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EFFECTS OF ASYMMETRIC NASAL HIGH FLOW CANNULA ON CARBON DIOXIDE IN HYPERCAPNIC PATIENTS: A RANDOMIZED CROSSOVER PHYSIOLOGICAL PILOT STUDY

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ABSTRACT

Introduction and Objectives: Nasal high flow (NHF) therapy is an established form of non-invasive respiratory support used in acute and chronic care. Recently, a new high flow nasal cannula with asymmetric prongs was approved for clinical use. Despite in vitro promising data, the clinical benefits of the new cannula have not yet been defined and to data, no evidence are available on the use of asymmetric NHF support in patient with Chronic Obstructive Pulmonary Disease (COPD). The present doctoral thesis aims to describe the possible mechanisms through which NHF could benefit patients with stable COPD based on the published scientific literature. Additionally, it presents the results of a physiological study comparing two different nasal cannulas (asymmetric vs. standard nasal interface) in hypercapnic COPD patients conducted at the Respiratory and Critical Care Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna (CODUET Study).

Patients or Materials and Methods: We conducted a single-center, prospective, physiologic, crossover, randomized study to investigate the effects on partial pressure of carbon dioxide ($PaCO_2$) levels of two different nasal cannula ("asymmetric" vs "standard" nasal interface) in COPD hypercapnic patients recovering from an acute severe exacerbation. A total of 20 patients who had a known diagnosis of COPD with post-bronchodilator forced expiratory volume at 1 s/forced vital capacity (FEV1/FVC) < 70% were included. All patients were recovering from an acute exacerbation that required hospitalization and had persistent hypercapnia, despite having attained a stable pH (i.e. pH > 7.35 and $PaCO_2$ > 50 mmHg on 3 consecutive measurements). After enrolment, two 90-minute trials with the asymmetric nasal high flow interface (Optiflow + Duet, Fisher & Paykel Healthcare Ltd., New Zealand) or the standard interface (Optiflow, Fisher & Paykel Healthcare Ltd., New Zealand) were randomly applied and a washout period of 60 min between the two treatments was performed for minimizing the carryover effect.

Results: Study results suggested that both the asymmetric and standard NHF cannula were equally effective in reducing $PaCO_2$ levels with similar performances also in terms diaphragm activity, dyspnea, and patient's comfort. Interestingly, asymmetric NHF cannula performed significantly better in reducing the dead space ventilation and increasing the ventilatory efficiency in more advanced COPD patients with more severe hypercapnia higher baseline $PaCO_2$ values ($PaCO_2 \geq 65$ mmHg at baseline).

Conclusions: Although the clinical benefit of NHF remains unclear, some research findings would support the use of HHFT in chronic respiratory diseases. In patients recovering from an episode of acute respiratory failure (ARF) due to COPD exacerbation, the asymmetrical cannula did not significantly decrease $PaCO_2$ compared with the standard cannula. Similar performances were also observed in terms of diaphragm activity, dyspnea, and patient's comfort. Interestingly, asymmetrical NHF cannula performed significantly better in reducing the dead space ventilation and increasing the ventilatory efficiency in more severe COPD patients with higher baseline $PaCO_2$ values.

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1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the now third leading cause of death globally [1]. The improvement in both oxygenation and ventilation has shown to reduce mortality. For this reason, non-invasive ventilation (NIV) and long-term oxygen therapy (LTOT) are the mainstream options for hypoxemic and hypercapnic patients with severe COPD. However, an insufficient heating and humidification leads to poor adherence to LTOT, and on the other hand, NIV is sometimes inapplicable due to poor mask tolerance. Despite that, NIV and LTOT are still the preferred modalities for respiratory support in chronic stable COPD. Recently, HFNC oxygen delivery has gained attention as an alternative of respiratory support for this population.

Nasal high flow (NHF) therapy is an established form of non-invasive respiratory support used in acute and chronic care [2 ,3, 4]. NHF is usually defined as the administration of gas flows above 15 L/min. It is a non-invasive respiratory support that delivers heated (up to 38° C), humidified (100% Relative Humidity, RH; >30 mg H2O/L Absolute Humidity, AH) [5, 6], oxygen-enriched air, when necessary, through a nasal cannula or a tracheostomy interface, and is typically administered in the 30–50 L/min range in clinical practice.

NHF was first introduced in the paediatric setting in the 1990s to treat apnoea of pre-maturity as an alternative to nasal Continuous Positive Airway Pressure (CPAP), due to the distending pressure generated by nasal cannula flow in neonatal patients [7,8]. Additionally, in the 1990s, the first study showing that NHF improved exercise tolerance compared to low-flow oxygen in patients affected by COPD was published [9]. Years later, NHF gained popularity as an alternative method of respiratory support for critically ill hypoxemic patients. Nevertheless, the first systematic review published in 2010 included only eight articles, all of which were abstracts or poster presentations

from scientific meetings, resulting in poor data quality for analysis [10]. Over the last few years, the use of NFH in critically ill hypoxemic adults has increased. The most recent systematic reviews and meta-analyses [11, 12] have shown that, although NFH does not reduce mortality in patients with acute hypoxemic respiratory failure, it may reduce the need for intubation when compared to standard oxygen therapy (SOT), and that it is not inferior to NIV in terms of reducing the incidence of reintubation. Its role in the management of hypercapnic respiratory failure has also been increasingly explored in recent years. The physiological effects that enhance the outcomes of patients with COPD, are now well known. Recently, a new high flow nasal cannula with asymmetric prongs was approved for clinical use. The present doctoral thesis aims to describe the possible mechanisms through which NHF could benefit patients with stable COPD based on the published scientific literature. Additionally, it presents the results of a physiological study comparing two different nasal cannulas (asymmetric vs. standard nasal interface) in hypercapnic COPD patients conducted at the Respiratory and Critical Care Unit, IRCCS Azienda Ospedaliero Universitaria di Bologna (CODUET Study).

2. The Potential Mechanisms by Which NHF May Offer Advantages to Stable Hypoxemic and/or Hypercapnic COPD Patients

A. improved lung mucociliary clearance and decreased inspiratory resistance by providing heated and humidified gas;
B. washout of anatomic dead space;
C. mild distending pressure; and
D. increased alveolar PO2.

2. A. Improvement in Lung Mucociliary Clearance and Attenuation of Inspiratory Resistance Providing Heated and Humidified Gas

In normal conditions, as air moves from the nasopharynx to the carina (the isothermal saturation boundary), it becomes fully saturated with water vapor (AH = 44 mg/L and RH = 100%). These conditions are optimal for maintaining the normal functioning of the epithelial cells and the ciliary function. The respiratory epithelium (Figure 1) is a delicate interface between us and the air we breathe. This wall epithelium is lined with microscopic, hair-like structures called cilia which are surrounded by a thin film of fluid, called the sol layer (aqueous). The superficial gel layer, produced by the goblet cells, is a sticky mucoid substance which contains chemicals, antibodies and immune cells to destroy any bacteria and viruses. If this layer is well represented, the cilia move correctly and move the mucus. As the secretions have a good content of water and need to be adequately mobilized, it is necessary that epithelial cell shave a normal function of the absorption of sodium mechanism and elimination of chlorine. Studies have shown that deficient airway surface

hydration may play a critical role in the pathogenesis of airway inflammation with chronic airway mucus obstruction [13, 14]. Mall et al. [15] studied the natural progression of lung disease caused by airway surface dehydration in mice. They demonstrated that airway surface dehydration is sufficient to initiate persistent neutrophilic inflammation with chronic airway mucus obstruction and to cause transient eosinophilic airway inflammation and emphysema. This may suggest that deficient hydration may trigger the mechanisms leading to chronic pulmonary diseases of different aetiologies. In addition, Kilgour et al [16]. tested whether reducing the air temperature would affect mucus transport velocity and ciliary beat frequency. They conclude that delivering inspired gas at 30 °C or even 34 °C with 100% RH may not be enough to prevent epithelial damage in animal models after 6 h of exposure. Furthermore, when using a fraction of inspired oxygen (FiO2) above 21%, the air temperature and ciliary beat may fall even further. Other problems associated with under-humidification are discomfort [17, 18] and bronchoconstriction [19, 20]. When inspiratory gas is drawn across the nose, retraction of the nasopharyngeal boundaries increases inspiratory resistance significantly [21]. Moreover, inhalation of cold and dry air activates specific receptors and osmoreceptors in the nasal mucosa, causing bronchoconstriction in both healthy individuals and COPD patients [19,22].

NHF effectively provides gas humidified and heated to the airway to enhance lung mucociliary clearance. Chidekel and colleagues [23] hypothesized that different levels of humidification have different effects on respiratory epithelial cell monolayers. Epithelial cell cultures (Calu-3) were placed in environmental chambers at 37°C with three different levels of humidity: relative humidity (RH) <20% (dry), 69% (non-interventional sample) and >90% (NHF) for 4 and 8 hours. The transepithelial resistance and cellular viability decreased over time ($p < 0.001$) in the Dry group

compared with the NHF group ($p < 0.001$). Moreover, the production of inflammatory cytokines [interleukin(IL) −6 and IL-8] after 8 hours was greater in the Dry group compared with that in the other groups. Finally, at 4 and 8 hours, only in the Dry Group, cytology showed morphological abnormalities of epithelial cells (puffed nuclei, intracellular and nuclear vacuoles, diffuse cytoplasm and cellular detritus). By supplying adequately warmed and humidified gas, NHF may be crucial for chronically hypersecretory patients who require airway clearance optimization or for patients suffering from bronchial hyperreactivity. Patients with a persistent productive cough or difficulties expectorating sputum should be encouraged to improve airway clearance [24]. Rea et al. demonstrated that NHF decreased exacerbation frequency and exacerbation days and increased time to the first exacerbation in a cohort of 108 stable patients diagnosed with COPD or bronchiectasis [25], compared to standard therapy. A post-hoc analysis regarding only patients with bronchiectasis (45 patients; 41.7%) revealed that the exacerbation rate was significantly reduced (2.39 vs. 3.48 exacerbations per patient per year; rate ratio 0.69; 95% CI 0.49–0.97; p = 0.03), and quality of life improved in the NHF group, suggesting that NHF is a potential treatment option for patients with bronchiectasis. Hasani et al. evaluated 10 bronchiectasic patients with NHF (flow rate 20–25 L/m, temperature 37 °C); they proved, using radiomarked aerosolized particles at baseline and after 7 days of treatment, that warm air humidification treatment can increase mucociliary clearance [26]. In hospitalized patients with a diagnosis of acute exacerbation of COPD and concurrent bronchiectasis, NHF appeared to be beneficial in improving gas exchange and reducing respiratory rate and dyspnoea [27].

2. B. Anatomical dead space and CO2 washout

In a normally functioning lung, alveolar ventilation is near 70%. This "effective ventilation", which participates in gas exchange, can be significantly reduced in various disease states. "Washing out" the expired air in the upper airways and decreasing CO2 rebreathing improves ventilation efficiency, resulting in alveolar ventilation with a higher proportion of minute ventilation. It was demonstrated that the CO2 clearance rate from the anatomical dead space is linearly related to the flow rate. A study using upper airway models showed that CO2 clearance was greater when the flow was increased from 15 to 30 L/min, rather than from 30 to 45 L/min [28]. In another study with healthy volunteers' patients, the investigators found a link between a decrease in CO2 rebreathing (by 1 to 3 mL per breath) and a similar increase in inspired O2, corresponding to a reduction in dead space by 20–60 mL after increasing the flow rate from 15 to 45 L/min [29]. A study of ten healthy volunteers found that dead space washout is present up to high flows of 40 L/m, identifying no further increase in washout at higher flows (60 L/m), assuming a "plateau effect" when flows are set above 40 L/m [30]. The existing literature demonstrates adequate physiological rationale to proceed with trailing these devices in the long-term management of COPD. For example, in a randomized crossover trial comparing NHF plus LTOT with SOT in patients with stable hypercapnic COPD, 6 weeks of treatment with NHF improved health-related quality of life and decreased the arterial partial pressure of carbon dioxide by at least 10% (adjusted treatment effect, −4.1 mm Hg; 95% confidence interval, −6.5 to −1.7 mm Hg), pH (adjusted treatment effect, +0.02; 95% confidence interval, 0.01 to 0.02), and median nocturnal transcutaneous carbon dioxide pressure (adjusted treatment effect, −5.1 mmHg; 95% confidence interval,−8.4 to −1.8 mm Hg) [31]. Similarly, compared to LTOT, NHF reduced the transcutaneous

carbon dioxide (TcCO2) and respiratory rate in patients with stable oxygen-dependent COPD. The authors argued that the decrease in TcCO2 is related to the consistent rise in tidal volume, which is followed by dead space and CO2 washout [32]. Storgaard et al. carried out a post-hoc analysis from a previous randomized controlled trial comparing SOT vs. NHF plus oxygen [33], in which they included 74 patients with concomitant persistent hypercapnic failure (>45 mmHg). After 12 months, there was a 1.3% decrease in PaCO2 in patients using NHF and a 7% increase in controls before NHF use on site (p = 0.003), concluding that NHF stabilizes patients with COPD with persistent hypoxic and hypercapnic failures in terms of PaCO2, exacerbations, and number of hospitalizations, whereas those not receiving NHF worsened [34]. In line with these findings, Pisani et al. found that in COPD patients recovering from an episode of an acute hypercapnic respiratory failure who had attained a normal pH, using NHF was related to a statistically significant drop in PaCO2 and respiratory rate. The subset of patients with a lower pH level had the best response. However, the authors of this study were able to establish that COPD patients with the overlap syndrome had a different response [35]. This evidence suggests that NHF may be a viable alternative to SOT for stable hypercapnic patients with COPD. Furthermore, NHF has been compared to NIV in 102 stable COPD patients during a 6-week crossover study. NHF may be a feasible alternative to NIV in terms of PaCO2 reduction and quality of life improvement in COPD patients who refuse NIV or are intolerant. Interestingly, this study showed that a significant subset of patients in both groups (around 15–20%) did not improve or even worsen their PaCO2. There were three patients whose PaCO2 levels increased by more than 5 mmHg using both devices, five using only NHF, and four using NIV [36]. This may suggest that when hypercapnia does not improve with one specific non-invasive support (either NIV or NHF), a trial with the alternative method is

mandatory. Indeed, NHF may be a viable alternative to SOT during NIV pauses since it may be more comfortable or result in better outcomes for dyspnoea [37].

2. C. NHF may provide a mild distending pressure and increase expiratory resistance

This effect may optimize lung mechanics by improving lung compliance and gas exchange while maintaining alveolar patency. Distending pressure provided by NHF is dependent on the leak rate, which is determined by the nasopharyngeal anatomy as well as the relationship between nasal prong size and the nares of the nose and whether the mouth is open or closed [38, 39]. Parke et al. [40] observed that for each increase of 10 L/minutes in flow rate, mean airway pressure increased by 0.69 cmH2O ($p < 0.01$) when subjects breathed with their mouths closed, and by 0.35 cmH2O($p < 0.03$) with their mouths open. High flows could also act as a resistance to exhalation when the mouth is closed [41,42]. Nonetheless, NHF distending pressure is unlikely to be above 2–4 cmH2O, and it does not likely deliver a clinically relevant level of positive pressure in terms of lung recruitment, as CPAP does [43, 44]. The mechanisms for increasing expiratory positive pressure differ between NHF and CPAP. NHF increases the expiratory resistance and may exert a jet-flow effect that creates a pressure gradient across the flow-restricted nose segment (zero at the nares and positive inside the nasal cavity), whereas CPAP increases pressure in the nares without creating a further pressure gradient and without affecting the expiratory resistance of the upper airway [45, 46]. The increase in expiratory resistance leads to a longer expiratory phase, lowering the respiratory rate and minute ventilation [47]. Surprisingly, it may appear paradoxical that COPD patients could benefit from the mechanism of increasing expiratory resistance, but it

is, actually, a similar effect to the pursed lips breathing pattern adopted by these patients, which might be useful by keeping the airway open and improving exercise capacity [48]. Additionally, this mild positive airway pressure mentioned before may counterbalance intrinsic positive end-expiratory pressure (PEEP) in COPD patients and reduce the respiratory workload while also improving exercise tolerance [49]. A physiological study [47] comparing the effects of standard oxygen, NIV and NHF in stable hypercapnic COPD patient revealed a decrease in respiratory muscle effort when comparing NHF with standard oxygen therapy. Both transdiaphragmatic pressure swing (Pdi) and pressure time product of the diaphragm (PTPdi) were reduced, as well as respiratory rate (RR) and PaCO2 levels.

2. D. Matching patient's inspiratory flow (stable FiO2) and Increasing Alveolar PO2

NHF can be used just as effectively without the addition of additional oxygen. However, oxygen therapy is one of the most commonly used drugs in hospitals and is highly used at home. More than 1.5 million people worldwide with a variety of respiratory disorders use LTOT to enhance their quality of life and prolong survival [50, 51]. The difference between low- or moderate-flow devices, such as standard nasal cannulas or face masks, and NHF is that high flows maintain a stable FiO2 (and high, when necessary) by providing flow rates higher than spontaneous inspiratory flow (the patient's ventilatory demand). This reduces the amount of entrained room air. As FiO2 is related to the proportion of pure oxygen coming from the interface (with 100% FiO2) and from the room air (21% FiO2), if the patient's ventilatory demand exceeds the device's flows, the patient will breathe some atmospheric air (entrainment effect) and FiO2 will decrease or

become less accurate. Therefore, in low- to moderate-flow systems, usually called standard oxygen therapy (SOT), the "real" FiO2 depends on the patient's breathing pattern and effort, determining the inspiratory flow [52]. Ritchie et al. demonstrated that when there is a large difference between the device flow rate and the patient's peak inspiratory flow rate, the delivered FiO2 could decrease by 20% [53]. This advantage of NHF could be relevant for a COPD patient undergoing home rehabilitation or exercise, or for patients during daily activities. During NHF, patients with COPD and exercise limitations can exercise longer with less dyspnoea, a better breathing pattern and SaO2, less muscular fatigue and lower arterial pressure [54, 55].

Finally, it is important to mention that the humidification and heating process has its cost in terms of energy. Under normal conditions (temperature of 21°C room with RH of 50%), an adult person who breathes with a tidal volume of 500 mL and a respiratory rate of 12 breaths/minutes may require about 156 calories/minutes for the conditioning of the inspired gas. This is even more important in terms of a pulmonary disorder in which an increase in minute ventilation determines a greater quantity of air to be humidified [56]. All these considerations may contribute to a rational justification that warm and moisture high flows in patients with stable COPD may improve comfort and patient adherence to treatment.

3. CODUET STUDY

Bench studies performed on models replicating upper airway anatomy have shown that administering NHF with larger nasal cannula increases airway pressure (Paw) and PEEP, but the effect on CO2 clearance is reduced, particularly in tachypnoeic patients [57, 58]. This effect is, on the contrary, more consistent when smaller calibre cannulas are used. Today, there is no clear recommendation for the size of nasal cannulas since the use of different sizes results in distinct physiological effects. The selection of cannula dimensions (and hence the possibility of obtaining a benefit in terms of ventilatory mechanics) is further complicated by anatomical differences across the nostrils.

The new Fisher & Paykel Duet interface ^{TM} consists of two asymmetrical prongs: the larger one may improve pressure support, while the smaller one may improve CO2 clearance from the anatomical dead space.

In an adult upper-airway model, Taktov and colleagues [59] demonstrated that the larger prong optimizes pressure, while the smaller prong allows for leak, generating a greater CO2 elimination especially when time for clearance is reduced. Despite in vitro promising data, the clinical and physiological benefits of the new cannula have not yet been defined especially in hypercapnic patients with COPD, where theoretically this device should find the main indication.

Thus, the purpose of this pilot randomized cross-over study, was to investigate the physiological effects on PaCO2 levels of two different nasal cannulas (“asymmetric” vs “standard” nasal interface) in COPD hypercapnic patients recovering from an acute severe exacerbation.

3. 1 MATERIALS AND METHODS

3.1.a) Participants.

We enrolled 20 adult patients who had a known diagnosis of COPD with post-bronchodilator forced expiratory volume at 1 s/forced vital capacity (FEV1/FVC) < 70% [60]. All patients were recovering from an acute exacerbation that required treatment with NIV. After the initial management and stabilization, patients weaned from NIV and with pH ≥7.35 and PaCO2 >50 mmHg on 3 consecutive measurements were considered for the study. Body mass index >30 kg/m2, known or clinically suspected diagnosis of sleep-disorders, restrictive pulmonary/chest wall disease, clinical cardiovascular instability, renal insufficiency, lack of collaboration, impaired sensorium (Kelly Matthay score≥5) [61] were considered exclusion criteria. The local Ethic Committee approved the study (CE AVEC: 174/2022/Disp/AOUBo) and written informed consent was obtained from all the patients. The study was registered at the Clinical Trial Registry (NCT05528289).

3.1.b) Study design and primary and secondary endpoints.

This was a single-center, prospective, physiologic, crossover, randomized study.

The primary endpoint was the change in PaCO2 levels in patients supported with the asymmetric nasal high flow cannula compared to the standard interface. Other outcomes included a comparison of nasal high flow treatments with both interface vs SOT, gas exchange, hemodynamics parameters, RR, tidal volume (VT), minute ventilation (Ve), diaphragm ultrasound thickening fraction (TFdi), comfort and dyspnoea scores.

3.1.c) Measurements.

At inclusion all patients were on SOT. After enrolment, two 90-minute trials with the asymmetric nasal high flow interface (Optiflow + Duet, Fisher & Paykel Healthcare Ltd., New Zealand) or the conventional interface (Optiflow, Fisher & Paykel Healthcare Ltd., New Zealand) were randomly applied. All patients received NHF (AIRVO™ 2, Fisher & Paykel Healthcare, Auckland, New Zealand) provided at flow rate of 40 L/min and set initial temperature of 31 °C increased up to 37°C according to patient tolerance.

Originally, as per registered protocol, the FiO2 was chosen to target a peripheral saturation of 92-94% on pulse oximetry during Venturi oxygen mask (VM) and flow rate set at 30 L/min. However, we adjusted FiO2 to maintain a target SpO2 range of 88% to 92% instead of 92-94% in accordance with the recommendations for patients with COPD [62]. This target saturation was kept constant during all study's phases. In addition, because the washout of dead space is flow and time dependent and our patients were enrolled in a subacute phase, a flow rate of 40 L/min was considered more efficient than 30L/min for carbon dioxide removal. Both changes (target FiO2 and flow rate) were reported as protocol deviation.

The cannula size was selected to occlude patient's nostril of about 2/3 for the standard interface, while the larger size was chosen for the asymmetric interface to enhance its maximum effect. The randomization sequence was established by computer software (Research Randomizer 4.0). In addition, a washout period of 60 min with VM between the two treatments was performed for minimizing the carryover effect. In the case after this time frame the level of PaCO2 was still

reduced by >10% from baseline, the following trial was postponed by another 60 min or more. Unfortunately, blinding was not possible. No recommendations were given to patients on the mouth position (open or closed) during the different trials. At inclusion, demographic variables (age, sex, BMI, comorbidities, lung function, smoking status etc) were recorded. The number of comorbidities was evaluated using Charlson Comorbidity Index scoring system [63]. Continuous heart rate (HR), blood pressure (BP), and peripheral oxygen saturation (SpO2) were measured during all trial period for each patient. Moreover, Ve and VT were monitored by using a bioelectrical impedance monitor and a single-use Pad Set sensor placed on the surface of the chest wall (ExSpiron, Respiratory Motion Inc. USA) [64, 65]. This device has been validated in several studies [64, 66, 67]. With the patient in a semi-recumbent position, by using a 6-12 MHz linear array probe (GE L6-12-RS Linear Transducer, Ge HealthCare) and after excluding the presence of a hemidiaphragm chronic elevation and/or paralysis, two investigators independently performed bedside sonographic evaluation as previously described [68, 69] .The diaphragm thickness was measured at both end- expiration and inspiration, and TFdi was calculated as the average of three respiratory cycles, according to the formula: TFdi (%) = (inspiratory thickness-expiratory thickness)/expiratory thickness*100 [70,71]. At the end of each trial and during a 5-minute period of stable pattern the following variables were collected: pH, PaCO2, PaO2/FiO2 ratio, RR, VT, Ve, SpO2, HR, systolic blood pressure, diastolic blood pressure, and TFdi. In addition, interface comfort and dyspnoea were also assessed by using 0–10 visual analogue scales (VAS) (10 representing maximum comfort and 0 indicates maximum discomfort patient could imagine) and Borg scale respectively [72].

3.1.d) Statistical analysis

Descriptive statistics were used to describe the baseline characteristic of the entire population: numbers and percentages were used for categorical variables and medians and interquartile ranges for continuous variables. This study was designed as a pilot study. A priori, standardized effect size comparing the two different devices is not known. For this reason, we were not able to calculate the optimal sample size. To reach a statistical power of almost 80%, we assumed to enrol 20 subjects with a minimum of 12 subjects having full data available [73, 74, 75]. Comparisons between different interfaces were analysed using the Wilcoxon rank test for paired data. We also conducted a post hoc subgroup analysis, which included patients with $PaCO_2 \geq 65$ mmHg at enrolment. This threshold of $PaCO_2$ was based on the results of a large study which clearly demonstrated that, compared to a $PaCO_2$ (air) of 6.5 kPa, a $PaCO_2$ range of 8.5-9 kPa increased mortality by approximately 25% in oxygen-dependent COPD patients [76]. In addition, tests for period effects and for carryover effects (i.e., treatment period interactions) were performed. Missing data was omitted from the analysis. We considered two-sided p values less than 0.05 to be statistically significant. Analyses were conducted using Prism (version 8.0; GraphPad Software, Inc, La Jolla, CA, USA)

3.2. RESULTS

As shown in **Figure 2**, we evaluated for enrolment 58 consecutively admitted patients and excluded 38 patients. Of 20 included patients, 16 (80%) were male and 13 (65%) were already on LTOT. At enrolment patients had a median PaCO2 of 64.6 mmHg (57.2-74.1) and moderate to severe FEV1% impairment [48% (42-58)]. The main demographic and clinical characteristics of the population are shown in **Table 1**. Lower temperature was associated with higher patient comfort and all included patients preferred the initial set temperature (31°C) during NHF trials.

We did not find statistically difference between the two interfaces in terms of CO2 improvement. All secondary outcomes were also similar between trials **(Tables 2).** Interestingly, both standard and asymmetric cannula reduced PaCO2 levels and improved pH, despite being in the normal range, compared to the conventional oxygen therapy (p= 0.0007 and 0.0006 for PaCO2 respectively and p= 0.0007 and 0.0006 for pH respectively) **(Table 3)**. Vital signs as well as diaphragm ultrasound variables were also similar between trials, while comfort, but not dyspnoea, was higher during SOT as compared to standard NHF configuration (p= 0.039) **(Table 3)**.

Additional subgroup analyses were performed considering only patients with baseline PaCO2≥ 65 mmHg (n=7). In this subgroup of patients, asymmetrically shaped prongs significantly decreased PaCO2 levels compared to the standard NHF cannula (p= 0.039) (**Figure 3.A**) with no differences in terms of respiratory pattern (**Figure 3.B,C,D**). In addition, diaphragm thickness at both end-inspiration and end-expiration as well as TFdi were not different among trials (**Table 4**). Finally, both comfort and dyspnoea were similar between the two groups (p = 0.25 and p=0.5 respectively) (**Table 4**).

3.3. DISCUSSION

In this physiological pilot randomized crossover study we compared, for the first time, the efficacy of the new asymmetric NHF cannula to the standard configuration in 20 hypercapnic COPD patients recovering from a severe exacerbation. The main study findings were: 1) the asymmetrical cannula did not significantly decrease PaCO2 compared with the standard cannula. 2) similar comfort and secondary outcomes were also found between the two interfaces. 3) the PaCO2 improvement was statistically significant in the subgroup of patients with more advanced disease and more severe hypercapnia (PaCO2≥ 65 mmHg at baseline).

Although NHF does not provide a "true" active inspiratory pressure**,** it is a validate non-invasive respiratory used both in acute and chronic setting. Among the potential mechanisms of NHF therapy, the capacity to supply adequate warmed and humidified gas flows, the washout effect in pharyngeal dead space, the reduction of inspiratory resistances, and the concomitant rise in resistance during expiration are considering key factors for supporting the use of NHF therapy in COPD population [3, 77] . In spite of this, it is important to keep in mind that the washout of dead space is flow and time dependent [78] and it is reduced at higher respiratory rate [79]. In addition, the generation of modest levels of positive pressure in the nasopharynx with NHF mainly depends on the flow rate, resistance to flow and cannula size [57, 58] . Moreover, the level of this mild distending pressure seems also to be dependent on mouth opening or closure (80). However, both pressure generation and dead space clearance appear to be affected by cannula size [78]. In fact, by varying the diameter of the cannula from a small to a large size it is possible to increase the pressure generated in the airways. On the other hand, this leads to greater noise, discomfort for

the patient who is often prone to open the mouth and finally reduces the clearance of the dead space due to reduction of the leakage area between the cannula and the nasal cavity. To try to optimize the NHF therapy and overcome these limitations a new cannula with asymmetric prongs has been developed. In an upper airway model [59], it was clearly demonstrated that asymmetrically shaped nasal prongs increase anatomical dead space clearance more efficiently as compared to the standard interface particularly when time for clearance is reduced, that occurs at higher respiratory rate, or when expiratory flow limitation is present [59]. In addition, the relationship between dead space clearance and PEEP effect is more linear with asymmetric cannula than with the standard interface, remaining valid the concept that theoretically to achieve the highest effectiveness in both, the highest flow should be set (i.e. 60 L/ min) and use the cannula with the largest diameter (size L) [59]. Interestingly by using two pressure ports located in the nasal cavities, the Authors [59] demonstrated that the differential pressure between cavities was higher with asymmetric prongs compared to standard one. This differential pressure increased from inspiration to expiration and remained elevated positive between the breathing phases only with asymmetric configuration, probably contributing to improve positive pressure and to increase expiratory resistances generated by the nasal high flow therapy [59]. To date, the application of this new interface has been studied in small groups of patients with mixed results. Slobod et al [81] showed that asymmetric NHF interface reduces minute ventilation and work of breathing in 10 non-intubated patients with mild-to-moderate acute hypoxemic respiratory failure. Conversely, no relevant differences in terms of lung aeration, ventilatory efficiency and gas exchange between the two NHF cannula were found in 20 patients experiencing acute respiratory failure after extubation [71]. However, in contrast with our findings, Boscolo and colleagues [71]

showed a better patient comfort with asymmetric NHF cannula compared to standard NHF interface. Therefore, identifying the patients who might benefit the most from asymmetric NHF cannula should be crucial. In recent years the evidence surrounding the use of NHT support in COPD population has increased. It has been proved that NHF therapy contributes to improve breathing pattern and respiratory mechanics of COPD patients as well demonstrated by several short-term studies [82, 47, 83]. In agreement with previous studies [84,35] we reported a significant reduction of PaCO2 values during both trials with NHF compared to standard oxygen. The reason why the asymmetric cannula did not result in a significant overall reduction in the level of hypercapnia, may be related that recovering from an acute episode of hypercapnic respiratory failure, our patients were still quite tachypnoeic, while as said before, the CO2 washout is greater at a lower respiratory frequency. However, patients with PaCO2≥ 65 mmHg at enrolment showed a greater reduction of PaCO2 value with asymmetric NHF cannula. In oxygen-dependent COPD patients the association between carbon dioxide and mortality has a U shape prognostic model with the worst prognosis for high PaCO2 values. In our analysis, most patients (65%) received long term oxygen therapy , had moderate to severe airflow obstruction (IQR value of FEV1 42-58 %) and a severe Charlson comorbidity index (CCI) score (≥ 5).To note, at baseline the median of PaCO2 was 64.6 mmHg namely >8.0 kPa which is the cut off that rises mortality by more than 15% in the above-mentioned prognostic model [76]. In addition, carbon dioxide directly controls the activity of inspiratory muscles alone and its reduction may lead to a decrease in diaphragmatic effort. We found that the decrease of PaCO2 was also associated with a trend toward a reduction in tidal volume and diaphragm thickening fraction confirming a crucial role of the washout of the upper airways that allow a higher fraction of minute ventilation to participate in gas exchange. Based on

our results and the fact that we did not find any difference in terms of comfort compared to the standard cannula, we can hypothesize that the asymmetrical cannula may have a role especially in COPD patients with higher dead space ventilation. However, this needs to be validated in specific designed clinical trials. Finally, COPD patients with persistent hypercapnia following recovery from the acute episode experience an increased mortality and early rehospitalization compared to those who have reversible hypercapnia [85].The guidelines on long-term home non-invasive ventilation for management of COPD suggest starting NIV treatment 2-4 weeks after resolution of acute exacerbation only if hypercapnia persists [86].However, the adherence to long term NIV is scarce and NIV is not well tolerated in all patients. Considering NHF effects on reducing carbon dioxide, its ease of use and patient comfort, NHF has been proposed an alternative to NIV in this setting [84]. In the direct comparison with domiciliary NIV, home NHF resulted in similar clinical outcomes, but it was not assessed whether there is or is not a "critical" PaCO2 threshold above or below which one of the two methods is preferable [84]. Therefore, based on our data we can hypothesize a potential advantage of using asymmetric NHF cannula over standard interface as alternative to NIV in COPD patient with persistent hypercapnia after an acute exacerbation. Ongoing studies will confirm or not this hypothesis (NCT05167201). This study has several limitations. First, it represents an exploratory analysis with a small sample size, thus the study might be underpowered to detect a clinically important difference for the primary outcome between the two interventions. Second, since experiments were time consuming and some patients tolerated only few measurements, it was not possible to test the effect of higher flow rates or different cannula size. In fact, both NHF rate and size of cannula can have an impact on the CO2 washout from anatomical dead space and on the resistance-dependent generated

positive pressure. Third, we did not control for the potential effect of open mouth breathing, although this may have an impact in both types of NHF. Finally, despite we know all limitations of the ultrasound for assessing the diaphragm activity, we preferred diaphragm thickening fraction rather than the transdiaphragmatic pressure for technical reasons. In fact, we cannot exclude that the presence of the balloon catheter in the nostrils of patient can interfere with the reverse flow generated by the asymmetric cannula potentially reducing its effect. Therefore, more studies are needed to confirm our results and to further elucidate the efficacy of asymmetrical NHF in this patient population.

4. CONCLUSIONS

Despite several potential positive physiological mechanisms, the use of NHF in chronic hypercapnia needs still to be confirmed in larger randomized controlled trials. Promising results were obtained when NHF was compared with SOT, in terms of reducing the level of PaCO2. Studies suggest that NHF may be used during NIV intervals instead of SOT.

In this physiological study, we found that, asymmetrical cannula did not significantly decrease PaCO2 compared with the standard cannula in patients recovering from an episode of acute respiratory failure due to COPD exacerbation. Similar performances were also observed in terms of diaphragm activity, dyspnoea, and patient's comfort. Interestingly, asymmetrical NHF cannula performed significantly better in reducing the dead space ventilation and increasing the ventilatory efficiency in more severe COPD patients with higher baseline PaCO2 values.

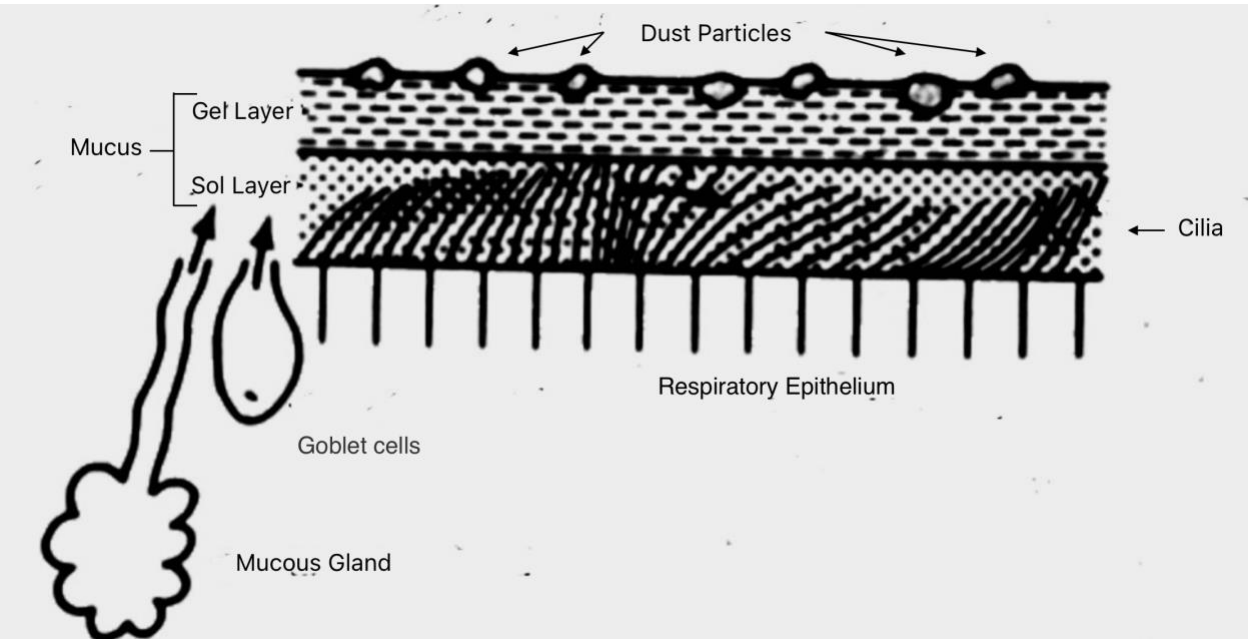

Figure 1. The mucous is produced by glands in the respiratory epithelium and comprises of sol (watery) and gel (sticky) layers. The sol layer is less viscous than the gel layer, allowing the cilia to beat freely. Epithelial cilia transport the sol layer and the gel layer into the larynx. Dust particles trapped in the mucus are expelled when coughing or swallowing.

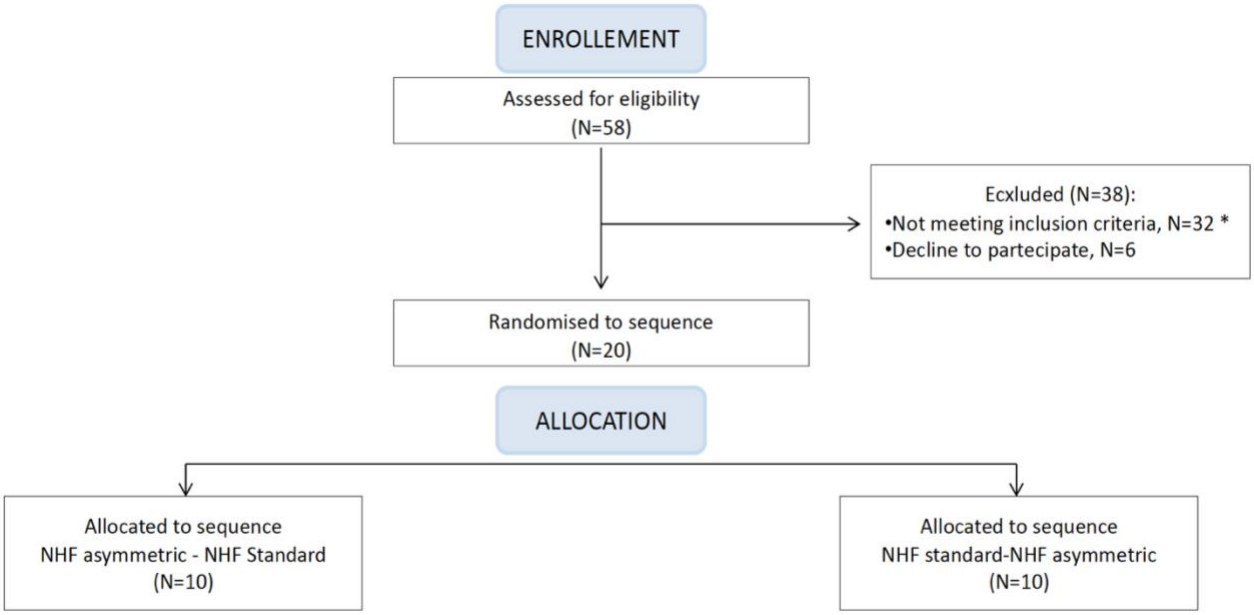

Figure 2. Participant Flow Diagram.

*Patients not meeting the inclusion criteria: arterial blood gas levels did not meet inclusion criteria N=13; BMI> 30 kg/m2 N=8; known or clinically suspected diagnosis of sleep-disorders N=6; restrictive pulmonary/chest wall disease=3 ; lack of collaboration N=2.

Abbreviations: BMI=body mass index, NHF =Nasal High Flow.

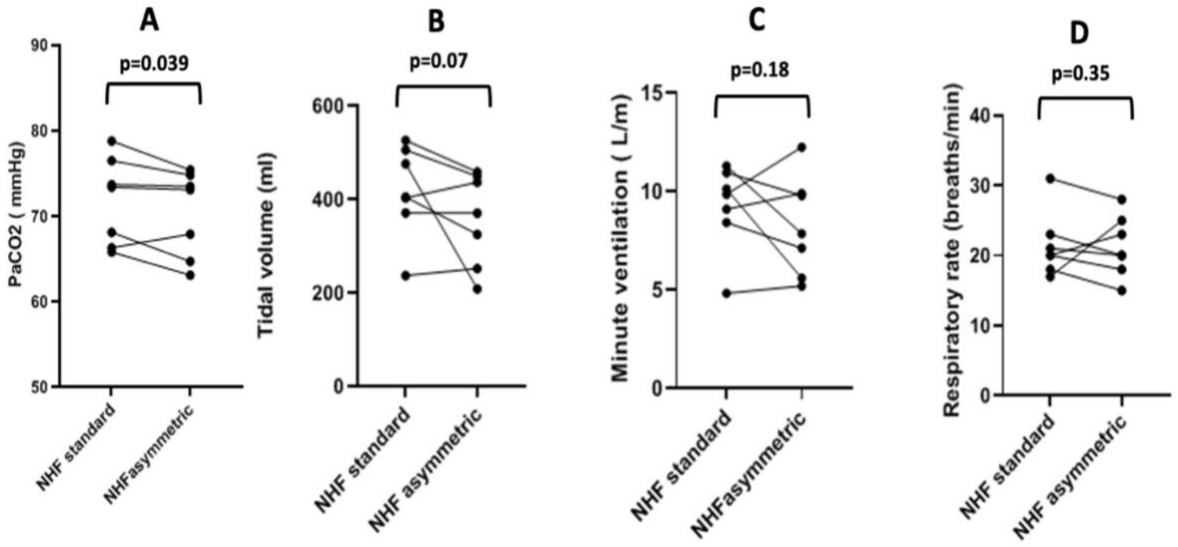

Figure 3 A. Comparison of PaCO2 between standard and asymmetric NHF therapy in subgroup of patients (n=7) with PaCO2 baseline ≥ 65 mmHg. Respiratory pattern between standard and asymmetric NHF therapy in the same subgroup of patients (B. tidal volume; C. minute ventilation and D. respiratory rate)

Abbreviations: NHF: nasal high flow, PaCO2: partial pressure of carbon dioxide

Table 1. Baseline characteristics of the study group

	n=20
Age, yrs	78 [75-85]
Sex (male ,%)	16 (80%)
BMI, kg/m2	24[19-27]
FEV1 (% pred)	48 [42-58%]
LTOT (n/%)	13(65%)
Smoking status, never/present/former (n, %)	2(10%)/6(30%)/12(60%)
Charlson Index	6 [5-6]
SAPS II score	30[27-37]
pH	7.41[7.38-7.44]
PaCO2 (mmHg)	64.6[57.2-74.1]
PaO2(mmHg)	65.2[60.7-71.9]
PaO2/FiO2 ratio	226[202-262]
Respiratory rate (breaths/min)	22[17.7-26.7]
Tidal volume (ml)	449[333-502]

Continuous variables are expressed as median [interquartile range] and categorical variables as absolute value (%).

Abbreviations: BMI=body mass index; FEV1=Forced Expiratory Volume in the 1st second, LTOT=long-term oxygen therapy, SAPS II score: Simplified Acute Physiology Score, PaCO2=arterial partial pressure of carbon dioxide, PaO2=arterial partial pressure of oxygen FiO2=inspiratory fraction of oxygen

Table 2*:* Gas exchange, vital signs, diaphragm ultrasound evaluation, dyspnea, and comfort.

Variable	Standard NHF (n=20)	Asymmetric NHF (n=20)	p value
pH	7.44[7.41-7.46]	7.44[7.42-7.45]	0.90
PaCO2 (mmHg)	58.6[54.8-67.6]	61.3[55-67.4]	0.96
PaO2(mmHg)	64.3[60.9-67.1]	62.7[58.5-65.1]	0.42
PaO2/FiO2 ratio	216[179.-250]	205[164-229]	0.55
Respiratory rate (breaths/min)	20[18-26]	23[18-26]	0.61
SPB, mmHg	121[111-128]	116[108-134]	0.57
DPB,mmHg	70[56-74]	64[59-71]	0.72
Tidal volume (ml)	432[370-499]	408[355-458]	0.17
End-expiration diaphragm thickness (mm)	1.9[1.5-2.6]	1.8[1.4-2.6]	0.67
End-inspiration diaphragm thickness (mm)	2.5[2.1-3.5]	2.7[2.1-2.9]	0.65
TFdi (%)	37.5[25-68.7]	31.2[23.5-53.8]	0.37
Comfort (range 0-10)	8[6.2-9.7]	8[6-10]	0.71
Dyspnoea (range 0-10)	1[0-3]	1[0-5]	0.18

Variables are expressed as median, with an interquartile range [IQR].

Abbreviations: PaCO2=arterial partial pressure of carbon dioxide, PaO2=arterial partial pressure of oxygen FiO2=inspiratory fraction of oxygen, SPB=systolic blood pressure, DPB= diastolic blood pressure TFdi=diaphragm thickening fraction

Table 3*:* Comparison of nasal high flow treatment with any interface vs standard oxygen

Variable	Standard NHF a (n=20)	Asymmetric NHF b (n=20)	SOT c (n=20)	p value (a-c)	p value (b-c)
pH	7.44[7.41-7.46]	7.44[7.42-7.45]	7.41[7.38-7.44]	<0.0001	0.0011
PaCO2 (mmHg)	58.6[54.8-67.6]	61.3[55-67.4]	64.6[57.2-74.1]	0.0007	0.0006
PaO2(mmHg)	64.3[60.9-67.1]	62.7[58.5-65.1]	65.2[60.7-71.9]	0.23	0.15
PaO2/FiO2 ratio	216[179.-250]	205[164-229]	226[202-262]	0.18	0.04
Respiratory rate (breaths/min)	20[18-26]	23[18-26]	22[17.7-26.7]	0.7	0.75
SPB, mmHg	121[111-128]	116[108-134]	123[110-135]	0.39	0.30
DPB,mmHg	70[56-74]	64[59-71]	68[60-63]	0.34	0.37
Tidal volume (ml)	432[370-499]	408[355-458]	449[333-502]	0.67	0.18
End-expiration diaphragm thickness (mm)	1.9[1.5-2.6]	1.8[1.4-2.6]	1.8[1.3-2.4]	0.66	0.19
End-inspiration diaphragm thickness (mm)	2.5[2.1-3.5]	2.7[2.1-2.9]	2.7 [1.9-3.3]	0.25	0.48
TFdi (%)	37.5[25-68.7]	31.2[23.5-53.8]	41.7[21.9-55.2]	0.7	0.37
Comfort (range 0-10)	8[6.2-9.7]	8[6-10]	9[8-10]	0.039	0.12
Dyspnoea (range 0-10)	1[0-3]	1[0-5]	1[0-4.7]	0.9	0.28

Variables are expressed as median, with an interquartile range [IQR]. a = Standard Nasal High Flow (NHF); b = Asymmetric Nasal High Flow; c = Standard Oxygen Therapy (SOT) *Abbreviations*: PaCO2=arterial partial pressure of carbon dioxide, PaO2=arterial partial pressure of oxygen FiO2=inspiratory fraction of oxygen, SPB=systolic blood pressure, DPB= diastolic blood pressure TFdi=diaphragm thickening fraction

Table 4: Subset analysis: PaCO2, respiratory rate, tidal volume, diaphragm ultrasound evaluation, dyspnea, and comfort.

Variable	Standard NHF a (n=7)	Asymmetric NHF b (n=7)	p value a-b
PaCO2 (mmHg)	73.4[66.3-76.5]	73.1[64.74.8]	**0.039**
Respiratory rate (breaths/min)	20[18-23]	20[18-25]	0.35
Tidal volume (ml)	405[371-505]	370[252-450]	0.07
Minute ventilation (L/min)	9.9 [8.4-10.7]	7.9[5.6-9.9]	0.18
End-expiration diaphragm thickness (mm)	1.3[1.7-4]	1.8[1.3-3.2]	0.34
End-inspiration diaphragm thickness (mm)	3.4[1.9-4.6]	2.8[1.9-5.2]	0.5
TFdi (%)	68.7[35.5-90]	53.8[28.45-61.50]	0.06
Comfort (range 0-10)	8[7-9]	9[6-10]	0.25
Dyspnoea (range 0-10)	0.5[0-3]	1.5[0-3]	0.5

Only patients with PaCO2 >65 mmHg at baseline were analyzed. Variables are expressed as median, with an interquartile range [IQR]. a = Standard Nasal High Flow (NHF); b = Asymmetric Nasal High Flow
Abbreviations: PaCO2=arterial partial pressure of carbon dioxide, TFdi=diaphragm thickening fraction

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