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Effects of heated and humidified high flow gases during high-intensity constant-load exercise on severe COPD patients with ventilatory limitation

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ABSTRACT

Introduction: High flow nasal cannula (HFNC) was shown to washout the anatomical dead space, permitting a higher fraction of minute ventilation to participate in gas pulmonary exchanges. Moreover, it is able to guarantee the desired inhaled oxygen fraction (FiO_2) even at high level of patient's minute ventilation by minimizing the room air entrainment. The effect of HFNC has never been investigated on stable severe COPD patients in term of endurance capacity with standardised laboratory tests.
Method/Design: We performed, in a randomized crossover study, two constant load exercise tests at the 75% of maximum workload achieved at a previous incremental exercise test on cycle-ergometer: with (HFNC-test) and without HFNC (Control-test). Both constant load tests were fulfilled at the same inhaled oxygen fraction (isoFiO_2).
Results: The endurance time significantly increased in the HFNC-test compared to the Control-test (the mean difference between the two groups was 109 ± 104 s, $p < 0.015$). At iso-time, HFNC-test showed a better oxygen saturation (95 ± 3% vs 89 ± 3%, respectively, $p < 0.005$) either in the subgroup of patients who used supplemental oxygen and in the subgroup who did not. Moreover, a significantly lower dyspnea (median of 5.5 vs 10, respectively, $p = 0.002$) and leg fatigue score (median of 5 vs 9.5, $p = 0.002$) was recorded at iso-time during HFNC-test.
Conclusion: HFNC may improve the exercise performance in severe COPD patients with ventilatory limitation. This effect is associated to an improvement of SaO_2 and perceived symptoms at iso-time. In a Pulmonary Rehabilitation program HFNC may allow a given high intensity load to be sustained for a longer time with less symptoms.

1. Introduction

Chronic obstructive pulmonary disease (COPD) patients often complain about exercise limitation as a main symptom, due to a severe dyspnea and/or muscular weakness [1]. Current literature clearly shows the benefit of pulmonary rehabilitation in symptomatic COPD [2,3]. However, these patients are frequently unable to sustain a workload high enough to obtain full benefits from the training program [2]. The most important mechanism underlying the exercise-induced dyspnea is an imbalance between ventilatory capacity and ventilatory demand [2]. The development of hypoxia [4] and the increase of dead space [5] explain to a large extent the out-of-proportion increase in ventilation during effort, reaching prematurely the ventilatory reserve. Recent studies performed on heated and humidified high flow gases delivered through nasal cannula (HFNC), showed to (i) decrease respiratory rate, (ii) increase tidal volume (iii) and reduce the work of breathing [6] in patients with different forms of respiratory failure. The main mechanism of action is the dead space washing-out, permitting a higher fraction of minute ventilation to take part in gas exchange. Moreover, HFNC is able to guarantee the desired inhaled oxygen fraction (FiO_2) even in patients with very high inspiratory flow rates (like during exercise) better than any other oxygen delivery system [6]. We postulated that, in severe COPD patients with exercise

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limitation, the HFNC could improve the efficiency of ventilation, leading to an increase in their exercise performance.

To assess this hypothesis, we performed a randomized crossover study evaluating the effect of HFNC on the endurance time of stable severe COPD patients.

2. Materials and methods

2.1. Participants

This was a single-centre, pilot study with a randomized crossover design performed on 12 clinically stable severe COPD patients admitted to our Pulmonary Rehabilitation Unit for an inpatient exercise training program. Patients with Forced Expiratory Volume in 1 s (FEV1)< 50% of predicted value and a 6-min walked distance <75% of the predicted value [7] associated to a ventilatory limitation were included in the study. Ventilatory limitation was assessed by measuring the Minute Ventilation with a pneumotachograph (Spiropalm®, Cosmed-Italy) during the 6-min walking test and was defined as the ratio of peak-Minute Ventilation and Maximal Voluntary Ventilation (peakVe/MVV) > 70%, or MVV-peakVe < 11 L/min [8]. Exclusion criteria were: left heart failure, pulmonary disorder other than COPD, neuromuscular disease, osteoarticular limitation, recent COPD exacerbation (last three months), recent change in medication status (within 1 month) and anaemia. All enrolled patients signed a written informed consent form. The study protocol was approved by the medical ethics committee of the Fondazione Salvatore Maugeri of Pavia (protocol number 1086).

2.2. Study design

The study was performed in three separate days. On the first day, the patient underwent a symptom-limited incremental exercise test on cycle-ergometer (Ergoselect100P, Cosmed-Italy) in order to assess his/her maximal exercise capacity and to determine the FiO_2 to be used during the two following constant load tests. If oxygen saturation (SaO_2) during the incremental test reached values lower than 85%, the incremental test was repeated with a Venturi mask at a FiO_2 able to maintain a mean SaO_2 during the test higher than 88%. In the following two days, patients performed, in a random order, two constant-load, symptom-limited exercise tests at 75% of maximum workload achieved with the incremental test, with (HFNC-test) and without (Control-test) HFNC. If a Venturi mask was added during the incremental test, the same FiO_2 was kept in both constant-load tests. To minimize the bias due to the unblinded design, the two constant-load tests were performed randomly during the two consecutive days. Moreover, in patients who did not need additional oxygen, Control-test was actually performed with a Venturi mask connected to compressed air in place of oxygen. Because the Venturi mask is not routinely used to give oxygen during exercise in our department, all patients were instructed to receive two different tools (Venturi mask and HFNC) both potentially able to increase their exercise performance. HFNC was administered through nasal cannula (Optiflow™, Fisher&Paykel-NewZealand) using the AIRVO2® (Fisher&Paykel-NewZealand), a turbine-based system able to generate heated and humidified gas flow up to 60 L/min. Adding an oxygen flow-rate to the system, it is possible to ensure FiO_2 from 0.21 (if no oxygen was added) to 1.0 (if the oxygen flow added and the set flow are equal). The system allows to set a Temperature and a Flow and to measure the supplied FiO_2 through an inbuilt ultrasonic analyser. As the expected effects of dead space washout and enhancement of pharyngeal oxygen concentration are both flow-dependent, the Flow was set at the highest value tolerated by the patients up to 60 L/min. In the 24 h between each test, the patient was asked to refrain from exercise and smoking and to avoid caffeine. The endurance time for each constant-load test was recorded (Tlim); furthermore peripheral SaO_2, heart rate (HR), blood pressure (BP), 0–10 Borg scale for dyspnea (Borg-D) and leg fatigue (Borg-F) were recorded every minute until the end of the test.

2.3. Statistical analysis

Results are presented as mean ± SD or median (range). Paired *t*-test for parametrical data or Wilcoxon test for non-parametric data was used to compare each variable in the two constant-load tests, HFNC-test and Control-test, at isotime, defined as the time the shortest test ended. A p-value < 0.05 was considered statistically significant.

3. Results

We enrolled 12 consecutive COPD patients. Anthropometric and functional data are reported in Table 1. There were no dropouts from the study. No adverse events were detected during the incremental test and during the two constant-load tests. Mean workload imposed during the constant-load tests was 44 ± 17 W. Four out of 12 patients performed the tests on ambient air, while the other 8 needed the addition of oxygen with a mean FiO_2 0.44 ± 0.11. The mean flow used during HFNC was 58.7 L/min (range 55–60 L/min).

As showed in Fig. 1, Tlim was significantly higher during the HFNC-test (mean difference of 109 ± 104 s, $p < 0.015$) compared to the Control-test, resulting in a mean increase of 41 ± 36%. At isotime Borg-D and Borg-F were significantly reduced (Fig. 2), while mean SaO_2 significantly increased during HFNC test ($p < 0.005$) (Fig. 3A). Mean SaO_2 was significantly higher during the HFNC-test, both in the subgroup of patients who used oxygen (Fig. 3B) and in the subgroup that did not (89 ± 3% vs 92 ± 3% at isotime, during Control-test and HFNC-test respectively, Fig. 3 C).

4. Discussion

In this pilot study we demonstrated that HFNC was able to significantly improve the duration of exercise in advanced COPD patients with exercise limitation, by improving SaO_2 and reducing symptoms. Surely, due to the lack of measurement of tidal volume and respiratory frequency, this study was not able to explain the mechanism underlying this improvement. However we can speculate that the main mechanism may be the already described reduction of ineffective ventilation due to dead space, that is washed-out by the high flows [9]. In fact, it was demonstrated that exercise intolerance in COPD is partially due to high dead space causing a compensatory and out-of proportion increase in minute

Table 1
Anthropometric and functional data.

Age, yr	70 ± 8
Male:female, n	10:2
FEV1/FVC, %	40 ± 10
FEV1, % predicted	35 ± 12
PaO_2, mmHg	73 ± 13
$PaCO_2$, mmHg	41.7 ± 5.3
peakVe/MVV, %	87 ± 12
MVV-peakVe, L/min	3 ± 4

Data are presented as mean ± SD. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; PaO_2: arterial oxygen tension; $PaCO_2$: arterial carbon dioxide tension; peakVe: maximal minute ventilation at the end of six minute walking test; MVV: maximal voluntary ventilation.

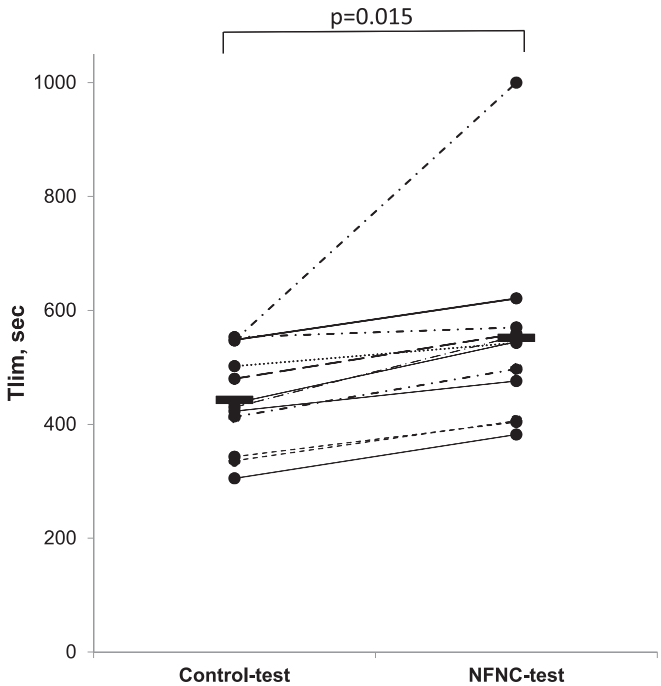

Fig. 1. Effect of the HFNC on exercise capacity during a constant-load test compared to a control condition in which the test was performed at the same FiO_2. In all patient HFNC significantly increased the exercise performance. Tlim = exercise duration. *Solid line* = mean value.

In our study, it is possible that, in the 8 patients needing oxygen, the FiO_2 administered by the Venturi Mask decreased when the patient's peak inspiratory flow during the exercise exceeded the total flow administered by the Venturi system [11]. On the contrary, HFNC, administered almost at the highest available flow (mean flow used: 58.7 L/min), is likely to exceed the patient's peak inspiratory flow-rate in most cases and, consequently, kept constant the administered FiO_2. However, at iso-time mean SaO_2 was significantly higher during the HFNC-test (92 ± 3% vs 89 ± 3%, respectively), also in the 4 patients who performed both tests without additional oxygen. This result suggests that other mechanisms may be implicated in the improvement of the oxygenation, as the continuous flushing of the nasopharyngeal spaces with "fresh gases" which avoid the re-breathing of expired air from the anatomical dead space [6].

All the above described mechanisms, probably lead to a slower increase of minute ventilation during effort and, consequently, a delayed attainment of the patient's MVV. This may explain the significant reduction in Borg-D and Borg-F at iso-time during HFNC-test. However, the improvement of symptoms may also be due to a mild increase of mean expiratory airway pressure, proportional to the delivered flow and dependent on the ability of the patient to keep his/her mouth closed [12]. Differently from the CPAP effect, where airflow resistances during expiration remain relatively constant, HFNC increases resistance to expiratory air. This leads to an increase in peak expiratory pressure (PEP) during the expiratory phase depending on both the size of the nasal pillows and the expiratory flow rate [13]. This end-expiratory positive

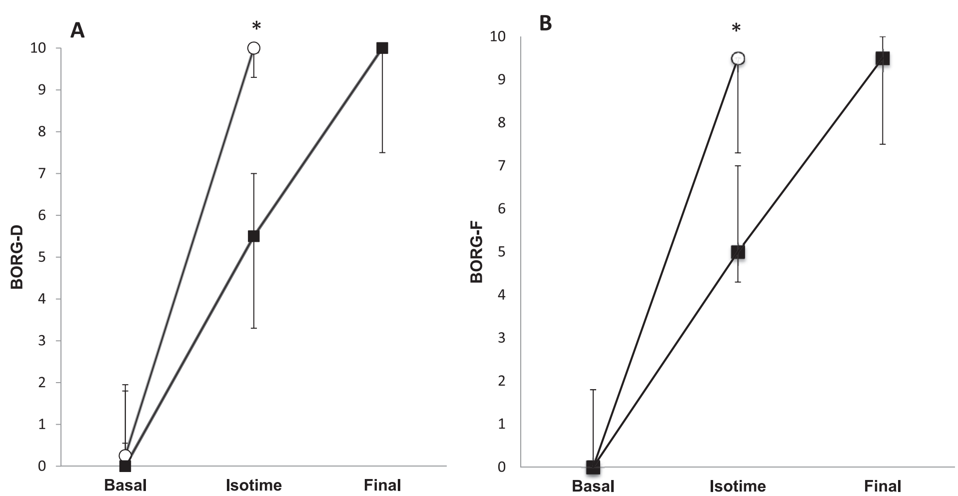

Fig. 2. Borg ratings of dyspnea (A) and leg discomfort (B) during the HFNC test (*solid squares*) and Control-test (*open circles*). Significant difference at isotime was found between the two tests (*p = 0.002). Values are represented as median and range.

ventilation, even in mild COPD [10]. By washing-out the resident gas mixture in the upper airways, HFNC may reduce the increase of ventilation due to dead space, delay the attainment of ventilatory limitation and consequently, may prolong the effort. Another possible explanation of the endurance time extension may be the improvement in oxygenation. In fact at iso-time the SaO_2 was significantly higher during the HFNC-test than in the Control-test, although FiO_2 was kept equal during both tests. This may be due to the high dependence of FiO_2 on the patient's inspiratory flow-rate when using the majority of oxygen delivery systems [11] whereas, in most cases, HFNC can generate flow exceeding the patient's peak inspiratory flow-rate, keeping constant the FiO_2 [12].

pressure may counter-balance the auto-peep generated by the dynamic hyperinflation during the effort, but may also increase the driving pressure [14].

Until now only one previous study has tested the effect on exercise endurance of heated and humidified high flow oxygen (HFO) administered by a different system (Vapoterm©) in 10 COPD with advanced airflow obstruction [15]. Chatila and colleagues' study showed a decrease of respiratory rate, T_I/T_{TOT} ratio and rapid shallow breathing index, resulting in better SaO_2 and longer cycle exercise compared with similar administered FiO_2. However this study differs significantly from ours. In fact, severe COPD patients were enrolled regardless of documented exercise limitation. The

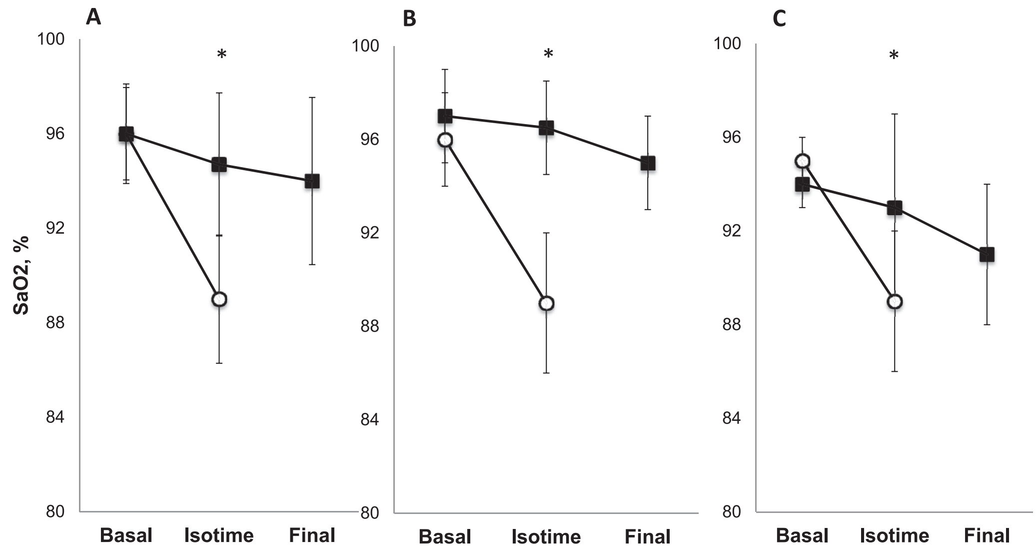

Fig. 3. Oxyhemoglobin saturation (SaO_2) during HFNC-test (*solid squares*) and Control-test (*open circles*) in the whole group (A), in the 8 patients who performed exercise with additional oxygen (B) and in the 4 patients who performed it at FiO_2 of 0.21 (C). In all groups meanSaO_2 at isotime was significantly higher during HFNC-test (*p = 0.0002). Values are represented as mean and standard deviation.

system was used at a flow of 20 L/min and through a mouthpiece. Patients were asked to exercise on an "unloaded" cycle ergometer for up to 12 min, which is not the gold standard test to study the efficacy of a treatment [16]. Moreover oxygen was added to the mouthpiece at a certain predefined flow, which was kept constant during the test and the FiO_2 was measured only at rest. This inevitably leads to a progressive and unknown reduction of the FiO_2 while the patient's inspiratory flow increases during the effort.

The effect of HFNC on the exercise performance in our study is clearly variable (Fig. 1). This may be due to the already described inter-patient variability in the airway pressure generated by the HFNC [14], the ability of the patients to keep their mouth closed and the size of the patient's nares relative to the nasal cannula [9,12,13].

The endurance training represents an important milestone in the rehabilitation program of a COPD patient, whose benefits are proportional to the applied intensity [17]. High intensities are commonly suggested but some individuals may not achieve that, even with close supervision [18]. HFNC may allow a given high intensity load to be sustained for a longer time with less symptoms.

The major limitation of the present study was the inability to measure minute ventilation. We cannot use a pneumotachograph due to the inability to use it during HFNC administration. Moreover the use of inductive plethysmography was limited by the numerous artefacts induced by the exercise movements. However, the aim of the study was to evaluate if there were an additional effect of HFNC on endurance capacity compared to the usual condition (that is either Oxygen or ambient air) at iso-FiO_2. The absence of a measurement of a breathing pattern surely limited the interpretation of the data, but did not affect the result. Another limitation is the lack of blinding, difficult to be performed using the specific device for HFNC. However none of patients had ever used either HFNC or Venturi Mask for Rehabilitation. So they cannot be motivated more from HFNC then from the Venturi device. Moreover we showed a significant improvement in SaO_2 at iso-time that is an objective data not influenced by the motivation.

In conclusion, this pilot study showed that HFNC may improve the exercise performance in severe COPD patients with ventilatory limitation. This effect is associated to an improvement of SaO_2 and perceived symptoms at iso-time. Further research should be considered to better explain the underlying mechanisms, and to explore the effect of addition of HFNC on the outcome of a training programme in this subgroup of patients.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2016.08.004.

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