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ORIGINAL ARTICLE

Nasal high flow does not improve exercise tolerance in COPD patients recovering from acute exacerbation: A randomized crossover study

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ABSTRACT

Background and objective: **We hypothesized that by reducing respiratory work and improving gas exchange, nasal high flow (NHF) would improve exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) following respiratory exacerbation.**

Methods: **This was a monocentric, randomized, controlled crossover study. Patients with severe to very severe COPD carried out two high-intensity constant work-rate exercise tests (CWRET) with and without NHF on two consecutive days. The primary outcome was the mean difference in endurance time between both conditions. The secondary aims included *vastus lateralis* oxygenation (StO_2), dyspnoea, leg discomfort, maximal inspiratory pressure (MIP), transcutaneous CO_2 pressure ($PtcCO_2$), respiratory rate (RR), heart rate (HR) and pulsed O_2 saturation (SpO_2), as well as the patients' opinions of the device.**

Results: **A total of 19 patients were included (mean forced expiratory volume in 1 s = 28.7 ± 10.8%, age = 62.1 ± 9.1 years). No significant differences in endurance time during the CWRET were found between the two test conditions (−66.58 (95% CI: −155.9 to 22.7) s, $P = 0.12$). StO_2, $PtCO_2$ and HR were reduced at the end of the exercise with NHF (−2.1% (95% CI: −4.3 to −0.0); −1.3 mm Hg (95% CI: −2.5 to −0.2); −2.7 bpm (95% CI: −5.0 to −0.5), respectively, $P \leq 0.05$). No significant differences were found for any of the other secondary outcomes. Half of the patients evaluated the device as being moderately to very uncomfortable.**

SUMMARY AT A GLANCE

The addition of nasal high flow during high-intensity exercise does not improve endurance in patients with chronic obstructive pulmonary disease participating in pulmonary rehabilitation following exacerbation.

Conclusion: **NHF during exercise did not increase endurance time in patients with COPD following exacerbation.**

Clinical trial registration: NCT03058081 at clinicaltrials.gov

Key words: chronic obstructive pulmonary disease, exercise, muscle oxygenation, nasal high flow, pulmonary rehabilitation.

INTRODUCTION

Exacerbations of chronic obstructive pulmonary disease (COPD) accelerate lung function decline and impair exercise tolerance for several months in affected individuals, which may not return to baseline.[1,2] Although pulmonary rehabilitation has been shown to improve exercise endurance of individuals with COPD, lack of exercise tolerance following exacerbation may cause abandonment of pulmonary rehabilitation.[3,4] The application of non-invasive ventilation (NIV) during exercise can improve exercise tolerance[5,6]; however, the procedure is complex, requires an expert supervision and could be poorly tolerated by patients.[7]

Several studies in patients with stable COPD with or without chronic hypercapnic respiratory failure have shown that nasal high flow (NHF) reduces respiratory rate (RR),[8–10] dead space,[11] respiratory work[12,13] and

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improves gas exchange.[8–10,14] The physiological effects of NHF could help to improve exercise tolerance in those with COPD and requires less technical expertise than NIV. A pilot study showed improvements in endurance, oxygenation and dyspnoea with NHF.[15] However, that study compared NHF with a Venturi mask which is not commonly used in rehabilitation. Furthermore, the patients included were in a stable state; thus, the results may differ regarding the use of NHF immediately following an exacerbation of COPD.

We hypothesized that NHF could be a simple and effective method to improve exercise tolerance in COPD patients recovering from acute exacerbation. The primary aim of this study was to evaluate the effect of NHF on endurance time limit (TLim).

METHODS

Study design

The study protocol was published previously[16] and is registered on ClinicalTrials.gov (NCT03058081). The study was conducted according to the protocol. Ethical approval was obtained from the Ethics Committees Nord-ouest III, Caen, France (No. ID RCB: 2016-A01325-46). Each participant provided written informed consent for participation.

The study was a randomized crossover trial to evaluate the effects of NHF on exercise tolerance. Each participant carried out two high-intensity constant work-rate exercise tests (CWRET) with NHF (NHF test) or without NHF (control test) in a randomized order.

Eligibility and enrolment

Patients were eligible for inclusion if they had a diagnosis of COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio < 0.7) and were participating in a post-exacerbation pulmonary rehabilitation programme (within 7 days of discharge from the Pulmonology Department). Non-inclusion criteria are presented in Appendix S1 in Supplementary Information.

Interventions

The baseline assessment was carried out on admission of the participant to the Pulmonary Rehabilitation Department. The study was carried out over 3 days. On Day 1 (baseline assessment), the participant underwent a CWRET at 80% of maximal estimated power (peak work rate, WR_{peak}) and a 6-min walk test (6MWT) from which the estimated WR_{peak} was calculated. No data from the Day 1 CWRET were analysed. The purpose was to familiarize the participant with the test and the environment. A 10-min period of familiarization with the NHF was also carried out on Day 1. Day 2 occurred 48 h after Day 1.

On Days 2 and 3, two CWRET with or without NHF were carried out on a cycle ergometer (CardioWise Xrcise Cycle, ErgoFit, Pirmasens, Germany) in a randomized order. On each day, the tests were carried out in the same conditions and at the same time of day. Days 2 and 3 were separated by 24 h to allow 'washout'. The tests were stopped if the participant could no longer maintain 60 ± 5 rpm for more than 10 s or if the participant asked to stop because he or she was too breathless. The maximum duration was fixed at 15 min. No encouragement was given during the tests. More details regarding the experimental conditions (technicians, instructions to the participants and performance of the tests) can be found in the protocol and Appendix S1 in Supplementary Information.[16]

Control test

Participants who did not have a prescription for oxygen during exercise carried out the tests on ambient air. Oxygen was administered via a nasal prongs for participants who were prescribed oxygen. Oxygen titration was carried out during the CWRET familiarization session on Day 1 with the aim of maintaining pulsed O_2 saturation (SpO_2) ≥ 90% during the exercise. The oxygen flow determined was then used for both test conditions on Days 2 and 3.

NHF test

NHF was administered via nasal cannula (Optiflow, Fisher & Paykel, Auckland, New Zealand) relayed to an AIRVO 2 device (Fisher & Paykel). The flow rate was set to 60 L/min. For patients under long-term oxygen therapy (LTOT), the device was enriched with oxygen (same flow as in the control condition). The air temperature generated by the device was 31°C.

Outcome measures

The primary outcome was endurance time on the ergometer (in s) during the CWRET. The warm-up period was not included in the calculation of endurance time.

Secondary outcomes were a non-invasive measure of tissue saturation of the *vastus lateralis* muscle (*vastus lateralis* oxygenation, StO_2) using near-infrared spectroscopy (NIRS) (Portamon, Artinis Medical Systems, Einsteinweg, the Netherlands). Heart rate (HR), SpO_2 and transcutaneous CO_2 pressure ($PtcCO_2$) were measured using a TOSCA 500 device (Radiometer, Copenhagen, Denmark). RR was monitored cycle-to-cycle by respiratory plethysmography by inductance using an Embletta Gold device (Embla, Broomfield, USA). These parameters were recorded before the exercise, each minute during the exercise and on cessation of exercise.

Dyspnoea and leg discomfort were evaluated using the modified Borg scale (from 0 to 10; 0:no fatigue or dyspnoea, 10: maximal effort). They were rated before the exercise, every 2 min during exercise and on cessation of exercise.

Maximal inspiratory pressure (MIP) was recorded using an electronic manometer MicroRPM (Micro Medical Limited, Chatham, UK) before the exercise and immediately on cessation.

NHF-related discomfort was evaluated using a Likert scale from 0 to 10 (0: no discomfort, 10: maximum discomfort).

Further information regarding the outcomes can be found in the published protocol and Appendix S1 in Supplementary Information.[16]

Randomization and blinding

After the familiarization period (Day 1), the test sequence was randomized using a 1:1 ratio by a computer-generated block randomization schedule to begin with either NHF or the control condition during the first recorded CWRET on Day 2. The other condition was then carried out on Day 3. The randomization sequence was given to the investigator in a sealed opaque envelope with the patient's inclusion number on it on Day 2, prior to beginning the first recorded CWRET. The investigator, the technicians and the patient could not be blinded for the reasons provided in the *Methodological considerations* section.

Statistical analysis

Sample size calculation is detailed in Appendix S1 in Supplementary Information. Descriptive statistics are reported as counts and percentages for categorical data. Continuous variables are expressed as means with SD or medians with interquartile ranges depending on their distribution. The effect of NHF on endurance time was analysed using a linear mixed model with a random intercept for each participant. In addition to the condition (NHF or control), the following fixed effects were included in the model: condition order and supplemental oxygen requirements. To assess if there was a carry-over effect, we tested whether the difference between the conditions was the same for both condition sequences. The effects of NHF on secondary outcomes were also evaluated using a linear mixed model with a random intercept for each participant, and with the condition and the time of the measurement (isotime or end of exercise) as fixed effects. All models were adjusted for the outcome's measure at baseline, the condition sequence and the need for supplemental oxygen. Interactions were analysed to determine if the difference between NHF and the control condition changed between isotime and the end of the exercise. All analyses were performed using R version 3.5.1 (R project, St. Louis, MI, USA) and the packages, lme4 and emmeans. A two-tailed *P*-value of 0.05 was considered significant for all analyses.

RESULTS

A total of 44 patients were admitted to the Pulmonary Rehabilitation Department between October 2017 and May 2018. All were screened for eligibility for

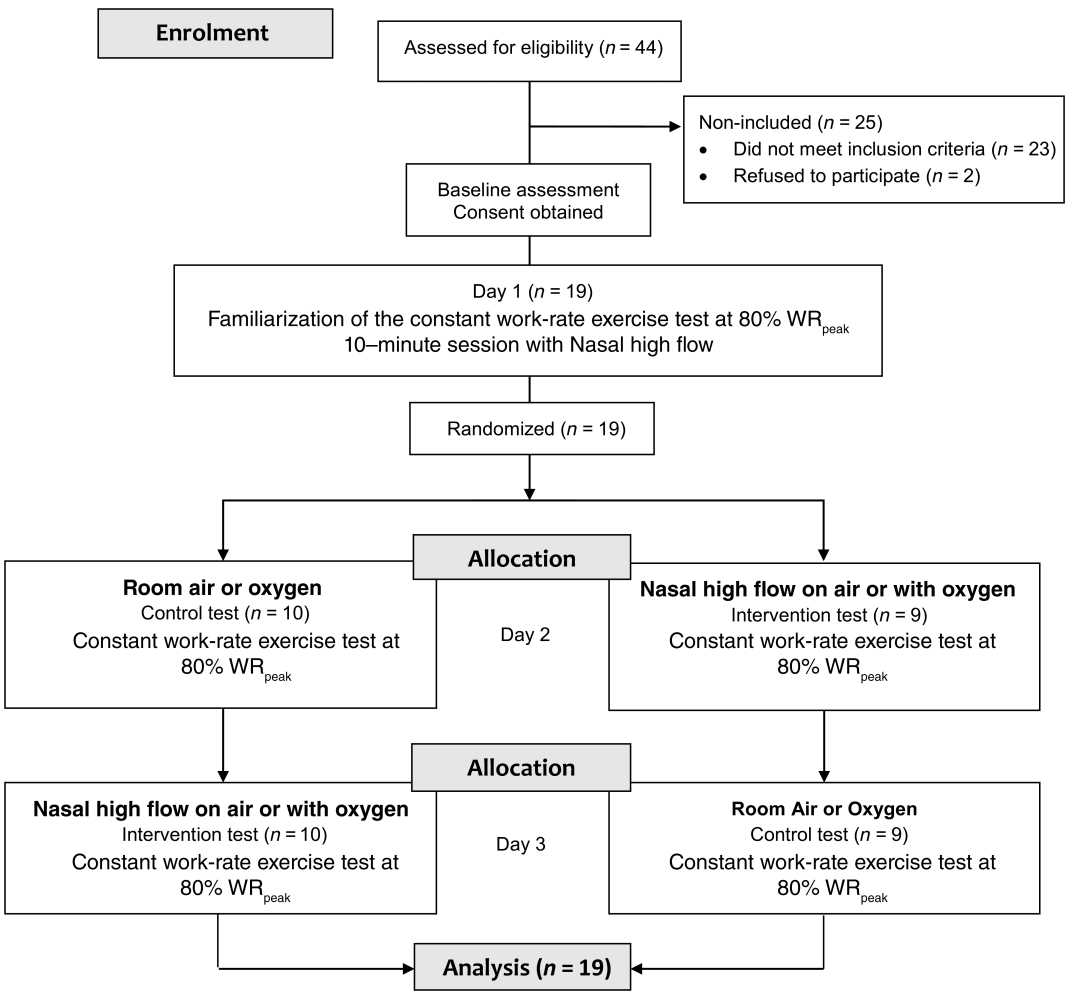

Figure 1 CONSORT diagram of the study population. WR_{peak}, peak work rate.

participation in the study and 19 were included and randomized (Fig. 1). Baseline characteristics of participants are presented in Table 1. The majority of patients included had a GOLD 4 (~74%) and the remaining patients (~26%) had a GOLD 3. Nine patients were receiving LTOT with a mean flow during exercise of 3.3 ± 2.3 L/min corresponding to 0.23 ± 0.03 of FiO_2 on NHF condition. All patients successfully completed both test conditions.

Primary outcome

There were no significant differences in endurance time between the NHF and control conditions (Fig. 2,Table 2). Only two patients increased their endurance time by more than 70 s in the NHF condition (Fig. 2). All patients stopped the exercise due to dyspnoea in both conditions.

Secondary outcomes

The values of the secondary outcomes at isotime and at the end of the exercise are shown in Table 2 and Figure 3.

At isotime, there were no significant differences between the two conditions for SpO_2, HR, $PtcCO_2$, StO_2, RR, dyspnoea or leg discomfort.

HR, $PtcCO_2$ and StO_2 measured at the end of exercise were lower with NHF than in the control condition. Leg discomfort (modified Borg scale) tended to be lower with NHF. There were no differences in dyspnoea between both the conditions.

There was no difference between conditions for the change in MIP at the end of exercise (Table 2).

With regard to device discomfort, the mean rating was 3.9 ± 2.2 out of 10. The device was rated as not or slightly uncomfortable by nine patients (~47%), moderately uncomfortable by seven patients (~37%) and uncomfortable or very uncomfortable by three patients (16%). Only three patients preferred to exercise with the NHF, although the endurance time of these patients reduced by 169 ± 159 s (~26 ± 18%) with NHF compared to the control condition.

Table 1 Baseline characteristics of the 19 patients

	Values	% Predicted value
Sex (M/F)	15/4	
Age	62.1 ± 9.1	
BMI (kg/m^2)	23.9 ± 6.1	
Smoking history (pack-years)	42.6 ± 25.5	
LTOT, *n* (%)	9 (47%)	
Oxygen flow at rest (L/min)	1.5 (1–2)	
Oxygen flow during CWRET (L/min)	3.3 ± 2.3	
Lung function		
FEV_1 (L)	0.86 ± 0.3	28.7 ± 10.8
FVC (L)	2.3 ± 0.6	60.2 ± 14.2
FEV_1/FVC (%)	36 (30–43)	47 (40–57.5)
TLC (L)	6.9 ± 1.8	107.6 ± 23.8
RV (L)	4.3 ± 1.3	187.2 ± 49.3
VR/TLC (%)	59.8 ± 10.7	158.2 ± 29.3
DL_{CO} (mmol/kPa/min)	3.3 ± 1.7	35 ± 19.9
Arterial blood gases (at rest)		
PaO_2 (mm Hg)	69 ± 21	
$PaCO_2$ (mm Hg)	44.2 ± 6	
pH	7.42 ± 0.02	
HCO_3^- (mmol/L)	29.6 ± 3	
SaO_2 (%)	94.3 ± 2.3	
Functional capacity and health status		
WR_{peak} estimated	51.3 ± 24.6	
6MWT (m)	411.3 ± 134.1	
mMRC score	3 (2–4)	
HAD score		
Anxiety	7.7 ± 4.7	
Depression	4 (2–11)	
SGRQ (% maximum)		
Symptoms	64.3 ± 18.6	
Activities	80 (66–88)	
Impacts	41.9 ± 21.3	
Total score	54.8 ± 17.1	

Mean ± SD or median (Q1–Q3). LTOT, FEV_1/FVC, mMRC score, oxygen flow at rest, HAD score (depression) and SGRQ (activities) are expressed as medians (Q1–Q3). Arterial blood gases were collected on room air for patients who were normoxic at rest and were collected under oxygen for patients with LTOT. Oxygen prescription was only for patients who were hypoxaemic at rest based on current recommendation for prescribing LTOT. Nine patients were receiving LTOT prior to the previous exacerbation. None of the prescriptions for oxygen were from the patients' recent admission for exacerbation.

6MWT, 6-min walk test; BMI, body mass index; CWRET, constant work-rate exercise test; DL_{CO}, carbon monoxide transfer factor; F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HAD, Hospital Anxiety Depression; LTOT, long-term oxygen therapy; M, male; mMRC, modified Medical Research Council; $PaCO_2$, arterial partial pressure of barbon dioxide; PaO_2, arterial partial pressure of oxygen; RV, residual volume; SaO_2, arterial saturation of oxygen; SGRQ, St George's Respiratory Questionnaire; TLC, total lung capacity; WR_{peak}, peak work rate.

DISCUSSION

This is the first study to evaluate the effect of NHF during high-intensity exercise on patients with severe COPD following an exacerbation. Contrary to our hypothesis, the use of NHF did not improve endurance time or symptoms (dyspnoea and leg discomfort) at the end of the exercise. However, HR, $PtCO_2$ and StO_2 were all lower with NHF than in the control condition.

Effect of NHF on exercise tolerance

In contrast to the results of the present study, Cirio *et al.* found an increase in endurance time with NHF.[15] In that study, the patients carried out the control test using a Venturi mask relayed to air or oxygen with the aim of providing the same FiO_2 in both conditions. For the patients under oxygen, although the FiO_2 setting was the same at the beginning of the exercise in both conditions, the increase in inspiratory flow during the exercise might have led to a relative drop in FiO_2 with the Venturi mask, in contrast to the NHF that

Table 2 Effects of NHF versus control condition on endurance time and physiological variables

Variables	NHF	Control	Adjusted mean differences (95% CI)	*P*-value
Endurance time (s)	418.5 (273.2 to 563.7)	485 (339.8 to 630.3)	−66.5 (−155.9 to 22.7)	0.119
Isotime				
StO_2 (%)	64.9 (62.9 to 66.9)	65.7 (63.7 to 67.8)	−0.8 (−2.9 to 1.3)	0.444
SpO_2 (%)	93.2 (91.6 to 94.9)	94.0 (92.3 to 95.7)	−0.8 (−1.8 to 0.2)	0.132
HR (bpm)	116.6 (110.0 to 123.1)	114.7 (108.2 to 121.3)	0.7 (−1.5 to 3.0)	0.517
RR (cpm)	28.9 (26.3 to 31.4)	28.3 (25.8 to 30.9)	0.6 (−2.0 to 3.1)	0.673
$PtcCO_2$ (mm Hg)	43.6 (41.2 to 45.6)	44.6 (42.5 to 46.7)	−1.0 (−2.2 to 0.0)	0.057
Breathlessness (mBorg)	5.3 (4.6 to 6.1)	5.2 (4.5 to 5.9)	0.1 (−0.7 to 0.9)	0.782
Leg discomfort (mBorg)	4.5 (3.5 to 5.5)	4.6 (3.6 to 5.6)	−0.1 (−0.7 to 0.5)	0.720
Time limit				
StO_2 (%)	64.9 (62.8 to 66.9)	67.0 (64.9 to 69.0)	−2.1 (−4.3 to −0.0)	0.048
SpO_2 (%)	93.1 (91.4 to 94.8)	93.4 (91.8 to 95.1)	−0.4 (−1.4 to 0.7)	0.481
HR (bpm)	115.8 (109.3 to 122.3)	117.5 (110.9 to 124)	−2.7 (−5.0 to −0.5)	0.019
RR (cpm)	28.4 (25.8 to 30.9)	29.3 (26.7 to 31.8)	−0.9 (−3.5 to 1.7)	0.477
$PtcCO_2$ (mm Hg)	43.7 (41.6 to 45.8)	45.0 (42.9 to 47.1)	−1.3 (−2.5 to −0.2)	0.019
Breathlessness (Borg)	6.0 (5.3 to 6.8)	6.3 (5.6 to 7.1)	−0.3 (−1.0 to 0.5)	0.492
Leg discomfort (Borg)	4.8 (3.8 to 5.8)	5.4 (4.4 to 6.4)	−0.6 (−1.2 to 0.0)	0.053
End of exercise				
MIP (cm H_2O)	90.2 (83.8 to 96.5)	89.9 (83.5 to 96.2)	0.3 (−6.3 to 6.9)	0.917

The results are presented as means (95% CI). The means were calculated using a mixed-effects model with a random intercept for each patient and each condition (NHF and control). The baseline value, measurement time (isotime and time limit), the order of the conditions and oxygen supplementation were fixed effects. The term isotime corresponds to the end of the shortest condition. The term time limit corresponds to the end of the effort in both conditions.

HR, heart rate; mBorg, modified Borg scale from 0 to 10, 0: no fatigue or dyspnoea, 10: maximal effort); MIP, maximal inspiratory pressure; NHF, nasal high flow; $PtcCO_2$, transcutaneous CO_2 pressure; RR, respiratory rate; SpO_2, pulsed O_2 saturation; StO_2, *vastus lateralis* oxygenation.

maintained FiO_2.[17,18] This could explain the large difference in SpO_2 and dyspnoea (rated on the modified Borg scale) between the two conditions at isotime in that study.[15] We chose not to use the Venturi mask as a comparison in our study. Although this choice could be debated, we believe it is more pragmatic as the Venturi mask is not usually used in clinical practice and provides no benefits to patients who are not under oxygen supplementation.

Endurance time tended to be lower in the NHF condition in the present study. Several hypotheses could explain these results: (i) In the NHF condition, SpO_2 and endurance time decreased in five patients receiving LTOT (Fig. S1, Supplementary Information). Although statistical analysis (mixed model) took into account the use or not of additional O_2, it is possible that this SpO_2 decrease has affected endurance time. (ii) Another hypothesis that could explain the lack of effectiveness of NHF on exercise tolerance is that NHF could increase dynamic hyperinflation in patients recovering from an exacerbation.[9,19] Dynamic measures of inspiratory capacity during exercise need to be carried out to test this hypothesis. (iii) This lower performance could be related to the discomfort caused by the device. Over half of the patients considered the device to be moderately to very uncomfortable. The use of a high flow of 60 L/min and the perception self-reported by patients that the inspired air was too hot (despite the fact that it was set at 31°C which corresponds to the minimal possible temperature of the device) might have contributed to the perception of discomfort.[9,10,20]

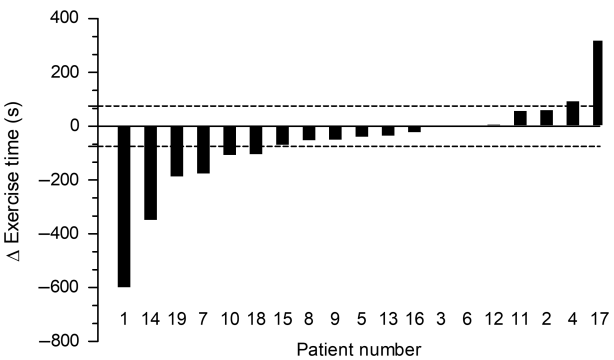

Figure 2 Effect of NHF (with or without oxygen) versus control (oxygen or room air) on endurance time during CWRET at 80% of the peak work rate in patients with severe COPD following exacerbation. Dashed horizontal lines denote the minimally clinically important difference in endurance time chosen for this study (70 s). Δ Exercise time, individual difference in endurance time in the NHF condition (endurance time for NHF condition − endurance time for control condition); COPD, chronic obstructive pulmonary disease; CWRET, constant work-rate exercise test; NHF, nasal high flow.

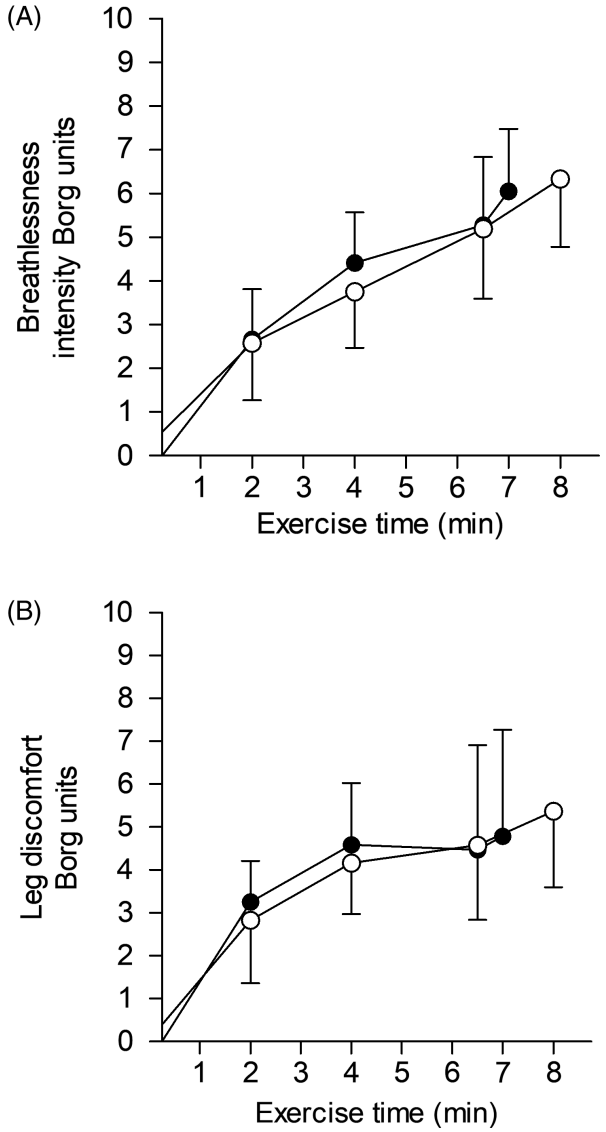

Figure 3 Time course of (A) breathlessness and (B) leg discomfort in the NHF condition (with or without oxygen) versus the control condition (oxygen or room air) during CWRET at 80% of the peak work rate in patients with severe COPD following exacerbation. Data are presented as mean ± SEM. —●—, NHF; —○—, control. COPD, chronic obstructive pulmonary disease; CWRET, constant work-rate exercise test; NHF, nasal high flow.

Effect of NHF on physiological parameters

We hypothesized that by reducing respiratory work,[21,22] the NHF might have improved tissue oxygenation by reducing the metaboreflex.[23,24] However, this is not what our results showed as tissue oxygenation was actually lower at the end of the exercise with NHF. A reduction in MIP after exercise is an indicator of respiratory muscle fatigue in healthy subjects.[25] Although this was a secondary outcome of the study and the result should be considered with caution, it appears that NHF did not increase respiratory muscle strength at the end of the exercise. This lack of difference between the two conditions may be due to (i) bias in the measurement from dynamic hyperinflation in patients with COPD[25] or (ii) mouth opening during exercise that reduces the 'positive end-expiratory pressure (PEEP)' effect.[14,26] Studies involving measurements of oesophageal pressure are required in order to evaluate the effects of NHF on work of breathing during exercise. Finally, the lower leg discomfort, HR and $PtcCO_2$ at the end of the exercise with NHF might simply be the consequence of a shorter endurance time than in the control condition, and the differences measured were not clinically important.

Methodological considerations

Although the number of patients included corresponded to the initial sample size estimation,[16] the SD of the endurance time for the NHF condition was actually higher than the SD used in the calculation of the sample size. This reduced the power of the study and increased the risk of type-2 errors. Another limitation is the fact that the investigator, technicians and patients could not be blinded to the conditions. The reasons for this are: (i) the patient would have noticed the difference between the two tests if no flow or a low flow was administered during the control condition; (ii) the size of the nasal cannula partially obstructs the nostrils; thus, no or a low flow might actually have increased inspiratory resistance and (iii) the noise produced by the device as a function of the flow used would have indicated the condition to the technicians and investigator.

In NHF condition, SpO_2 reduced to <90% in two patients receiving LTOT. This reduction in SpO_2 could be due to the dilution of the oxygen by the device. Oxygen titration should be carried out to either maintain $SpO_2 \geq 90\%$ or the same as the control condition. Moreover, we evaluated the same settings for all patients (60 L/min at 31°C). Studies have shown that a lower flow (20–30 L/min) in patients who are stable at rest is better tolerated than high flow. Further studies are necessary to confirm this result during exercise and to evaluate the impact on endurance.

In conclusion, this study found no significant difference in endurance time during exercise with and without NHF in patients recovering from acute exacerbation of COPD (AECOPD) in contrast to patients in the stable condition. However, future studies must evaluate more precisely the mechanisms of action of NHF during exercise, including different settings and in larger samples.

Data availability statement: All of the de-identified individual participant data collected during the trial are available (no end date). Proposals should be directed to gprieur.kine@gmail.com.

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J.Q., B.L., E.D.L. Supervision: J.Q., B.L., J.-C.B., G.R. Validation: G.P., E.D.L., B.L., J.-C.B., G.R. Visualization: G.P., E.D.L., J.-C.B., G.R., C.M., Y.C. Writing—original draft: G.P., E.D.L., J.-C.B., G.R. Writing—review and editing: C.M., Y.C., F.-E.G., T.B., J.-C.B., G.R., J.Q., B.L.

Abbreviations: 6MWT, 6-min walk test; CWRET, constant work-rate exercise test; FEV_1, forced expiratory volume in 1 s; FiO_2, fractional inspired oxygen; FVC, forced vital capacity; GOLD, Global initiative for chronic obstructive lung disease; HR, heart rate; LTOT, long-term oxygen therapy; MIP, maximal inspiratory pressure; NHF, nasal high flow; NIV, non-invasive ventilation; $PtcCO_2$, transcutaneous CO_2 pressure; RR, respiratory rate; SGRQ, St George's Respiratory Questionnaire; SpO_2, pulsed O_2 saturation; StO_2, *vastus lateralis* oxygenation; TLC, total lung capacity; WR_{peak}, peak work rate.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Methods and analysis.
Figure S1 SpO_2 at isotime for all patients (receiving O_2 or air) in both conditions (NHF and control).
Visual Abstract Nasal High-Flow does not improve exercise tolerance in COPD patients recovering from acute exacerbation