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# **The effect of heated humidified nasal high flow oxygen supply on exercise tolerance in patients with interstitial lung disease: a pilot study.**

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## **ABBREVIATIONS LIST**

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

COPD, chronic obstructive pulmonary disease

NHF, nasal high flow

FiO<sub>2</sub>, fraction of inspired oxygen

HR, heart rate

NIRS, near-infrared spectroscopy

SpO<sub>2</sub>, pulse oxygen saturation

SmO<sub>2</sub>, muscle oxygen saturation

K-BILD, King's brief interstitial lung disease questionnaire

VM, Venturi-Mask

**Key words:** nasal high flow, interstitial lung disease, endurance time, physiological response, functional symptoms.

## ABSTRACT

**Background and objectives:** Patients with interstitial lung disease (ILD) experience early symptoms of dyspnoea and leg fatigue during exercise together with severe and rapid oxygen desaturation. Heated and humidified nasal high flow oxygen (NHF) has been proven to enhance exercise endurance and physiological parameters in COPD patients. This study aims to evaluate the effect of NHF on exercise tolerance in ILD patients. **Methods:** Twenty-five patients (10 female) with severe ILD performed three constant-load (70% maximal workload) cycling tests to exhaustion under different breathing conditions: room air, oxygen supplementation (4 L·min<sup>-1</sup> O<sub>2</sub>) and NHF (inspiratory O<sub>2</sub> fraction 0.5, 30-50 L·min<sup>-1</sup>, heated 34°C and humidified). **Results:** Endurance time was significantly longer with NHF (618 ± 297 s) compared to O<sub>2</sub> (369 ± 217 s, p < 0.001) and room air (171 ± 76 s, p < 0.001). Kinetics of oxygen desaturation, chronotropic response, dyspnoea and leg fatigue sensations were delayed with NHF. At exhaustion with NHF, compared to the two other conditions, oxygen desaturation was less severe while heart rate, dyspnoea and leg fatigue were similar. **Conclusion:** NHF significantly improved endurance time, physiological parameters and sensations during exercise in severe ILD patients. NHF may be useful to improve functional capacities and facilitate pulmonary rehabilitation in ILD.

## INTRODUCTION

Interstitial lung disease (ILD) represents a heterogeneous group of rare disorders that include more than 200 entities characterized by inflammation and/or fibrosis of the lung parenchyma.<sup>1</sup> ILD can lead to progressive symptoms of dyspnoea, cough, and exercise intolerance.<sup>2,3</sup> Among those with advanced fibrotic ILD, severe hypoxemia is common.<sup>4</sup> Idiopathic pulmonary fibrosis (IPF) is the most common ILD, affecting five million persons worldwide.<sup>5,6</sup> IPF is a progressive, irreversible, and fatal fibrosing lung disease with a median survival of 2–5 years from diagnosis.<sup>7</sup>

Clinical guidelines on the management of ILDs are subject to limitations imposed by current gaps in knowledge. In recent years, there have been controlled trials leading to the approval of two antifibrotic agents for the treatment of IPF.<sup>8,9</sup> Important priorities for individuals with fibrotic ILD include improving dyspnoea, exercise capacity, and health-related quality of life.<sup>10</sup> Supplemental oxygen is commonly prescribed in routine clinical practice with these goals in mind.<sup>11,12</sup> However, several studies have failed to identify symptomatic or physiological benefits of oxygen therapy in ILD.<sup>13,14</sup>

Patients requiring a high inspiratory oxygen fraction ( $\text{FiO}_2$ ) are hampered by the available oxygen delivery systems: the nasal cannula, a low-flow system geared to the oxygen requirement at rest and with limited activity. However, at high flows (e.g.,  $6 \text{ L}\cdot\text{min}^{-1}$ ), the nasal cannula is poorly tolerated because of nasal dryness, crusting, and epistaxis.<sup>15</sup> Heated and humidified nasal high-flow oxygen therapy (NHF, also known as high-flow nasal cannula, or nasal high flow) has

become a promising novel approach to respiratory support in clinical settings for respiratory patients. Multiple physiological benefits of NHF have been demonstrated, such as providing stable inspiratory oxygen concentration,<sup>16</sup> increasing tidal volumes,<sup>17</sup> washing out dead space,<sup>18</sup> reducing work of breathing,<sup>19</sup> allowing sufficient humidification,<sup>20</sup> and positive airway pressure effect.<sup>21</sup> NHF has been shown to provide greater clinical benefits than conventional oxygen therapy in COPD patients.<sup>22</sup> During exercise, the observed clinical effects of NHF in patients with COPD include improvements in exercise tolerance, oxygenation, dyspnoea and muscle function.<sup>23-26</sup> The indication for NHF is mainly hypoxemia with a need for long-term oxygen therapy with an FiO<sub>2</sub> higher than 40% or a flow rate  $\geq 4 \text{ L}\cdot\text{min}^{-1}$ . NHF studies in ILD have shown reduced breathing rate at rest<sup>17</sup> and reduced short-term mortality rate in acute respiratory failure.<sup>27</sup> Only one study evaluated the effect of NHF during exercise in patients with fibrotic ILD and reported no significant improvement in exercise endurance with NHF compared to conventional oxygen therapy with a Venturi-Mask (VM).<sup>28</sup> Further investigations are however required to determine the functional and physiological consequences of NHF applied during exercise in ILD patients.

This study aims to evaluate the effect of NHF *versus* standard  $4 \text{ L}\cdot\text{min}^{-1}$  oxygen supplementation in ILD patients during exercise. We hypothesize that NHF would increase endurance time in ILD patients while improving physiological responses and symptoms compared to both room air and oxygen supplementation.

## **METHODS**

### **Subjects**

Twenty-five patients with a diagnosis of ILD confirmed by clinical and imaging data were recruited before initiating a pulmonary rehabilitation program in our institution. All subjects were fully informed about the study and signed a written informed consent before inclusion. This study was approved by a French ethics committee (CPP SUD-EST II, IDRCB number: 2019-A02104-53) and was conducted in accordance with the Declaration of Helsinki.

### **Study design**

The patients performed two testing sessions over two consecutive days. The first testing session consisted in a cardiopulmonary exercise test in room air to determine maximal cycling exercise responses. The protocol consisted of a 1-min warm-up at 10 W followed by 10 W increment every minute until symptom limitation. During the second testing session, the patients performed three endurance cycling tests at 70% of the maximal workload recorded during the first testing session (with an initial 30-sec warm-up at 0 W), in the following order: a first test while breathing room air, a second one breathing supplemental oxygen (4 L·min<sup>-1</sup>, nasal cannula, which is the highest flow tolerated in many patients under oxygen therapy<sup>15,29</sup>) and a third one using NHF. A 1-hour recovery period was allowed between two tests. Since the second and third exercise tests were expected to last longer and therefore to induce more fatigue, they were performed successively following the room air test. The tests took place between 1:30 pm and 5

pm. The patients were told the second and third tests were performed to assess the effect of oxygen supplementation but the principle of NHF was not explained to circumvent a placebo effect. The endurance cycling tests ended when the patient could not maintain a pedalling frequency >60 rpm or cycled for 20 min. NHF was provided through nasal cannula by an AIRVO™2 system (Fisher & Paykel, Auckland, New Zealand). High flow oxygen supply was heated at 34°C, 100% humidified and delivered with high flow between 30 and 40 L·min<sup>-1</sup> (depending on the patient's highest tolerated flow). A minimal expiratory positive pressure between 1.5 and 5.3 cmH<sub>2</sub>O was assured using adapted nasal cannulas. FiO<sub>2</sub> was fixed at 0.5 based on previous studies in COPD<sup>30-31</sup> and ILD<sup>28</sup> patients during exercise.

### **Measurements**

Subjects exercised on a computer-controlled electronically-braked cycle ergometer (Medisoft ergometer, Leeds, United Kingdom). Pulse oxygen saturation (SpO<sub>2</sub>) and heart rate (HR) were measured continuously (Onyx Vantage 9590 fingertip pulse oximeter, Nonin, Plymouth, USA). Dyspnoea and leg fatigue were assessed with a 0-10 category Borg scale.<sup>32</sup> Muscle oxygenation (SmO<sub>2</sub>) of the right *rectus femoris* was assessed using a previously validated near infra-red spectroscopy system (NIRS, Humon hex, Boston, USA).<sup>33</sup> The *rectus femoris* was chosen as the muscle to monitor in order to minimize fibre movement since this is the area of the leg where the fibres would remain most stable.<sup>33</sup> Quality of life was assessed using the validated King's brief interstitial lung disease questionnaire (K-BILD)<sup>34</sup>.

### **Statistical Analysis**

Power assessment for the primary outcome (change in exercise endurance) was based on a minimum expected improvement of 50% with NHF *versus* room air. With an  $\alpha$  level of 5% and

power of 90%, 20 patients were required. To account for potential drop-outs, 25 patients were recruited. In order to assess the effect of the conditions (room air *versus* oxygen supplementation *versus* NHF) on exercise endurance, a one-way ANOVA with Tukey post-hoc comparison was performed. In order to assess the effect of the condition on physiological responses and sensations during exercise, two-way (time  $\times$  conditions) ANOVA for repeated measurements with Tukey post-hoc comparison was performed for each dependent variable. Correlations were evaluated by Pearson coefficient. For all statistical analyses, a two-tailed alpha level of 0.05 was used as the cut-off for significance. Data are presented as mean  $\pm$  SD. All statistical procedures were performed on SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY).

## **RESULTS**

### **Participants' characteristics (Table 1)**

Seventy two percent of participants had IPF. Overall, patients had severely impaired lung function and low quality of life. Seventy two percent of them were under long-term oxygen therapy.

### **Effect of NHF on exercise endurance time**

Individual and group changes in endurance time are provided in figure 1. Patients' endurance time was significantly improved by oxygen supplementation compared to room air and by NHF compared to oxygen supplementation. Endurance time was improved by  $216 \pm 285\%$  under 4 L $\cdot$ min<sup>-1</sup> oxygen supplementation and by  $361 \pm 391\%$  under NHF compared to room air. All

patients had longer endurance time under 4 L·min<sup>-1</sup> oxygen supplementation and even longer under NHF compared to room air. Twenty-four and 18 out of 25 patients had an increase in endurance time >100 s with NHF and oxygen supplementation compared to room air, respectively. Twenty-two out of 25 patients had an increase in endurance time >100 s with NHF compared to 4 L·min<sup>-1</sup> oxygen supplementation. One patient cycled for 20 min (the limit of the protocol) under oxygen supplementation and NHF, three other patients cycled for 20 min under NHF.

### **Effect of NHF on physiological responses**

Pulse and muscle oxygen saturation at rest were higher under 4 L·min<sup>-1</sup> oxygen supplementation and even higher under NHF compared to room air (figure 2). SpO<sub>2</sub> stayed higher during the whole test, at iso-time and at the end of the test, with NHF compared to 4 L·min<sup>-1</sup> oxygen supplementation and room air. Under NHF, SpO<sub>2</sub> at exhaustion was > 90% in 17 patients (68%). At rest, HR was lower under 4 L·min<sup>-1</sup> oxygen supplementation and NHF compared to room air (figure 3). This was also true at iso-time, but the three tests ended at similar HR.

### **Effect of NHF on dyspnoea and leg fatigue perception**

At rest, dyspnoea and leg fatigue sensations were similar between the three conditions and then they increased during exercise (figure 4). Dyspnoea and leg fatigue sensations were less severe at iso-time under 4 L·min<sup>-1</sup> oxygen supplementation compared to room air and further more with NHF, but the tests ended with similar levels of dyspnoea and leg fatigue under the three conditions. Sixteen patients (64%) ended their NHF test with greater leg fatigue or lesser dyspnoea compared to the end of the test with 4 L·min<sup>-1</sup> oxygen supplementation. The other nine

patients (36%) ended their NHF test with the same leg fatigue and dyspnoea levels as the end of their test with 4 L·min<sup>-1</sup> oxygen supplementation.

## **DISCUSSION**

Our results show that cycling endurance time is prolonged using standard 4 L·min<sup>-1</sup> oxygen supplementation and furthermore under NHF in severe ILD patients. This greater exercise endurance with NHF is associated with less reduction in SpO<sub>2</sub> and SmO<sub>2</sub> and delayed increase in HR and dyspnoea and leg fatigue sensations. These results suggest that NHF may be a useful tool to improve functional capacities in ILD patients.

The increase in dyspnoea and leg fatigue was significantly delayed and less severe at iso-time with NHF compared to both 4 L·min<sup>-1</sup> oxygen supplementation and room air conditions. This may be due to a larger inspiratory oxygen supply (i.e. higher FiO<sub>2</sub>) and subsequent improvement in arterial blood oxygenation and oxygen delivery to the muscles as demonstrated by arterial and muscle oxygen saturation measurements. Interestingly, this study demonstrates the low muscle oxygenation of ILD patients both at rest (50 ± 8%) and at end of exercise (44 ± 11%) compared to both healthy subjects (usually >60%) and patients with COPD and chronic heart failure (usually >55%) under room air.<sup>35</sup> The lower HR at isotime with NHF also indicates that a lower chronotropic response and cardiac output increase were required for a given submaximal exercise intensity, therefore contributing to improved sensations and greater cardiorespiratory reserve to cycle longer. Meanwhile, HR was similar at the end of the three tests, suggesting that patients provided similar effort and reached the same maximal cardiovascular responses in the

three tests. They also ended the three tests with the same levels of dyspnoea and leg fatigue further suggesting that they provided maximal effort in the three tests. Most patients ended the NHF test with higher leg fatigue or lower dyspnoea level compared to standard 4 L·min<sup>-1</sup> oxygen supplementation, suggesting they were able to recruit their muscles to a greater level before being limited by dyspnoea as compared to exercise condition with standard 4 L·min<sup>-1</sup> oxygen supplementation .

Patients expressed comfort that can be resulting from the humidified and heated delivery system and the high flow that can reduce respiratory rate together with the potential beneficial effect of continuous positive pressure. Indeed, based on the literature of the NHF delivery system, heat and humidification reduce dryness and add comfort to breathing.<sup>36</sup> The high flow rate may also decrease physiological dead space by flushing expired carbon dioxide from the upper airway, a process that may partly explain the decrease in the work of breathing.<sup>37</sup> In patients with acute respiratory failure of various origins, NHF has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask.<sup>38,39</sup> Hence, although the present study cannot distinguish the respective role of each mechanism, the large FiO<sub>2</sub>, the high flow of air delivery as well as the heating and humidifying of the air delivered are all factors potentially contributing to the improved exercise tolerance in severe ILD patients.

Previous studies have evaluated the effect of NHF on endurance time in COPD patients<sup>24,40,41</sup> showing that NHF led to longer endurance time than VM, exceeding the minimal clinically significant difference of 100 seconds.<sup>42</sup> In our study, the effect of NHF is greater than the one observed in the COPD studies mentioned above which might be due to differences in disease related pathophysiological manifestations (obstructive *versus* restrictive diseases) and exercise

desaturation (known to be generally more severe in ILD than in COPD patients<sup>43</sup>) between COPD and ILD<sup>44</sup> but also to the difference in methods since we compared NHF to room air and the standard 4 L·min<sup>-1</sup> oxygen supplementation by nasal cannula. Only one previous study evaluated the effect of NHF on endurance time in ILD patients by comparing NHF (FiO<sub>2</sub> 0.5) to VM (15 L·min<sup>-1</sup>, FiO<sub>2</sub> 0.5) in a small group of ILD patients<sup>28</sup>. In that study, no significant difference in endurance time was found in the whole group of patients, but in a subgroup of responders NHF induced greater improvement in exercise endurance than VM. These results suggested that the larger FiO<sub>2</sub> is the main mechanism underlying the improvement in exercise tolerance with NHF, despite other specificities of NHF (i.e. high-flow, humidification, heating, positive end-expiratory pressure) that may provide additional benefits. Our study, by comparing the use of NHF to usual oxygen supplementation strategies, i.e., standard 4 L·min<sup>-1</sup> oxygen supplementation through nasal cannula, demonstrates for the first time a large improvement in exercise tolerance induced by heated humidified high-flow oxygen delivery through nasal cannula. These pilot data cannot however determine the mechanisms underlying this improvement in exercise endurance.

As regards to clinical implications, we proved that NHF can lead to longer endurance time compared to standard 4 L·min<sup>-1</sup> oxygen supplementation and room air, while improving physiological parameters and functional symptoms. Further studies are needed to evaluate the effect of using NHF during exercise training in the context of pulmonary rehabilitation in ILD patients, since it has been proven effective in severe COPD pulmonary rehabilitation.<sup>39,45</sup>

This study has several limitations. Firstly, the non-blinded setting could create a placebo effect. This potential bias was reduced by providing no information to the patients regarding the effect

of NHF. Secondly, the non-randomized order of the tests may induce a learning effect or may lead to fatigue accumulation. Since patients started the three tests with the same level of dyspnoea and leg fatigue, this suggests that the 1-hour break was sufficient to recover from one exercise test to another. In addition, if fatigue may have accumulated from one test to another, it would have led to an underestimation of the effect of NHF compared to room air and standard 4 L·min<sup>-1</sup> oxygen supplementation. Despite this potential fatigue effect, the improvement in cycling endurance with NHF was substantially larger than the minimal clinically significant difference of 100 seconds.<sup>42</sup> Thirdly, it could be suggested that higher oxygen flow should have been used (e.g., 6-10 L·min<sup>-1</sup>) to compare the effect of high flow humidified heated delivery system. Four-litre oxygen supplementation was chosen however as being the highest flow usually tolerated by patients based on our experience and previous observations.<sup>15,29</sup> Fourthly, ventilation and respiratory mechanics could not be measured in the present study and should be evaluated in future studies to further clarify the mechanisms leading to better exercise tolerance with NHF in ILD patients.

In conclusion, these preliminary results show that NHF improves exercise endurance in ILD patients while reducing dyspnoea and leg fatigue sensations, and correcting oxygen saturation. Future studies are needed to clarify the effect of NHF on exercise responses but also to determine whether NHF may be a useful tool for facilitating exercise training in this population of respiratory patients.

**Guarantor:** YAC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

**Author contributions:** YAC, DV, FH, and SV contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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**Table 1.** Characteristics of the ILD patients

	n or mean $\pm$ SD
Disease category	18 IPF/ 7 other
LTOT	18 yes / 7 no
Sex	15 ♂ / 10 ♀
Age (years)	72.8 $\pm$ 6.7
BMI (Kg·m <sup>-2</sup> )	25.2 $\pm$ 5.7
K-BILD	55.9 $\pm$ 22.0
FVC (% predicted)	62.2 $\pm$ 19.6
FEV1 (% predicted)	67.5 $\pm$ 22.0
DLCO (% predicted)	55.6 $\pm$ 24.5
PaO <sub>2</sub> (kPa)	8.3 $\pm$ 1.4

Data are mean  $\pm$  SD or n. IPF, idiopathic pulmonary fibrosis; other: one lymphangiomyomatosis, one dermatomyositis, one silicosis, one scleroderma, 2 hyper-sensibility and one genetic mutation; LTOT: long term oxygen therapy; BMI, body mass index; K-BILD, King's brief interstitial lung disease questionnaire; FVC, forced vital capacity; FEV1: forced expiratory volume in the 1<sup>st</sup> second. DLCO: lung diffusing capacity for carbon monoxide; PaO<sub>2</sub>: arterial oxygen partial pressure.

## Figure legends

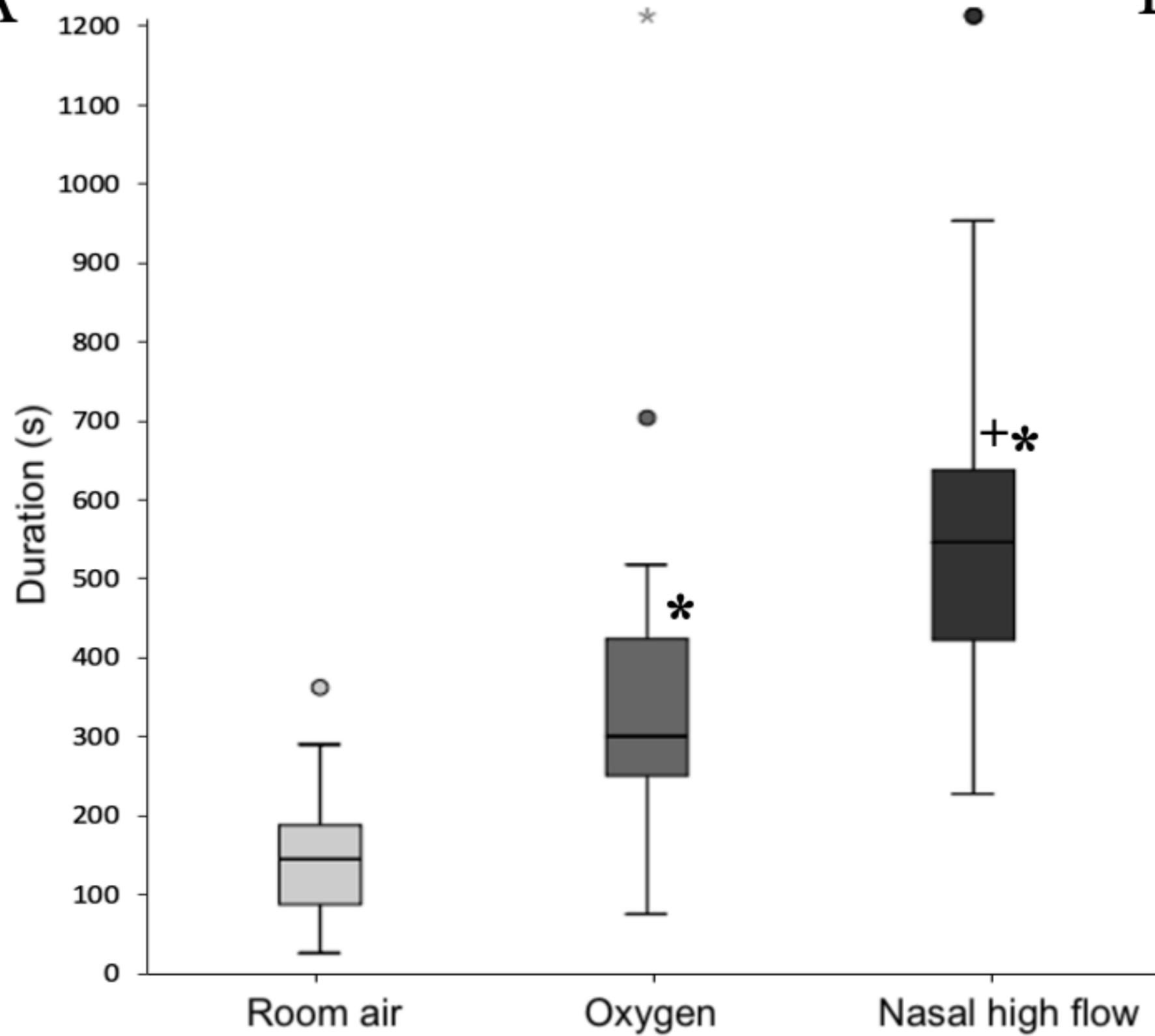
**Figure 1.** Exercise duration under three different conditions of oxygen supply (room air, standard oxygen supply at 4 L·min<sup>-1</sup> and nasal high flow oxygen supply heated humidified and with an inspired oxygen fraction of 0.5). Panel A, box plot for the whole group of patients; Panel B, individual cycling durations. Box plot anatomy: the horizontal line inside the box represents the median, the upper and lower lines of the box represent the upper and lower quartiles, and the highest and lowest lines at the end of the vertical represent the maximum and minimum endurance time. Points outside the boxplot reflect the extreme values. \* significantly different compared to room air ( $p < 0.001$ ); + significantly different compared to standard oxygen supplementation ( $p < 0.001$ ).

**Figure 2.** Pulse and muscle oxygen saturation under three different conditions of oxygen supply (room air, standard oxygen supply at 4 L·min<sup>-1</sup> and nasal high flow oxygen supply heated humidified and with an inspired oxygen fraction of 0.5). Panel A, pulse oxygen saturation (SpO<sub>2</sub>); Panel B: muscle oxygen saturation (SmO<sub>2</sub>). The four time points (and horizontal SD bars) correspond for each individual to rest, end of the ambient air condition, end of the oxygen supplementation condition and end of the NHF condition. \* significantly different compared to room air ( $p < 0.05$ ); + significantly different compared to standard oxygen supplementation ( $p < 0.05$ ).

**Figure 3.** Heart rate (HR) under three different conditions of oxygen supply (room air, standard oxygen supply at 4 L·min<sup>-1</sup> and nasal high flow oxygen supply heated humidified and with an inspired oxygen fraction of 0.5). The four time points (and horizontal SD bars) correspond for

each individual to rest, end of the ambient air condition, end of the oxygen supplementation condition and end of the NHF condition. \* significantly different compared to room air ( $p < 0.05$ ); + significantly different compared to standard oxygen supplementation ( $p < 0.05$ ).

**Figure 4.** Dyspnoea and leg fatigue perception assessed with a 0-10 category Borg scale under three different conditions of oxygen supply (room air, standard oxygen supply at  $4 \text{ L}\cdot\text{min}^{-1}$  and nasal high flow oxygen supply heated humidified and with an inspired oxygen fraction of 0.5). Panel A, dyspnoea; Panel B: leg fatigue. The four time points (and horizontal SD bars) correspond for each individual at rest, end of the ambient air condition, end of the oxygen supplementation condition and end of the NHF condition. \* significantly different compared to room air ( $p < 0.05$ ); + significantly different compared to standard oxygen supplementation ( $p < 0.05$ ).

**A****B**