health-Related Quality of Life (HRQL) by the Mageri Respiratory Failure questionnaire (MRF-26)<sup>34</sup> 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<sub>2</sub> supply. The workload was set at 80% of the maximal workload predicted from the 6MWD performed at T0<sup>21</sup>. Under monitoring of pulse oximetry and 1-lead electrocardiogram (EKG), patients had to maintain a pedaling frequency of 60 to 65 rpm<sup>35</sup>. The test was stopped when the dyspnea and/or fatigue scale<sup>36</sup> was above 8 on the Borg scale, SpO<sub>2</sub> 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<sub>2</sub>, SpO<sub>2</sub>/HR ratio, dyspnea and fatigue Borg scale were recorded before and at the end of the test. Nadir SpO<sub>2</sub> was also recorded. The endurance time (T<sub>lim</sub>) was recorded as the sum of the warm-up period and the test phase. The MCID of T<sub>lim</sub> after exercise training is a 150-s increase<sup>35</sup>.

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)<sup>35</sup>. 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](http://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 ( $BMI < 20 \text{ kg/m}^2$ ) 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  $27.6 \pm 2.2$  and  $26.5 \pm 1.9$  watts ( $p = .85$ ), the peak workloads were  $37.9 \pm 2.1$  and  $41.7 \pm 2.5$  watts, ( $p = .34$ ) for V-mask and HFOT, respectively. The  $FiO_2$  of V-mask group remained constant during training from  $35.1 \pm 10.0$  to  $36.2 \pm 9.2$  % 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  $47 \pm 13$  L/min (range 20-60 L/min), temperature at  $34 \pm 3$  °C (range: 30-37 °C), and  $\text{FiO}_2$  at  $36.5 \pm 8.8$  % remaining constant during all sessions (final  $\text{FiO}_2$   $36.1 \pm 10.5$  % with 8 out of 71 patients needing increase of  $\text{FiO}_2$ ). During the training program, the airflow was reduced 43 times in 22 patients, with a final value of  $45 \pm 12$  L/min (range 10-60); temperature was reduced 30 times, in 18 patients, with a final value of  $33 \pm 3$  °C (30-37 °C).

## **[H2]Outcomes**

Figure 3 shows the time course of training sessions. Workload, heart rate, dyspnea, fatigue perception, and  $\text{SpO}_2$  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 ( $\text{PaO}_2$ ), 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  $104 \pm 133\%$  in V-mask and  $160 \pm 246\%$  in HFOT ( $p = .100$ ) while 6MWD improved by  $19 \pm 25\%$  in V-mask and  $25 \pm 24\%$  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 ( $p = .890$ ).

**ROLE OF THE FUNDING SOURCE:** This work was supported by the Ricerca Corrente Funding scheme of the Ministry of Health, Italy. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## [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,<sup>36</sup> 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.<sup>15,37,38</sup> One study showed that a 6-week

treatment with HFOT improved HRQL and reduced hypercapnia in patients with stable hypercapnic COPD<sup>39</sup>. 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  $FiO_2$ <sup>17</sup>. The endurance time significantly increased under HFOT. At iso-time, HFOT resulted in better oxygen saturation, lower dyspnea and leg fatigue<sup>17</sup>.

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<sup>8-11</sup>, whereas only 1 study<sup>12</sup> 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<sup>5</sup>. 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,  $T_{lim}$  improved about 60% more with HFOT than with V-mask, however this difference did not reach the statistical significance. In contrast, in another study<sup>40</sup>, 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<sup>40</sup>. 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<sup>35</sup>. Physiological conditions may be not the same in the tests we used<sup>41,42</sup>, 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<sup>30</sup> or the Barthel Dyspnea Index<sup>31</sup> 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<sup>43</sup>. Furthermore, HFOT can produce noise that can be reduced by attaching an intake filter<sup>44</sup>.

## *[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<sup>45</sup> 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.

### **Author Contributions and Acknowledgments**

Concept / idea / research design: M. Vitacca, M. Paneroni, A. Carlucci, S. Cirio, G. Pappacoda, L. Trianni, A. Brogneri, S. Belli, E. Paracchini, M. Aliani, V. Spinelli, M. Lazzeri, E.M. Clini

Writing: M. Vitacca, M. Paneroni, A. Carlucci, S. Cirio, G. Pappacoda, L. Trianni, A. Brogneri, S. Belli, E. Paracchini, M. Aliani, V. Spinelli, M. Lazzeri, E.M. Clini, A. Malovini, N. Ambrosino

Data collection: M. Vitacca, M. Paneroni, E. Zampogna, A. Carlucci, S. Cirio, P. Banfi, G. Pappacoda, L. Trianni, A. Brogneri, S. Belli, E. Paracchini, M. Aliani, V. Spinelli, F. Gigliotti, B. Lanini, M. Lazzeri

Data analysis: M. Vitacca, M. Paneroni, E. Zampogna, S. Belli, F. Gigliotti, A. Malovini, N. Ambrosino

Project management: M. Vitacca, E. Zampogna, A. Carlucci

Fund procurement: M. Vitacca

Providing participants: M. Vitacca, M. Paneroni, E. Zampogna, D. Visca, P. Banfi, F. Gigliotti, B. Lanini

Providing facilities / equipment: M. Vitacca, E. Zampogna, F. Gigliotti

Providing institutional liaisons: E. Zampogna

Consultation (including review of manuscript before submitting): M. Vitacca, M. Paneroni, S. Cirio, G. Pappacoda, L. Trianni, A. Brogneri, E. Paracchini, F. Gigliotti, M. Lazzeri, A. Malovini, N. Ambrosino

This manuscript was submitted on behalf of Associazione Italiana Riabilitatori Insufficienza Respiratoria and Associazione Italiana Pneumologi Ospedalieri rehabilitation group. The authors thank Fischer & Paykel for free use of devices during the research time, Rosemary Allpress for English language editing, and Laura Comini and Adriana Olivares for technical assistance.

### **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).

### **Funding**

This work was supported by the Ricerca Corrente Funding scheme of the Ministry of Health, Italy. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### **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.

## **REFERENCES**

1. Global strategy for prevention, diagnosis and management of COPD. 2019 Report. 2019. <http://goldcopd.org/gold-reports/>. Date last updated: February 21, 2019. Accessed February 24, 2020.
2. Spruit MA, Singh SJ, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188:e13–64.
3. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2015;CD003793.
4. Paneroni M, Simonelli C, Vitacca M, Ambrosino N. Aerobic exercise training in very severe chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Am J Phys Med Rehabil*. 2017;96:541–548.
5. Carone M, Patessio A, Ambrosino N, et al. Efficacy of pulmonary rehabilitation in chronic respiratory failure (CRF) due to chronic obstructive pulmonary disease (COPD): The Maugeri Study. *Respir Med*. 2007;101:2447–2453.
6. Camillo CA, Osadnik CR, van Remoortel H, Burtin C, Janssens W, Troosters T. Effect of "add-on" interventions on exercise training in individuals with COPD: a systematic review. *ERJ Open Res*. 2016;2:00078–2015.
7. Vitacca M, Ambrosino N. Non-Invasive ventilation as an adjunct to exercise training in chronic ventilatory failure: a narrative review. *Respiration*. 2019;97:3–11.
8. Rooyackers JM, Dekhuijzen PN, Van Herwaarden CL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. *Eur Respir J*. 1997;10:1278–1284.
9. Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. *Thorax*. 2000;55:539–543.

10. Wadell K, Henriksson-Larsén K, Lundgren R. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. *J Rehabil Med.* 2001;33:200–205.
11. Alison JA, McKeough ZJ, Leung RWM, et al. Oxygen compared to air during exercise training in COPD with exercise-induced desaturation. *Eur Respir J.* 2019;53:1802429.
12. Emtner M, Porszasz J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am J Respir Crit Care Med.* 2003;168:1034–1042.
13. Braunlich J, Kohler M, Wirtz H. Nasal high-flow improves ventilation in patients with COPD. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1077–1085.
14. Biselli PJ, Kirkness JP, Grote L, et al. Nasal high flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study. *J Appl Physiol.* 2017;122:82–88.
15. Fraser JF, Spooner AJ, Dunster KR, Anstey CM, Corley A. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax.* 2016;71:759–761.
16. Pisani L, Fasano L, Corcione N, et al. Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. *Thorax.* 2017;72:373–375.
17. Cirio S, Piran M, Vitacca M, et al. Effects of heated and humidified high flow gases during high-intensity constant-load exercise on severe Patients with COPD with ventilatory limitation. *Respir Med.* 2016;118:128–132.
18. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P, Group CN. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT Extension for nonpharmacologic trial abstracts. *Ann Intern Med.* 2017;167:40–47.

19. Vitacca M, Pietta I, Lazzeri M, Paneroni M on behalf of Associazione Italiana Riabilitatori Insufficienza Respiratoria (ARIR) and Associazione Italiana Pneumologi Ospedalieri (AIPO) rehabilitation group. Effect of high-flow nasal therapy during exercise training in patients with COPD with chronic respiratory failure: study protocol for a randomized controlled trial. *Trials*. 2019;20:336
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189–198.
21. Luxton N, Alison JA, Wu J, Mackey MG. Relationship between field walking tests and incremental cycle ergometry in COPD. *Respirology*. 2008;13:856–862.
22. Maltais F, LeBlanc P, Jobin J, et al. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1997;155:555–561.
23. Borg E, Borg G, Larsson K, Letzter M, Sundblad BM. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. 2010;20:644–650.
24. Prieur G, Medrinal C, Combret Y, et al. Effect of high-flow nasal therapy during acute aerobic exercise in patients with chronic obstructive pulmonary disease after exacerbation: protocol for a randomised, controlled, cross-over trial. *BMJ Open Respir Res* 2017;4:e000191–2017-000191. eCollection 2017.
25. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc*. 1968;16:622–626.
26. Quanjer PH. Standardized lung function testing. Report working party standardization of lung function tests. European Community for coal and steel. *Bull Eur Physiopathol Respir*. 1983;19:1–95
27. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. 2014;44:1428–1446.

28. American Thoracic Society/European Respiratory S. ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166:518–624.
29. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. *Phys Ther.* 1996;76:248–259.
30. Paternostro-Sluga T, Grim-Stieger M, Posch M, et al. Reliability and validity of the Medical Research Council (MRC) scale and a modified scale for testing muscle strength in patients with radial palsy. *J Rehabil Med.* 2008;40:665–671.
31. Vitacca M, Paneroni M, Baiardi P, et al. Development of a Barthel Index based on dyspnea for patients with respiratory diseases. *Int J Chron Obstruct Pulmon Dis.* 2016;11:1199–1206.
32. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud.* 1988;10:61–63.
33. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Resp J.* 2009;34:648–654.
34. Vidotto G, Carone M, Jones PW, Salini S, Bertolotti G, Ques G. Mageri Respiratory Failure questionnaire reduced form: a method for improving the questionnaire using the Rasch model. *Disabil Rehabil.* 2007;29:991–998.
35. Puente-Maestu L, Palange P, Casaburi R, et al. Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. *Eur Resp J.* 2016;47:429–460.
36. Helviz Y, Einav S. A systematic review of the high-flow nasal cannula for adult patients. *Crit Care.* 2018;22:71.
37. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest.* 2015;148:253–261.
38. Pisani L, Vega ML. Use of nasal high flow in stable COPD: rationale and physiology. *COPD.* 2017;14:346–350.

39. Nagata K, Kikuchi T, Horie T, et al. Domiciliary high-flow nasal cannula oxygen therapy for patients with stable hypercapnic chronic obstructive pulmonary disease. a multicenter randomized crossover trial. *Ann Am Thorac Soc*. 2018;15:432–439.
40. Vitacca M, Kaymaz D, Lanini B, et al. Non-invasive ventilation during cycle exercise training in patients with chronic respiratory failure on long-term ventilatory support: a randomized controlled trial. *Respirology*. 2018;23:182–189.
41. Poulain M, Durand F, Palomba B, et al. 6-Minute Walk Testing is more sensitive than maximal incremental cycle testing for detecting oxygen desaturation in patients with COPD *Chest* 2003; 123:1401–1407.
42. Man WD, Soliman MG, Gearing J, et al. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2003;168:562–567.
43. Hui DS, Chow BK, Lo T, et al. Exhaled air dispersion during high flow nasal cannula therapy versus CPAP via different masks. *Eur Resp J*. 2019;53:1802339.
44. Kubo T, Nakajima H, Shimoda R, et al. Noise exposure from high-flow nasal cannula oxygen therapy: a bench study on noise reduction. *Resp Care*. 2018;63:267–273.
45. Sillen MJ, Vercoulen JH, van 't Hul AJ, et al. Inaccuracy of estimating peak work rate from six-minute walk distance in patients with COPD. *COPD*. 2012;9:281–288.

**Table 1.** Demographic, Physiological, and Clinical Characteristics of the Enrolled Patients.<sup>a</sup>

Measures	HFOT	V-mask
	(n = 84)	(n = 87)
Males, %	73.8	68.9
Age, years	71.1 ± 7.8	71.8 ± 8.4
BMI, Kg/m <sup>2</sup>	26.4 ± 6.3	25.7 ± 5.6
FEV <sub>1</sub> ,% pred	41.0 ± 15.6	42.6 ± 16.8
FVC,% pred	65.9 ± 17.5	68.4 ± 19.2
FEV <sub>1</sub> /FVC, ratio	0.45 ± 0.17	0.46 ± 0.13
RV, % pred	170.1 ± 49.1	166.2 ± 44.2
MIP, cmH <sub>2</sub> O	62.3 ± 18.4	67.8 ± 18.9
MEP, cmH <sub>2</sub> O	69.0 (24.9)	71.4 (22.4)
CIRS, 1 <sup>st</sup> item, score	1.70 ± 0.30	1.63 ± 0.25
CIRS, 2 <sup>st</sup> item, score	2.93 ± 1.52	2.80 ± 1.43
PaO <sub>2</sub> <sup>b</sup> , mmHg	58.4 ± 9.5	60.5 ± 8.6
PaCO <sub>2</sub> <sup>b</sup> , 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

<b>MVC, quadriceps, Kg<sup>c</sup></b>	20.5 ± 6.9	21.7 ± 7.1
<b>MRF26, score</b>	12.1 ± 6.2	12.9 ± 5.6
<b>CAT, score</b>	19.6 ± 6.9	19.9 ± 7.5

<sup>a</sup> (n = 171, mean ± SD). 6MWD = 6 minute walking distance; CAT= COPD Assessment Test; CIRS = Cumulative Illness Rating Scale; FEV<sub>1</sub> = Forced Expiratory Volume at 1 sec; FVC = Forced Vital Capacity; MRF26= Mageri Respiratory Failure-26 Scale; MEP = Maximal Expiratory Pressure; MIP = Maximal Inspiratory Pressure; MRC= Medical Research Council score; MVC = maximal voluntary contraction; PaCO<sub>2</sub> = arterial carbon dioxide tension; PaO<sub>2</sub>= arterial oxygen tension; pred = predicted; RV = Residual Volume; Tlim = Endurance time on CWRET.

<sup>b</sup> Breathing room air.

<sup>c</sup>Data available on 46 patients.

UNCORRECTED MANUSCRIPT

**Table 2. Distribution of Outcomes by Experimental Group and Time in Patients Who Completed the Study<sup>a</sup>**

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	<i>P</i> <sup>b</sup>	Mean ± SD	Mean ± SD	<i>P</i> <sup>c</sup>	Mean Delta (95% CI)	<i>P</i> <sup>d</sup>
<b>Tlim, seconds</b>	349.07 ± 272.9	663.87 ± 515.41	< .001 <sup>e</sup>	315.74 ± 202.59	772.39 ± 612.96	< .001	141.85 (-18.72:302.42)	0.083
<b>6MWD, meters</b>	284.88 ± 89.94	328.15 ± 86.01	< .001 <sup>e</sup>	289.25 ± 93.43	349.66 ± 97.22	< .001	17.14 (0.87:33.43)	0.039 <sup>e</sup>
<b>PaO<sub>2</sub>, mmHg</b>	60.28 ± 9.37	62.86 ± 9.34	.013 <sup>e</sup>	58.62 ± 9.83	63.2 ± 9.07	< .001	2.01 (-0.77:4.78)	0.156
<b>PaCO<sub>2</sub>, mmHg</b>	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
<b>BORG fatigue at rest, score</b>	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
<b>MIP, cmH<sub>2</sub>O</b>	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
<b>MEP, cmH<sub>2</sub>O</b>	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
<b>MVC quadriceps, Kg</b>	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
<b>MVC bicipities, kg</b>	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
<b>MRC, score</b>	3.02 ± 0.91	2.31 ± 0.95	< .001 <sup>e</sup>	2.8 ± 1.1	2.01 ± 0.96	< .001	-0.08 (-0.4:0.24)	0.615
<b>CAT, score</b>	20.58 ± 7.76	15.38 ± 7.42	< .001 <sup>e</sup>	19.56 ± 7.39	14.83 ± 7.35	< .001	0.47 (-1.27:2.21)	0.592
<b>MRF26, score</b>	13.36 ± 5.92	10.61 ± 5.59	< .001 <sup>e</sup>	12.34 ± 6.58	9.76 ± 6.18	< .001	0.18 (-1.13:1.49)	0.785
<b>Barthel index, score</b>	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

<sup>a</sup>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 = Mageri Respiratory Failure-26 Scale; MVC = maximal voluntary contraction; PaCO<sub>2</sub> = arterial carbon dioxide tension; PaO<sub>2</sub> = arterial oxygen tension; 6MWD = 6-minute walking distance; Tlim = Endurance time on CWRET.

<sup>b</sup>P-value from linear mixed-effects models for the paired difference between Time = 0 and Time = 1 in group = 0.

<sup>c</sup>P-value from linear mixed-effects models for the paired difference between Time = 0 and Time = 1 in group = 1.

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

<sup>e</sup>Data available on 46 patients (24 for HFOT and 22 for V-mask).

UNCORRECTED MANUSCRIPT

## LEGENDS TO FIGURES

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

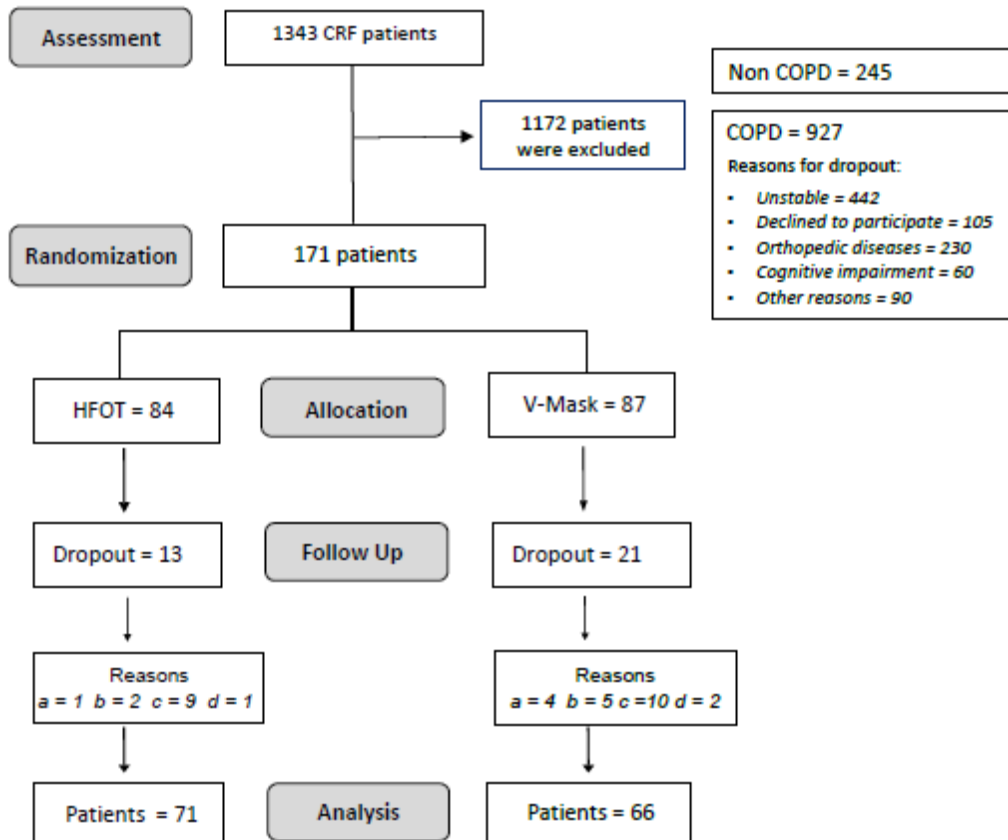


**Figure 1**

UNCORRECTED



**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.

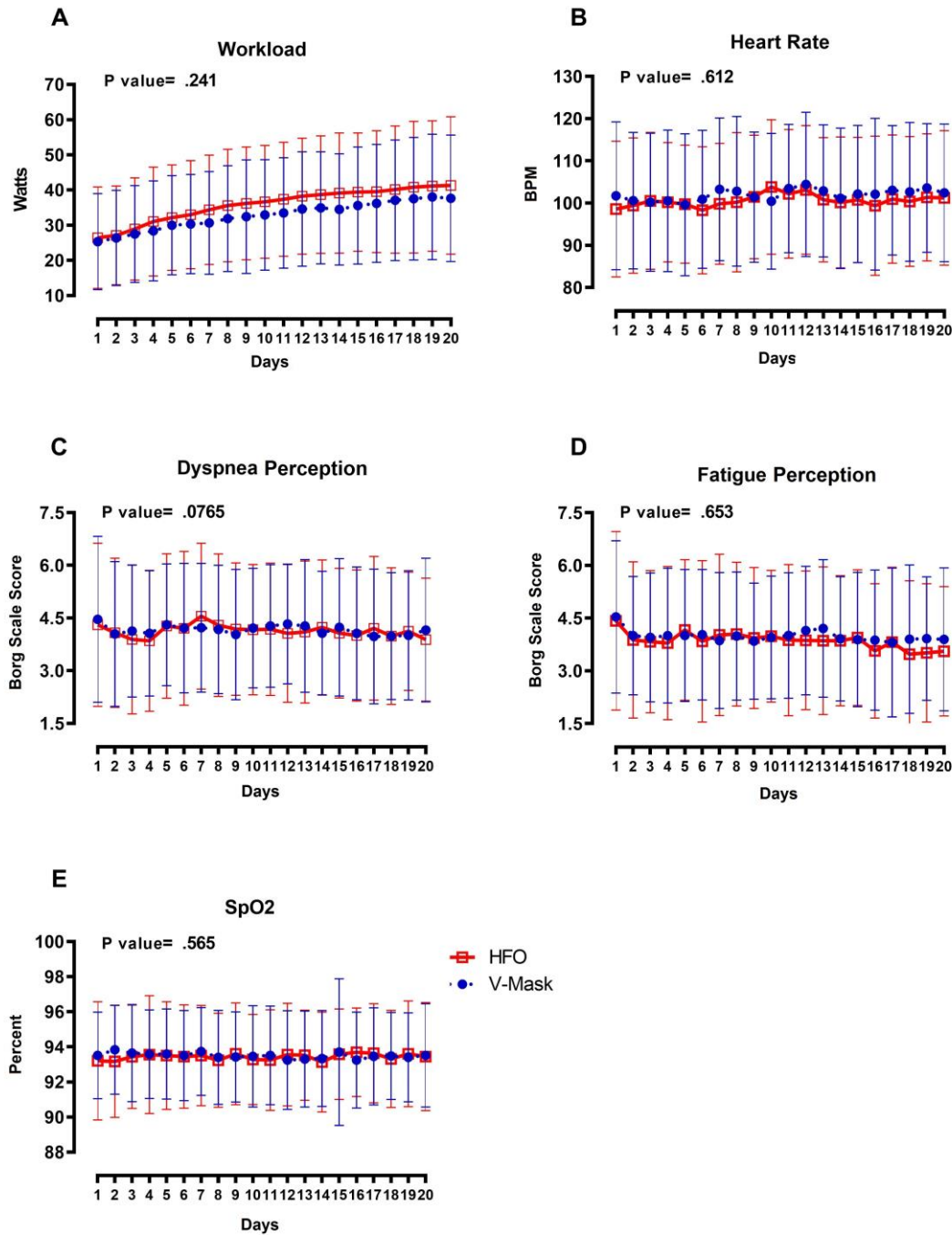


CRIPPT

UNCORRECTED

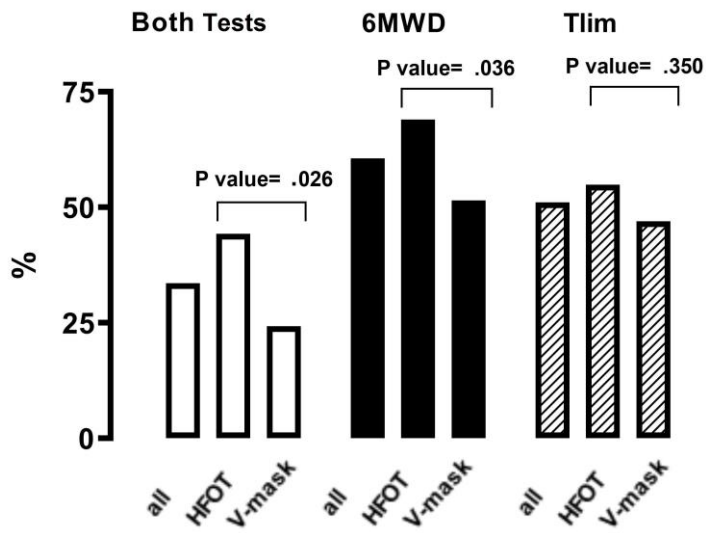
ACCEPT

**Figure 3.** Time course of workload, heart rate, dyspnea, fatigue perception, and SpO<sub>2</sub>. Data are presented as mean  $\pm$  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**