

Real-world data on home high-flow nasal cannula oxygen therapy in end-stage respiratory disease

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Abstract

High-flow nasal oxygen therapy (HFNOT) is a cornerstone treatment modality in severe acute hypoxemic respiratory failure, with benefits in improving oxygen deficit while normalizing breathing rate and having an effect on airway humidification. These physiological effects indicate a potential benefit in end-stage chronic respiratory failure. We aimed to assess the clinical impact of home HFNOT in reducing both exacerbation rates and overall disease burden in end-stage chronic respiratory disease. We designed a retrospective study including patients followed in the pulmonology department of a tertiary center who started home HFNOT until June 2023. Pre- and post-home HFNOT exacerbations and hospital admissions were registered, and each patient served as their own control for the statistical analysis. In total, 36 patients were included in the study: 24 patients (66.7%) with interstitial lung disease and 12 (33.3%) with obstructive lung disease. Overall, the median titrated fraction of inspired oxygen was significantly lower in obstructive patients; no significant differences were found between groups regarding titrated airflow. Obstructive patients had a significantly higher number of pre-treatment exacerbations and hospital stays. Both clinical subgroups presented fewer median overall post-treatment exacerbations and hospital admissions vs. pre-treatment start. Although mortality was high, home treatment was well tolerated by most patients, with only one patient interrupting high-flow therapy due to intolerance. Home HFNOT proved to be an overall feasible treatment strategy for patients with end-stage respiratory disease. Obstructive lung disease patients benefited the most from the treatment, possibly due to hypercapnia correction.

Key words: high-flow nasal oxygen, COPD, ILD, respiratory failure.

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Introduction

High-flow nasal oxygen therapy (HFNOT) has seen an exponential usage growth in the context of severe acute hypoxemic respiratory failure in recent years. Particularly since the SARS-CoV-2 pandemic, implementation of this treatment modality has grown outside of the scope of just intensive care units, becoming an applicable option in general medical wards for the management of severe respiratory distress in patients that are not candidates for intubation and subsequent invasive mechanical ventilation. By supplying a relatively high flow of heated, humidified and, optionally, oxygen-enriched air to the upper airway of a patient *via* a nasal cannula, HFNOT provides non-invasive respiratory support to patients ranging from neonates to adults [1]. While initially developed for preterm infants as an alternative to continuous or bi-level positive airway pressure therapy, its application in other pediatric settings such as acute respiratory distress, asthma and post-extubation support led to further developments in the adult setting, mainly hypoxemic respiratory failure [2-5]. Well-recognized benefits in improving oxygen deficit

while also normalizing breathing rate by reducing inspiratory effort [6], with added benefits on airway humidification, have led to an increase in HFNOT usage in exacerbations of chronic respiratory diseases [7,8]. Because of these physiological effects, it is hypothesized that HFNOT might be of value outside of exacerbations. Several studies examined the effect of HFNOT in chronic obstructive pulmonary disease (COPD), with most evidence for its long-term use in hypoxemic COPD patients that frequently exacerbate [9,10]. Since 2017, home prescription of HFNOT through the national healthcare system is possible in Portugal, provided the patients' respiratory well-being is no longer achievable with conventional long-term oxygen therapy (COT) alone.

With this study, we aimed to assess the clinical impact of home HFNOT in reducing both exacerbation rates and overall disease burden in end-stage chronic respiratory disease. Additionally, this study aims to demonstrate the feasibility of employing HFNOT in an outpatient setting, characterizing a population in which this was achieved after failure of other COT modalities.



Materials and Methods

Retrospective cohort study included patients ≥ 18 years old who were started on home HFNOT in the context of end-stage respiratory disease, defined as chronic respiratory disease associated with COT-refractory chronic hypoxic or mixed respiratory failure, between October 2017 and June 2023 in a tertiary hospital. Only stable patients who were adapted to HFNOT in an ambulatory setting were considered. Patients were considered candidates for HFNOT if fully adherent to both pharmacological and non-pharmacological (COT, pulmonary rehabilitation program) treatment modalities, except for intolerance to non-adherence to continuous/bi-level positive airway pressure. Patients concomitantly using positive airway pressure therapy were excluded from the final analysis.

All patients were adapted using a myAirvo™ 2 device (Fisher & Paykel Healthcare, Auckland, New Zealand), which was then issued for personal home usage. The myAirvo™ 2 device is a humidifier with an integrated flow generator that delivers high flow, warmed, and humidified respiratory gases to spontaneously breathing patients. During adaptation, both the fraction of inspired oxygen (FiO_2) and airflow were titrated according to the patients' peripheral oxygen saturation (SpO_2) and carbon dioxide (CO_2) levels using both an oximeter and a transcutaneous CO_2 monitor, while considering overall personal tolerance. Air temperature varied between 31 and 34 degrees Celsius according to the patients' level of comfort. Due to the terminal nature of each patient's chronic lung disease, treatment was prescribed for a minimum usage of 16 hours daily.

Besides general demographic data, clinical data, including specific respiratory disease diagnosis, smoking status, arterial blood gas (ABG) analysis, and pulmonary function testing, were collected. ABG analysis was conducted immediately prior to HFNOT adaptation and between 4 and 5 weeks after the start of treatment. Pre- and post-home HFNOT exacerbations and hospital admissions were registered; regarding events prior to HFNOT, only exacerbations and hospital admissions occurring in the previous 12 months were considered. Exacerbations were defined as aggravated respiratory symptoms leading to an emergency department admission and subsequent need for active treatment. Only hospital admissions related to worsened respiratory symptoms were considered – while all admissions represented exacerbations in this context (severe exacerbations), not all exacerbations led to hospital admission (mild to moderate exacerbations). Since this severity stratification score applies mostly to COPD patients, the total number of exacerbations,

rather than the proportion of each severity grade, was used to generally evaluate outcomes in the overall population.

The SPSS 28.0 package (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables are expressed as mean and standard deviation or median and interquartile range. Qualitative variables are indicated as absolute values and percentages. Normality in the distribution of variables was assessed by using the Kolmogorov-Smirnov test. T-student and Mann-Whitney tests were applied for continuous variables and the chi-square test was used to compare categorical variables. The Wilcoxon signed-rank test was used to test differences between non-parametric related data.

Results

A total of 36 patients were included in the study, the majority male (61.1%). The mean age at the start of home HFNOT was 65.5 ± 11.6 years old. Most of the sample had a clinical background of interstitial lung disease (ILD) (66.7%; $n=24$), followed by COPD (33.3%; $n=12$); 2 patients (5.6%) in the ILD subgroup presented pulmonary hypertension. Table 1 presents all chronic respiratory clinical diagnoses for the overall sample. Most patients were either former or active smokers (69.4%). Both patients who were active smokers ($n=2$) prior to HFNOT initiation stopped smoking at the start of treatment. All COPD patients were under triple inhaler therapy. All fibrotic ILD patients ($n=22$) were actively treated with antifibrotic therapy (either pirfenidone or nintedanib); patients with fibrotic hypersensitivity pneumonitis were concomitantly treated with immunosuppressants. All patients had integrated some rehabilitation program throughout their chronic respiratory disease follow-up. However, at the time of home-HFNOT adaptation and thereafter, only patients actively listed for lung transplantation ($n=14$; 38.9%) remained in-program. Four patients (11.1%) were concomitantly followed by palliative care in an outpatient setting.

Prior to the start of HFNOT, all patients had been prescribed COT for a minimum of 16 hours daily. While all ILD patients progressed from pulsatile oxygen concentrators (POC) towards liquid oxygen devices (6-15 L/min) due to sustained hypoxemia requiring higher FiO_2 , only half the patients with COPD required FiO_2 debits higher than those provided by POC (setting 5). Additionally, all hypercapnic COPD patients (58.3%) were first adapted to bi-level positive airway pressure therapy, and only after treatment cessation due to intolerance was HFNOT started. All patients presented hypoxemic respiratory failure at the time of HFNOT adaptation; additionally, 36.1% ($n=13$) presented concomitant hypercapnic respiratory failure. While overall median arterial pH was 7.427 (7.320-7.518), less than half the patients (47.2%; $n=17$) maintained a pH within the standardized normal range (7.35-7.45); most uncorrected acid-base disturbances were related to respiratory alkalosis (38.9%; $n=14$) and, less frequently, respiratory acidosis (13.9%; $n=5$). Median overall SpO_2 assessed during room air was 85.3% (60.0-97.0); other ABG analysis parameters are described in Table 2.

Median time from respiratory-related outpatient follow-up to home HFNOT start was 35 months (2-141). Overall median titrated FiO_2 was 45% (30-70) and significantly different between ILD patients and COPD patients, with ILD patients presenting a median titrated FiO_2 of 50% (30-70) vs. 35% (30-65) for COPD patients ($p=0.035$). No statistically significant differences in FiO_2 were found concerning the presence/absence of pre-treatment acid-base disturbances, either corrected or sustained. Median titrated airflow

Table 1. Chronic respiratory disease diagnosis according to major clinical subgroup.

Diagnosis	
Interstitial lung diseases	24 (66.7)
Fibrotic hypersensitivity pneumonitis	8 (22.2)
Idiopathic pulmonary fibrosis	5 (13.9)
Fibrotic non-specific interstitial pneumonia	4 (11.1)
Connective tissue disease-related interstitial lung disease	4 (11.1)
Desquamative interstitial pneumonia	1 (2.8)
Pulmonary alveolar proteinosis	1 (2.8)
Unclassifiable fibrotic interstitial lung disease	1 (2.8)
Chronic obstructive pulmonary disease	12 (33.3)
With concomitant bronchiectasis	2 (5.6)
With concomitant lung cancer	1 (2.8)

Qualitative variables presented as absolute number (percentage).



Table 2. Baseline characteristics of the sample, according to clinical subgroup.

	ILD subgroup (n=24)	COPD subgroup (n=12)	TOTAL (n=36)
Age at HFNOT start (years)	65.0 (8.0)	66.5 (17.0)	65.5 (11.6)
Sex (male)	15 (62.5)	7 (58.3)	22 (61.1)
Smoking Status			
Non-smoker	9 (37.5)	2 (16.6)	11 (30.6)
Former smoker	15 (62.5)	5 (41.7)	20 (55.5)
Active smoker	0 (0)	5 (41.7)	5 (13.9)
Pulmonary function testing			
FEV1, % predicted	61.4 (25.3-106.3)	42.3 (16.0-91.5)	59.9 (16.0-106.3)
FVC, % predicted	53.8 (33.2-116.3)	72.2 (47.0-107.0)	63.2 (33.2-116.3)
FEV1/FVC, %	87.7 (51.7-95.8)	48.4 (26.2-85.4)	83.4 (26.2-95.8)
RV, % predicted	64.0 (31.0-110.3)	117 (46.8-227.9)	74.1 (31.0-227.9)
TLC, % predicted	60.6 (35.3-104.8)	95.6 (55.9-137.2)	64.5 (35.3-137.2)
Arterial blood gas analysis			
pH	7.43 (7.32-7.52)	7.42 (7.33-7.49)	7.43 (7.32-7.52)
SpO ₂	85.1 (72.0-97.0)	85.3 (60.0-94.1)	85.3 (60.0-97.0)
PaO ₂	50.5 (41.7-56.7)	48.1 (35.0-59.2)	49.8 (35.0-59.2)
PaCO ₂	38.2 (28.7-52.0)	47.7 (28.1-76.3)	40.2 (28.1-76.3)
HCO ₃ ⁻	24.5 (17.0-35.1)	26.7 (21.0-40.4)	25.7 (17.0-40.4)
Follow-up until HFNOT (months)	35 (6-141)	44 (2-127)	35 (2-141)
HFNOT titration parameters			
FiO ₂	50 (30-70)	35 (30-65)	45 (30-70)
Air flow rate	37.5 (20-50)	35 (15-60)	35 (15-60)
Post-HFNOT follow-up (months)	9 (6-31)	14.5 (4-34)	10 (4-34)
Mortality	19 (79.2)	9 (75.0)	28 (77.8)

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; FiO₂, fraction of inspired oxygen; FVC, forced vital capacity; HFNOT, high-flow nasal oxygen therapy; ILD, interstitial lung disease; RV, residual volume; SpO₂, peripheral oxygen saturation; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood; TLC, total lung capacity. Continuous variables presented as median (interquartile range) except for age as mean (standard deviation) and qualitative variables presented as absolute number (percentage).

was 35 L/min (15-60) with no significant differences either between clinical background subgroups (ILD vs. COPD) or main ABG acid-base disturbance.

Regarding post-HFNOT blood gas reassessment, for the overall sample, both SpO₂ and partial pressure of oxygen in arterial blood (PaO₂) showed a significant increase within the first month of follow-up; median SpO₂ increased from 85.3% to 96% ($p<0.001$), while median PaO₂ increased from 49.8 mmHg (35.0-59.2) to 79.2 (38.3-108.4) ($p<0.001$). No statistically significant differences were found in the overall sample regarding the pre- and post-HFNOT partial pressure of carbon dioxide in arterial blood (PaCO₂) values [median pre-HFNOT PaCO₂ of 40.2 mmHg (28.1-76.3) vs. median post-HFNOT PaCO₂ of 43 mmHg (32-57); $p=0.198$]. These relationships remained statistically significant, in the case of SpO₂ and PaO₂, and non-significant, in the case of PaCO₂, for each clinical subgroup when considered separately. However, when specifically analyzing the pool of patients with pre-HFNOT hypercapnia ($n=13$), there was a significant improvement of post-HFNOT PaCO₂ towards median levels within the normal range [median pre-HFNOT PaCO₂ of 48.3 mmHg (45.9-76.3) vs. median post-HFNOT PaCO₂ of 44.2 mmHg (37.6-57.0); $p=0.019$]. Similarly, while no statistically significant differences were found between pre- and post-HFNOT arterial pH in the overall sample, when considering patients with uncorrected acid-base disturbances individually, both those with respiratory alkalosis [median pre-HFNOT arterial pH of 7.47 (7.45-7.52) vs. median post-HFNOT arterial pH of 7.43 (7.38-7.56); $p=0.011$] as well as those with respiratory acidosis [median pre-HFNOT arterial pH of 7.33 (7.32-7.34) vs. median post-HFNOT arterial pH of 7.37 (7.34-7.44); $p=0.043$] presented significantly improved arterial pH values post-HFNOT initiation.

COPD patients had a significantly higher number of both pre-HFNOT emergency department admissions [6 (1-17) vs. 2 (0-16); $p=0.038$] and hospital stays [3 (2-12) vs. 2 (0-7); $p=0.026$]. The median hospital stay duration was 10 days (1-54), with no statistically significant differences between the two clinical subgroups. Post-home HFNOT start, emergency department admissions and hospital stays were significantly lower for the overall population ($p<0.001$) (Figures 1 and 2). A total of 26 patients (72.2%) presented lower post-HFNOT emergency department admissions vs. the 12-month pre-HFNOT follow-up period, while only 5 patients (13.9%) had more emergency visits after home therapy initiation. This translated into 25 patients (69.4%) presenting significantly less hospital admissions after treatment. This relationship remained significant for each clinical subgroup individually (Table 3). When considering any type of exacerbation, 28 patients (77.8%) showed improvement after starting HFNOT; while 66.7% ($n=16$) of ILD patients improved their exacerbation rate after treatment, the relationship was significantly stronger for COPD patients, whom all benefited in the form of less post-home HFNOT exacerbations (100%; $p=0.033$).

Overall median treatment duration was 10 months (4-34), and almost all patients maintained adherence until either the end of this study's follow-up or death (88.9%; $n=32$). Of the 4 patients that terminated treatment prior to the end of follow-up, 3 stopped home HFNOT due to overall clinical improvement after lung transplantation; the remaining patient terminated HFNOT due to intolerance. Mortality was high in our sample, with a death rate of 77.8% ($n=28$). Deceased patients showed significantly shorter follow-up periods of their respiratory disease until the decision to start home HFNOT [25 months (2-141) vs. 92 months (35-127); $p=0.004$]. Higher cumulative time spent admitted to the hospital during the 12-month period



prior to home HFNOT and subsequent follow-up after treatment initiation was associated with higher mortality [41.5 days (1-222) vs. 14.5 days (1-48); $p=0.015$]. Mortality was also higher for patients with superior median hospital stay duration [deceased: 13.1 days (1.0-54.5); survivors: 5.2 days (3.0-10.0); $p=0.005$]. Finally, deceased patients presented higher post-HFNOT mild to moderate exacerbation rates [median post-HFNOT exacerbations: 1 (0-8) vs. 0 (0-3); $p=0.012$].

Discussion

The benefits of HFNOT in the context of chronic end-stage respiratory disease seem to extend beyond the palliation of symptoms, as demonstrated by different studies worldwide, most of which focus

on COPD patients. Criner *et al.* have proposed that home HFNOT following a recent COPD hospitalization results in improved disease-specific quality of life and respiratory symptoms [11]. While this study focused on subjective benefits of HFNOT such as symptomatic relief perception, and there were no statistically significant changes in objective secondary outcomes such as spirometry, ABG, and the 6-minute walking test, other studies have pointed towards a relationship between home HFNOT and improved exacerbation rates. In a recent meta-analysis comparing the use of HFNOT vs. COT in patients with hypercapnic COPD, Zhang *et al.* reported that, specifically in the chronic setting, HFNOT was able to reduce the exacerbation rate despite failing to reach the same degree of PaCO_2 correction seen in the acute setting [12].

While in our study, HFNOT was indeed able to correct hypercapnia in this subset of patients, its benefits in reducing exacerbation

Table 3. Comparison between pre- and post-home high-flow nasal oxygen therapy clinical and analytical data for each main subgroup.

	Pre-HFNOT	ILD subgroup Post-HFNOT	p	Pre-HFNOT	COPD subgroup Post-HFNOT	p
Arterial blood gas analysis						
pH	7.43 (7.32-7.52)	7.42 (7.34-7.56)	0.626	7.42 (7.33-7.49)	7.42 (7.27-7.47)	0.756
SpO ₂	85.1 (72.0-97.0)	96.3 (85.0-98.1)	<0.001	85.3 (60.0-94.1)	94.4 (86.0-98.1)	0.002
PaO ₂	50.5 (41.7-56.7)	79.9 (38.3-108.4)	<0.001	48.1 (35.0-59.2)	73.7 (55.2-98.6)	0.002
PaCO ₂	38.2 (28.7-52.0)	43.0 (32.0-51.5)	0.057	47.7 (28.1-76.3)	44.5 (36.4-57.0)	0.695
HCO ₃ ⁻	24.5 (17.0-35.1)	27.6 (21.0-34.6)	0.045	26.7 (21.0-40.4)	27.3 (23.0-35.4)	1.00 ⁰
Exacerbations ¹						
Mild to moderate	2 (0-16)	1 (0-8)	0.002	6 (1-17)	1 (0-3)	0.005
Severe	2 (0-7)	1 (0-6)	0.020	3 (2-12)	0 (0-4)	0.003
Total	4.5 (0-21)	2 (0-14)	0.001	8.5 (3-24)	1.5 (0-7)	0.002

COPD, chronic obstructive pulmonary disease; HFNOT, high-flow nasal oxygen therapy; ILD, interstitial lung disease. ¹Pre-HFNOT considered until 12 months prior treatment initiation vs. subsequent post-HFNOT follow-up. Continuous variables presented as median (interquartile range) and qualitative variables presented as absolute number (percentage).

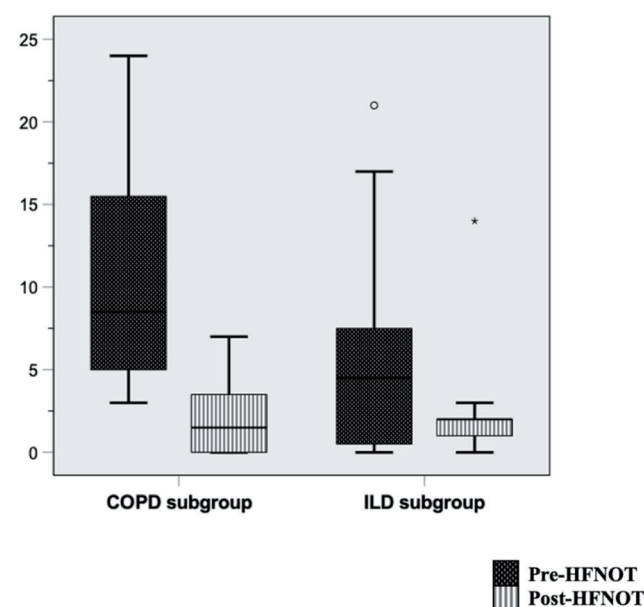


Figure 1. Pre- and post-home high-flow nasal oxygen therapy (HFNOT) total number of exacerbations (all severity) within 12 months of treatment initiation, according to the main underlying clinical subgroup ($p<0.001$). COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

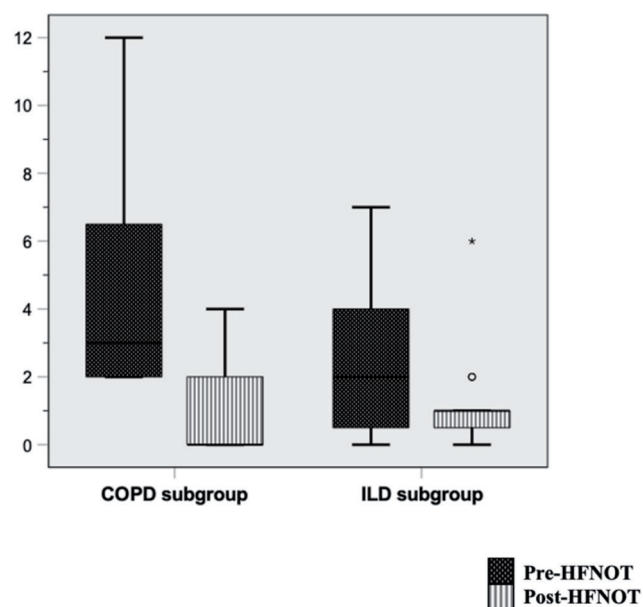


Figure 2. Pre- and post-home high-flow nasal oxygen therapy (HFNOT) total number of hospital admissions within 12 months of treatment initiation, according to the main underlying clinical subgroup ($p<0.001$). COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

rates extended beyond the effect on PaCO₂. In another study, Rea *et al.* demonstrated that time to first exacerbation was significantly delayed in patients with COPD or bronchiectasis treated with HFNOT when compared with those receiving COT alone [13]. Opposite to our study, however, home HFNOT failed to significantly improve the number of exacerbations during a 1-year follow-up between each group. In this study, patients in the HFNOT arm only received treatment for a short period of time (1.6 hours daily), which vastly differs from the 16-hour prescription our patients received. Since ours was a real-life study and no full adherence reports detailing time spent with HFNOT were available, mean usage times can only be subjectively extrapolated from information provided by the patients. Overall time spent using HFNOT seems to indeed be relevant towards higher efficacy, as demonstrated by Storgaard *et al.* [14]; in this study, patients treated with HFNOT for a mean period of 7 hours per day had lower rates of exacerbation when compared with COT alone. In a randomized clinical trial, Nagata *et al.* assessed the effects of long-term home HFNOT in hypercapnic patients treated with long-term oxygen for moderate-to-severe COPD, concluding that the number of moderate or severe exacerbations during the 1-year follow-up significantly decreased [15]. Other studies combining HFNOT with non-invasive positive pressure ventilation (NPPV) in end-stage COPD have also demonstrated its benefit in reducing hospitalization rates [16]. One difference between our study and the ones previously described is that opposite from our prescriptions, patients were started on pre-specified HFNOT parameters concerning FiO₂ and flow rates, instead of the in-hospital titration process that occurred for all our patients. While this is of paramount importance when considering that not only COPD but also ILD patients were included, even when only considering each clinical subgroup alone, one can theorize that both adherence and efficacy will be higher when tailoring treatment to each patient individually. Median overall titrated flow rate was higher in our sample than in all these previously cited studies (35 L/min vs. 20-30 L/min); in conjunction with the fact that they maintained treatment for longer periods per day, this might explain the significantly higher rate of success achieved regarding exacerbation rates reduction.

It is relevant to point out that our study's population represents a more heterogeneous sample, as patient selection was based on the presence of chronic hypoxic or mixed respiratory failure. In fact, most of our patients presented a clinical background of ILD. A recent meta-analysis by Vega Pittao *et al.* identified 12 studies in the field of HFNOT focusing on chronic respiratory disease and outpatient treatment, almost all focusing on either COPD patients or bronchiectasis [17]. The exception was a study by Harada *et al.*, which focuses on patients with idiopathic pulmonary fibrosis and the introduction of HFNOT to improve exercise-induced oxygen desaturation [18]. Similarly, to our study, these ILD patients were adapted to higher FiO₂ levels, although this was predetermined and not the result of a prior titration; likewise, airflow rate was also not titrated according to any objective parameters. Moreover, this study only focused on HFNOT usage during exercise, and not everyday use; nevertheless, HFNOT resulted in better exercise duration, minimum SpO₂ and leg fatigue in patients exhibiting exercise-induced hypoxemia vs. COT. Other pilot studies have also pointed towards a symptomatic benefit of home HFNOT in the context of ILD [19,20]; in a physiological study by Bräunlich *et al.* [21], HFNOT achieved an improvement in respiratory rate, minute volume and hypercapnia in hypercapnic ILD patients, but only hospital-admitted patients were included. To the best of our knowledge, ours is the first study reporting long-term usage of home HFNOT in this clinical context.

Although not as impactful as in COPD, ILD patients have also shown significant reductions in both total and severe exacerbation rates post-HFNOT. The need for significantly higher FiO₂ levels when compared to COPD patients did not negatively impact PaCO₂ levels; in fact, HFNOT initiation normalized the overall sample, mitigating ABG differences that were previously found between each clinical subgroup. Irrespective of the primary underlying chronic respiratory disease, HFNOT was able to improve PaO₂ levels in the overall sample when compared with COT. This effect has been theorized by pre-clinical studies to be a direct consequence of the more stable FiO₂ gas flow provided by HFNOT vs. conventional low-flow oxygen delivery [22]. Additionally, this constant flow is what creates a certain amount of peak expiratory end pressure (PEEP), seemingly mimicking the effect of NPPV [17,23]. With more recent studies, however, this PEEP effect has been demonstrated as limited, particularly at relatively lower HFNOT flow rates than 60 L/min [24,25]. Therefore, we theorize a possible explanation for the better overall correction of both hypoxia and hypercapnia in this chronic setting lies with a more efficient delivery of FiO₂ when compared with COT – while the long-term oxygen therapy was prescribed at a varying FiO₂ depending on the underlying disease severity, all prescriptions were ≥6 L/min and up to 15 L/min. Although necessary for hypoxia correction, due to the difference in final FiO₂ when compared to the HFNOT prescription we can infer that patients were at a higher risk of iatrogenic hypercapnia while on COT, and thus the switch to an improved delivery system was able to mitigate both respiratory defects. An additional benefit of HFNOT that can also explain the improvement seen in PaCO₂ is related to the washout of physiological dead space, although this effect is difficult to assess and has only been demonstrated in scarce studies [26,27], some of which based on the improvement of ventilatory ratio as a surrogate of dead space volume [28].

Most clinical studies have reported a subjective clinical benefit of HFNOT through quality-of-life questionnaires [13]. While this was not possible due to the retrospective nature of our study, overall treatment tolerance can be extrapolated from clinical registries showcasing good treatment adherence throughout follow-up. Because all our patients were considered as end-stage, possible hindrances related to HFNOT might not be as relevant as for more active patients. Adherence for long periods during the day might become an inconvenience when considering that the devices currently available for prescription have no portability; limiting the mobility of an otherwise still active patient might lead to worse overall adherence and even tolerance. One possible solution is to advise night treatment, as done by Nagata *et al.* with favorable results [15]. Still on the topic of quality of life and patient comfort, it is important to note that, as seen with different reports in the acute setting [29,30], not all patients tolerate the use of NPPV therapy. Indeed, mask intolerance is one of the main causes of NPPV therapy failure in this context [31,32], and likely to account for even more challenges with continuous usage. When pooled against NPPV and COT, patients reported overall better comfort and tolerability with HFNOT [33,34], something that should be considered by clinicians when faced with low adherence to other modalities. In a systematic review focusing on symptom-based outcomes, Cortegiani *et al.* identified a trend towards a better control of dyspnea, improved comfort and decreased respiratory rate in favor of HFNOT in acute settings [35]. Our results fall in line with this seemingly improved tolerability rate seen with HFNOT, as all hypercapnic COPD patients had, indeed, failed to adhere to NPPV.

This study has some limitations. Being retrospective, it is



dependent on the quality of the available clinical information. The small sample and single-center design may limit the generalizability of the results. Although significant median treatment durations were achieved, not all patients completed a full year of home HFNOT, which could impact the consistency of outcome measures, particularly in the subset of ILD patients, since exacerbations were traced back until 12 months prior to HFNOT start. Additionally, since no adherence reports were actively collected and provided to the prescriber, information regarding median HFNOT daily usage is lacking, which hinders any conclusions concerning the cumulative effect of this therapy and its association with positive clinical outcomes. Having a structured adherence report, such as the ones provided for patients treated with continuous or bi-level positive airway pressure therapy, would help determine whether the benefits of HFNOT are incremental or if the daily treatment duration can be reduced. Since only exacerbations resulting in an emergency department visit and/or hospital admission were considered, exacerbation rates may be underestimated, especially for patients managing their exacerbations at home due to access to outpatient palliative care. Finally, as different underlying diseases were present, heterogeneity in the patient population was significant, which could impact clinical outcomes. Nevertheless, considering the lack of data currently available worldwide on this topic, we believe our findings retain their significance towards a better understanding of the potential benefit of home HFNOT in the context of chronic respiratory diseases. Future prospective studies with a larger sample size, active adherence monitoring, and including quality of life assessment are needed to enhance our understanding of home HFNOT's clinical impact.

Conclusions

Our study suggests home HFNOT is capable of reducing exacerbation rates not only for severe COPD but also for other clinical subgroups such as ILD. Prospective studies are needed to validate these findings and better assess the impact of this therapy regarding overall quality of life parameters. Technological advancements towards more portable devices with on-demand adherence and treatment reports might bring forth the possibility of worldwide home prescription concomitantly with COT and/or NPPV.

References

- Hebbink RHJ, Duiverman ML, Wijkstra PJ, Hagmeijer R. Upper airway pressure distribution during nasal high-flow therapy. *Med Eng Phys* 2022;104:103805.
- Coletti KD, Bagdure DN, Walker LK, et al. High-flow nasal cannula utilization in pediatric critical care. *Respir Care* 2017;62:1023-9.
- Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018;378:1121-31.
- Mauri T, Turrini C, Eronia N, et al. Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017;195:1207-15.
- Oczkowski S, Ergon B, Bos L, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022;59:2101574.
- Gotera C, Díaz Lobato S, Pinto T, Winck JC. Clinical evidence on high flow oxygen therapy and active humidification in adults. *Rev Port Pneumol* 2013;19:217-27.
- Bräunlich J, Köhler M, Wirtz H. Nasal highflow improves ventilation in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:1077-85.
- Biselli PJC, 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;122:82-8.
- Elshof J, Duiverman ML. Clinical evidence of nasal high-flow therapy in chronic obstructive pulmonary disease patients. *Respiration* 2020;99:140-53.
- Weinreich UM, Juhl KS, Søbø Christophersen M, et al. The Danish respiratory society guideline for long-term high flow nasal cannula treatment, with or without supplementary oxygen. *Eur Clin Respir J* 2023;10:2178600.
- Criner GJ, Criner LYH, George SA, et al. Feasibility of using daily home high-flow nasal therapy in copd patients following a recent COPD hospitalization. *Chronic Obstr Pulm Dis* 2022;9:4-14.
- Zhang L, Wang Y, Ye Y, et al. Comparison of high-flow nasal cannula with conventional oxygen therapy in patients with hypercapnic chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2023;18:895-906.
- Rea H, McAuley S, Jayaram L, et al. The clinical utility of long-term humidification therapy in chronic airway disease. *Respir Med* 2010;104:525-33.
- Storgaard LH, Hockey H, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. *Int J Chron Obstruct Pulmon Dis* 2018;13:1195-205.
- Nagata K, Horie T, Chohnabayashi N, et al. Home high-flow nasal cannula oxygen therapy for stable hypercapnic COPD: a randomized clinical trial. *Am J Respir Crit Care Med* 2022;206:1326-35.
- Weinreich UM, Storgaard LH. A real-life study of combined treatment with long-term non-invasive ventilation and high flow nasal cannula in patients with end-stage chronic obstructive lung disease. *J Clin Med* 2023;12:4485.
- Vega Pittao ML, Schiffino G, Pisani L, Nava S. Home high-flow therapy in patients with chronic respiratory diseases: physiological rationale and clinical results. *J Clin Med* 2023;12:2663.
- Harada J, Nagata K, Morimoto T, et al. Effect of high-flow nasal cannula oxygen therapy on exercise tolerance in patients with idiopathic pulmonary fibrosis: a randomized crossover trial. *Respirology* 2022;27:144-51.
- Weinreich UM, Burchardt C, Huremovic J. The effect of domiciliary high flow nasal cannula treatment on dyspnea and walking distance in patients with interstitial lung disease – a pilot study. *Chron Respir Dis* 2022;19:147997312211370.
- Al Chikhanie Y, Veale D, Verges S, Hérengrt F. The effect of heated humidified nasal high flow oxygen supply on exercise tolerance in patients with interstitial lung disease: a pilot study. *Respir Med* 2021;186:106523.
- Bräunlich J, Köhler M, Wirtz H. Nasal high-flow (NHF) improves ventilation in patients with interstitial lung disease (ILD)—a physiological study. *J Clin Med* 2023;12:5853.
- Nishimura M. High-flow nasal cannula oxygen therapy in adults. *J Intensive Care* 2015;3:15.
- Garofalo E, Bruni A, Pelaia C, et al. Evaluation of a new interface combining high-flow nasal cannula and CPAP. *Respir Care*



- 2019;64:1231-9.
24. Ejiofor BD, Carroll RW, Bortcosh W, Kacmarek RM. PEEP Generated by high-flow nasal cannula in a pediatric model. *Respir Care* 2019;64:1240-9.
 25. Sun Y, Dai B, Peng Y, Tan W, Zhao H. Factors affecting FiO₂ and PEEP during high-flow nasal cannula oxygen therapy: a bench study. *Clin Respir J* 2019;13:758-64.
 26. Bräunlich J, Goldner F, Wirtz H. Nasal highflow eliminates CO₂ from lower airways. *Respir Physiol Neurobiol* 2017;242:86-8.
 27. Biselli P, Fricke K, Grote L, et al. Reductions in dead space ventilation with nasal high flow depend on physiological dead space volume: metabolic hood measurements during sleep in patients with COPD and controls. *Eur Respir J* 2018;51:1702251.
 28. Piquilloud L, Olivier PY, Richard JC, et al. High flow nasal cannula improves breathing efficiency and ventilatory ratio in COPD patients recovering from an exacerbation. *J Crit Care* 2022;69:154023.
 29. Pavlov I, Plamondon P, Delisle S. Nasal high-flow therapy for type II respiratory failure in COPD: a report of four cases. *Respir Med Case Rep* 2017;20:87-8.
 30. Plotnikow G, Thille AW, Vasquez D, et al. High-flow nasal cannula oxygen for reverting severe acute exacerbation of chronic obstructive pulmonary disease: a case report. *Med Intensiva* 2017;41:571-2.
 31. Pisani L, Astuto M, Prediletto I, Longhini F. High flow through nasal cannula in exacerbated COPD patients: a systematic review. *Pulmonology* 2019;25:348-54.
 32. Squadrone E, Frigerio P, Fogliati C, et al. Noninvasive vs invasive ventilation in COPD patients with severe acute respiratory failure deemed to require ventilatory assistance. *Intensive Care Med* 2004;30:1303-10.
 33. Longhini F, Pisani L, Lungu R, et al. High-flow oxygen therapy after noninvasive ventilation interruption in patients recovering from hypercapnic acute respiratory failure: a physiological crossover trial. *Crit Care Med* 2019;47:e506-11.
 34. Jing G, Li J, Hao D, Wang T, et al. Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: a pilot randomized controlled trial. *Res Nurs Health* 2019;42:217-25.
 35. Cortegiani A, Crimi C, Noto A, et al. Effect of high-flow nasal therapy on dyspnea, comfort, and respiratory rate. *Crit Care* 2019;23:201.

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