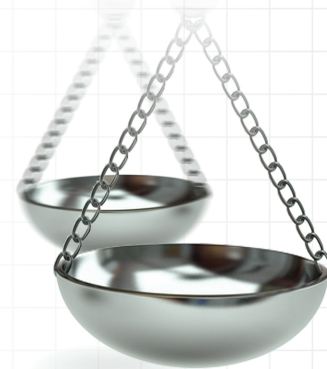




Why, whether and how to use high-flow nasal therapy in acute exacerbations of chronic obstructive pulmonary disease

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Claudia Crimi¹ & Andrea Cortegiani^{*,2,3}

¹Respiratory Medicine Unit, Policlinico 'G. Rodolico-San Marco' University Hospital, Via S. Sofia, 78, Catania 95123, Italy

²Department of Surgical, Oncological & Oral Science (Di.Chir.On.S.), University of Palermo, Palermo, Italy

³Department of Anesthesia, Intensive Care and Emergency, Policlinico Paolo Giaccone, University of Palermo, Via del Vespro, 129, Palermo 90127, Italy

*Author for correspondence: andrea.cortegiani@unipa.it

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Treatment of acute exacerbation of chronic obstructive pulmonary disease: tradition & beyond

Noninvasive ventilation (NIV) represents the standard of care for respiratory support of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) developing acute hypercapnic respiratory failure (AHRF) [1]. NIV has been shown to reduce patient's work of breathing and mortality and be feasibly implemented in various hospital location facilities at different timing, based on the severity of AHRF [2] and it is also widely used in clinical practice by physicians [3]. However, clinicians' knowledge, experience and expertise in the management of NIV are crucial for its success in order to overcome common problems that may lower its effectiveness such as patients' discomfort due to the interfaces (e.g., tight-fitting face masks), excessive air leaks from the masks and patient–ventilator asynchrony. Thus, despite improvements in mask and ventilator technology to enhance patients' comfort and clinicians' optimization of ventilator settings to improve patient–ventilator interactions, NIV tolerance is still a major issue that can cause NIV failure with rates ranging from 5 to over 50% [4].

The relatively recent introduction into clinical practice of high-flow nasal therapy (HFNT) as a new noninvasive respiratory support led to growing reports on the potential role of this technique in these settings [5]. HFNT delivers a mixture of heated and humidified air with or without supplementary oxygen with an adjustable flow rate ranging from 20 to 60 l/m through a nasal cannula. To date, clinical practice guidelines recommended using HFNT in patients with acute hypoxemic respiratory failure [6], as the scientific community is still seeking to understand all the underlying physiological mechanisms leading to its beneficial effects and exploring the clinical outcomes related to its use. Moreover, HFNT gained increased popularity during the COVID-19 pandemic making HFNT devices widely available [7] and used in the frontline within different wards in the hospitals and among physicians of different specialties [8].

HFNT in AECOPD: Why?

HFNT represents an intriguing and groundbreaking approach for managing patients with acute respiratory failure since it improves ventilatory efficiency and respiratory mechanics with a consequent reduction of respiratory rate and inspiratory effort. Moreover, it has the advantage of providing an accurate fraction of inspired oxygen (FiO_2) matching patient's inspiratory peak flow, washes out anatomical dead space reducing CO_2 rebreathing and provides a small degree of positive airway pressure that may counteract intrinsic PEEP and delivers warmed humidified gas that may enhance secretion removal [5]. Indeed, its compact, soft and ergonomic interface is simple to implement and

wear, lightening nurse workload and promoting patients' activities, allowing them for speaking, coughing, feeding, taking oral medications. It can also help implementing physiotherapy interventions and keeping patients' minimal personal care and hygiene independently without losing some of the benefits of positive pressures.

Considering the abovementioned physiological effects, HFNT may have potential specific clinical advantages for COPD patients with acute worsening of symptoms, such as increased sputum volume and breathlessness. The excessive production of thick, viscous mucus that leads to further airways obstruction might be tackled by the warmed and humidified air delivered by HFNT that may preserve and optimize mucociliary function and reduce mucus viscosity. Moreover, the dynamic hyperinflation and the shallow tidal volumes of COPD patients during exacerbation contributes to greater dead-space ventilation and determines an increase of the physiological ratio between dead space volume (VD) and tidal volume (VT; VD/VT) at rest; therefore, each tidal breath becomes less effective at removing CO₂. In this regard, the high gas flow flushes the upper airways with fresh oxygenated air replacing the expired CO₂ enriched gas of the anatomical dead space. Moreover, the positive airway pressure generated by HFNT during expiration may improve the patient's breathing pattern, similarly to the pursed-lip breathing, an involuntary compensatory mechanism often implemented by COPD patients to relieve shortness of breath.

On top of these several physiological effects, HFNT has the advantage of overcoming some of the major barriers of NIV use, such as the unavoidable skin contact pressure due to NIV interfaces and the need for patient cooperation. Nevertheless, rare side effects may also occur with HFNT, including epistaxis, noise or temperature-related discomfort [9]. Thus, theoretically, also patients who are considered poor candidates for NIV, such as those who reject the treatment, mild AECOPD with higher pH, uncooperative or agitated, may benefit from HFNT. Accurately monitoring of both HFNT and NIV is crucial to avoid treatment failure and delay in intubation.

Indeed, a cornerstone of modern medicine is to consider the relationship between disease processes, disease experience and clinical outcomes. This is specifically important for patients with AECOPD where clinicians should make a balanced decision when choosing the best possible noninvasive respiratory approach with the goal of improving overall care and not only targeting clinician-centered outcomes such as mortality, PaCO₂ reduction and pH improvement but also impacting patient centered outcomes like symptoms, patient satisfaction, treatment adherence, ease of mucus expectoration, basic daily activity limitation and mood state.

Whether or not to use HFNT in AECOPD: the evidence

Few uncontrolled observational studies examined the use of HFNT in the management of AECOPD patients, including a wide heterogeneous subpopulations of AECOPD in different clinical settings.

Plotnikov and colleagues [10], in their multicenter prospective observational study of 138 patients admitted to the ICU in five centers in Argentina, showed that HFNT delivered through high velocity nasal insufflation as an initial ventilatory strategy in moderate-to-severe COPD patients with AHRF determined a significant reduction in PaCO₂ (57 vs 52 mmHg, $p < 0.001$) and respiratory rate (29 vs 21 breaths/min, $p < 0.001$) compared with baseline. Moreover, the authors found a reduction in accessory muscle recruitment and thoracoabdominal asynchronies as an expression of changes in lung mechanics [11]. Similarly, in a small feasibility study from our group [12] the use of HFNT in patients with AECOPD and copresence of bronchiectasis, HFNT was able to significantly improve dyspnea (Borg scale from 6.7 ± 1.4 to 4.1 ± 1.3 [$p < 0.001$]) and quantity of mucus production (1.1 ± 0.6 vs 2.4 ± 0.7 , $p < 0.001$), decreased respiratory rate from 29.6 ± 2.7 breaths/min to 23.2 ± 2.9 breaths/min ($p < 0.001$) and pCO₂ after 24 h (58.4 ± 13 versus 51.7 ± 8.2 [$p = 0.003$]). Sun *et al.* [13] performed a retrospective study in ICU settings, including patients with AHRF of various underlying etiology, including AECOPD, characterized by severe hypoxemia (PO₂ ≤ 45 mmHg) and moderate hypercapnia (PaCO₂ ≥ 50 mmHg) with pH ranging between 7.25 and 7.35. They found no difference in 28 day mortality between the 39 patients treated with HFNT and the 43 subjects who received NIV (HFNT 15.4 vs 14% NIV, $p = 0.824$), but a better tolerance in the HFNT group. Lee and coworkers [14] conducted an observational cohort study on 92 hospitalized AECOPD patients with moderate AHRF (>7.25 pH <7.35) in a Respiratory Unit. They found no difference in intubation rate (HFNT 25 vs NIV 27.3%, $p = 0.857$) and 30 day mortality rate (HFNT 15.9 vs NIV 18.2%, $p = 0.845$) between the two treatments and no difference in blood gases improvement at 6 and 24 h of HFNT application. However, the study was underpowered to detect a clinically important difference due to the small sample size and did not describe treatment settings and how the outcomes were assessed. Doshi and coworkers also reported similar findings in a subgroup analysis of 65 patients with AHRF due to AECOPD from

a large randomized controlled trials (RCT) comparing a form of HFNT, high velocity nasal insufflation, to NIV and showing noninferiority between the two treatments in terms of failure at 72 h [15].

A small number of RCTs has directly compared HFNT versus NIV in AECOPD with similar results.

Cong and coworkers [16] in their RCT of 168 male patients with AECOPD in China based in the Respiratory Unit settings showed both NIV and HFNT are effective in improving arterial blood gases at 12 h and 5 days with better comfort and higher nursing satisfaction in the HFNT arm and a reduction in hospital stay, using an average flow of 30–35 l/min. Braunlich *et al.* [17] explored the role of HFNT used for nearly 3 h at a mean flow rate of 25 l/min in 38 AECOPD patients with AHRF who did not tolerate NIV showing a significant reduction in PaCO₂ and an increase in pH, especially in the subsets of patients with less severe AHRF.

A very recent multicenter RCT with a noninferiority design enrolled 80 patients with mild-to-moderate AECOPD (pH 7.25–7.35, PaCO₂ ≥55 mmHg) before ventilator support to HFNT or NIV. HFNT significantly reduced PaCO₂ over the study time points (2 and 6 h) and was statistically noninferior to NIV in terms of PaCO₂ clearance. However, 32% of patients receiving HFNT required NIV by 6 h and almost 50% needed NIV during hospitalization. Indeed, patients who switched to NIV remained for a longer time on ventilation. The authors commented that although, the statistical noninferiority criteria were met, these results questioned the clinical effectiveness of HFNT in AECOPD when compared with NIV [18].

How should we translate this evidence into clinical practice? The interpretation of available evidence should consider different limitations.

Heterogeneity among the published studies concerning the severity of AHRF, the HFNT operational settings, the follow-up time points and instruments (scales of measurements) used for patient-centered outcomes assessment [19] and the clinical settings where the treatment was performed are the shortcomings that prevent to draw definitive conclusions. Therefore, clinicians need to use wise clinical judgment and caution when select and implement HFNT for AECOPD for an individual patient to avoid inappropriate or inadequate use of noninvasive respiratory support.

How to use HFNT in AECOPD & future trajectories

Theoretically, HFNT has the fulfillment of an ideal device and sounds like a ‘dream machine’ that may revolutionize clinicians’ and patients’ lives in the ward, being even more *noninvasive* than NIV. While NIV is still the gold standard for AECOPD patients, there is a strong pathophysiological rationale for using HFNT in AECOPD, showing a time window for the successful application of HFNT to tackle the various multifaceted aspects of COPD and reports from ongoing research are yet to come. However, the evidence to date is inconclusive and validated criteria for HFNT initiation, continuation, monitoring and withdrawal are lacking, suggesting caution against the widespread clinical use in this setting. Probably, from a clinical standpoint, a compromise between patient’s tolerance and comfort and treatment’s effectiveness and safety might be adopted. Clinicians should act differently on an individual basis, looking more at clinically meaningful markers that might help them address the complexity and heterogeneity of AECOPD phenotypes and promote patient empowerment to select the best treatment option [20]. Moreover, it is essential to consider that these two treatments are not competing but complementary in the management of AHRF due to AECOPD.

There are few medical interventions with the highest level of supporting evidence and large, long-lasting clinical application as NIV in AECOPD. HFNT has the potential to ‘help’ NIV in those situations where it may lack efficacy or be problematic. Based on an available data, future studies evaluating comparisons of efficacy and safety should be performed with caution. Indeed, future research should compare larger AECOPD patients’ cohorts HFNT to NIV to find suitable patients’ targets in terms of severity and proper time of application. Indeed, a potential ‘rotational’ strategy combining NIV and HFNT may boost the advantages of both techniques concerning respiratory mechanics, gas exchanges and comfort. This may be translated in clinics into a cautious, timely and tailored personalized HFNT approach in selected COPD patients, alone or combined with NIV.

Insights for future research

In our opinion, well-designed superiority RCTs with sufficient study periods and population sizes are needed to unbiasedly assess without further assumptions the effect of HFNT in AECOPD compared with the established reference treatment with NIV, particularly aiming at assessing the correct timing of implementation and the duration of treatment effect. Future research should also focus on exploring whether the combined use of HFNT

during breaks off NIV might be a successful strategy to exploit the physiological effects and the ergonomic features of HFNT in ACOPD patients.

Author contributions

C Crimi and A Cortegiani wrote and critically revised the initial draft and agreed on the final version of the manuscript.

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