



Monaldi Archives for Chest Disease

eISSN 2532-5264

<https://www.monaldi-archives.org/>

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Monaldi Arch Chest Dis 2023 [Online ahead of print]

To cite this Article:

Rathi V. **Comments on “Post-extubation high-flow nasal cannula oxygen therapy versus non-invasive ventilation in chronic obstructive pulmonary disease with hypercapnic respiratory failure”**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2023.2737

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Comments on “Post-extubation high-flow nasal cannula oxygen therapy *versus* non-invasive ventilation in chronic obstructive pulmonary disease with hypercapnic respiratory failure”

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Contribution: VR, literature search, planning, conduct, writing the original draft of manuscript, and editing. VR is corresponding author and guarantor.

Conflict of interest: The author declares no conflict of interest regarding current study.

Funding: The current study is not funded.

Availability of data and material: The clinical data and the study materials available from the corresponding author on reasonable request.

Ethics approval: Not applicable

Patient consent: Not applicable

Key words: HFNO; hypercapnic respiratory failure; post-extubation.

Dear Editor,

The recent study published by Ketan *et al.* provides emerging evidence on the expanding indications for high flow nasal oxygen (HFNO) therapy in chronic obstructive pulmonary disease (COPD) [1]. The indications for hypoxemic respiratory failure being robust, the indications for HFNO in hypercapnic respiratory failure are emerging. The study by Ketan *et al.* concludes that HFNO can be used as an alternative to NIV in preventing post-extubation respiratory failure in COPD patients having hypercapnia with better tolerance. The authors, however, have not provided details on the type of devices used and the final oxygen requirements in both NIV and HFNO. Besides, cardiac comorbidities and underlying evidence of cardiac failure could also have influenced the settings of the modality used along with the outcome.

Recent practice guidelines suggest using non-invasive ventilation (NIV) over HFNO for non-surgical individuals with high risk of extubation failure after invasive mechanical ventilation (IMV) [2]. Individuals with respiratory disease and/or hypercapnia during pre-extubation spontaneous breathing trial were among the criteria used to describe high risk status. The suggestion was made for nonsurgical patients and not for COPD alone. This is important since NIV is clearly beneficial in diseases like congestive heart failure due to its ability to clear away pulmonary edema or in neuromuscular diseases [3], where NIV is required to assist respiratory muscles. In both these examples, the role of NIV is not primarily based on prevention of hypercapnic respiratory failure. It is therefore prudent to not universally apply the suggestion of using NIV over HFNO in post-extubation COPD patients.

A preliminary analysis of the data used in the European Respiratory Society (ERS) guidelines provides an intriguing picture [2]. The suggestion favouring NIV was based on an analysis of about 1550 individuals from six different studies. The analysis is however skewed by two trials that when put together constitute 80% weightage. The first trial, which contributed 52% weightage and included 690 individuals, found that the reintubation risk was greater with High flow oxygen therapy (HFOT) (22.8%) than NIV (19.1%), although this difference was not statistically significant [4]. Post-extubation respiratory failure was lower with HFOT (26.9%) than with NIV (36.8%). HFOT also achieved the non-inferiority threshold. A key aspect here is that only 116 out of 690 (16.81%) individuals had COPD and only 48 (6.96%) had an exacerbation of COPD. The authors did not specify if the outcomes were different in the subgroup of their study population which had hypercapnic COPD.

The second trial, which contributed 38% weightage, compared using HFOT alone to HFOT with intermittent NIV in the post-extubation period in individuals with high risk of reintubation. This trial did not have a NIV alone arm and should not have been used to draw an inference favouring NIV alone over HFOT alone [5]. Further, like the first trial mentioned above, there were non-COPD individuals. Among other diagnoses, left ventricular dysfunction or a history of cardiogenic pulmonary edema was present in 137 out of 641 individuals (21.37%).

Smaller randomized controlled trials comparing HFOT with NIV in the post-extubation period in COPD have found HFOT to be similar in performance to NIV. Ketan and colleagues studied 62 individuals and found reintubation rates to be similar (HFOT: 26.67%, NIV: 25%) [1]. The length of intensive care unit (ICU) stay was also similar (HFOT: 5.5d, NIV: 6.6d). Tan and colleagues found a composite endpoint incidence of reintubation or switch of therapy (from HFOT to NIV or vice-versa) to be similar in 86 individuals (HFOT: 26.67%, NIV: 25%) [6].

There are other advantages to HFOT that also need to be considered in COPD. Jing and colleagues studied comfort levels and the need for bronchoscopy to clear-off respiratory secretions in 42 COPD patients with hypercapnia at extubation. Both endpoints were significantly better with HFOT [7]. There is also evidence for similar performance of HFOT and NIV in acute hypercapnic COPD, not requiring IMV. Du and colleagues analyzed 7 trials with 481 patients total. They found no significant differences between the two treatment modalities in PaCO₂ levels, need for intubation, or mortality. They noted significantly lower complication and respiratory rates with HFOT [8].

There are a few proposed mechanistic bases for using HFOT in hypercapnic COPD: provision of constant fraction of inspired oxygen (FiO₂) and high inspiratory flow rates, washout of upper airway dead space and thus of carbon dioxide, humidified air and a comfortable unobtrusive nasal interface that increases patient compliance and allows secretion clearance, reduction of airway resistance during inhalation, and provision of end expiratory pressure (up to 3-6 cm of water). Better patient comfort and thus, better compliance is crucially important when considering HFOT versus NIV. A patient not tolerating NIV, due to high pressures or tight mask straps, tends to repeatedly remove their mask [9]. This interruption can potentially lead to NIV failure and reintubation. In this scenario, HFOT can prove to be pivotal in preventing invasive mechanical ventilation (IMV).

Finally, the greatest benefit may in fact lie in using both modalities together, rather than choosing one over the other. Thille and colleagues evaluated HFOT alone and HFOT with intermittent NIV in a subgroup analysis of the trial which was used as contributory evidence in the ERS guidelines [10]. This subgroup analysis included 150 individuals with COPD. Hypercapnia was present in 53 (35%). All 150 had been randomized to HFOT alone or HFOT with intermittent NIV. The total time period of NIV usage is 23 hours in the first two days. Seven-day reintubation rates were significantly better with HFOT and intermittent NIV than HFOT alone (13% vs 27%, $p=0.03$). ICU and 72-hour reintubation rates were also significantly better with intermittent NIV. There was no mortality difference between the two groups.

To conclude, there is a need for randomized trials with robust methodology and large sample size of patients comparing HFOT alone, NIV alone, and intermittent NIV with HFOT in COPD with hypercapnia. Perhaps, only then would the role of HFOT be fully established. However, at present, outside of research scenarios, NIV remains the preferred modality over HFOT in COPD patients in the post extubation period. HFOT may be used where NIV is not tolerated or is contraindicated. There is some evidence favouring the use of HFOT with intermittent NIV.

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