High-flow nasal oxygen versus noninvasive ventilation for hypoxemic respiratory failure: Do we know enough?

Giulia Spoletini, Nicholas S. Hill[1]

Respiratory Support and Sleep Centre, Papworth Hospital NHS Foundation Trust, Cambridge, UK, [1]Pulmonary, Critical Care and Sleep Division, Tufts Medical Center, Boston, MA, USA

Address for correspondence:
Prof. Nicholas S. Hill, Tufts Medical Center, 800 Washington Street, No. 257, Boston, MA 02111, USA.
E-mail: nhill@tuftsmedicalcenter.org

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Acute hypoxemic respiratory failure (AHRF) is a common reason for admission to Intensive Care Units (ICUs) and may be caused by a number of underlying processes including, but not limited to, acute cardiogenic pulmonary edema (ACPE), pneumonia, acute respiratory distress syndrome (ARDS), and sepsis.[1] In the absence of specific therapies for the lung injury underlying AHRF, the therapeutic approach is to treat contributing factors such as infection or fluid overload and provide supportive care while awaiting resolution. Oxygen supplementation is an important aspect of supportive care, and a number of techniques are used to provide it.

Conventional approaches to provide supplemental oxygen include nasal cannulae, face masks, shovel masks, and nonrebreather masks, selected on the basis of the patient's oxygen needs to attain a target level of oxygenation, comfort, and tolerance. These devices deliver relatively low flow oxygen and often provide lower than targeted FiO_2 due to air entrainment, as the dyspneic patient's inspiratory flow rate far exceeds the flow capabilities of the oxygen delivery devices.[2] Due to their intrinsic limitations, these systems often fail, leading to the need for endotracheal intubation and invasive mechanical ventilation.

Noninvasive ventilation (NIV), which assists ventilation by providing pressurized, oxygenated gas to the airways via a tight-fitting facial interface, has shown benefit for certain forms of acute respiratory failure (ARF) such as those due to exacerbation of chronic obstructive pulmonary disease or ACPE.[3] However, patients often tolerate these devices poorly due to discomfort and claustrophobia. In addition, with the exception of patients with ACPE, use of NIV has been controversial in patients with AHRF, with NIV failure rates as high as 70% as well as high mortality rates.[4] The high respiratory rates and minute volumes often seen in these patients lead to poor synchrony with the ventilator. High inspiratory and expiratory pressures, needed to alleviate respiratory distress and hypoxemia, often predispose to increased air leaks and the need to tighten the mask straps, which intensifies mask discomfort and leads to intolerance. These limitations of NIV have sparked interest in noninvasive alternatives to NIV.

One such alternative is high-flow nasal oxygen (HFNO), which has been in clinical development for the past two decades, initially in neonatal medicine, where it was introduced as an alternative to CPAP to treat neonatal respiratory distress syndrome.[5] These systems have more recently been adapted to deliver oxygenated gas to adults. They consist of a flow generator that can provide gas flow rates up to 60 L/min, an active humidifier that fully saturates the gas mixture at 31 to 37°C, even at the highest flow rates, and an air/oxygen blender that can vary FiO_2 from 0.21 to 1.0 independently of gas flow. The gas is delivered via heated tubing (to prevent condensation) through loose fitting large bore nasal prongs. The heated, humidified gas is usually well-tolerated by patients, even at the highest flow rates, presumably because it avoids the mucosal desiccation that accompanies nasally delivered dry gas mixtures. Initially, it was thought that its greatest benefit would be to keep secretions moist and promote mobilization, an effect for which there is some evidence,[6] but it soon became apparent that it also offers other advantages over standard oxygen (SO) delivery systems.

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For example, HFNO increases patients' comfort and tolerance compared to SO delivery systems[7-9] while it enhances oxygenation via several mechanisms. For one, the high flow rates come closer to the patient's inspiratory flow rate, thereby reducing entrainment of room air during inspiration.[10] HFNO also flushes out anatomical dead space in the nasopharynx and upper airways,[11] assuring more reliable delivery of FiO_2 and improving ventilatory efficiency. Furthermore, it provides a small amount of positive end-expiratory pressure (PEEP), amounting to roughly 1 cm H_2O for every 10 L/min flow when the mouth is closed.[12] This may further improve oxygenation and reduce work of breathing in patients with auto-PEEP. Presumably due to these physiologic effects, HFNO has manifested benefits such as enhanced comfort, reduced respiratory rate, and improved oxygenation compared to SO therapy in patients with ARF in the postsurgical[13,14] and postextubation settings[8,9,15,16] as well as in palliative settings for do-not-intubate patients.[17]

Until recently, clinical studies of HFNO to treat ARF were mainly small cohort studies or retrospective analyses, with a few small, underpowered randomized controlled trials (RCTs).[18] Within the past year, however, several studies have provided higher quality evidence. Frat *et al*.[19] reported in the New England Journal of Medicine the results of the first RCT assessing the efficacy of HFNO on intubation and mortality rates and other clinical outcomes in patients with *de novo* AHRF. Three hundred twenty subjects admitted to the ICU with AHRF (AHRF - defined as PaO_2/FiO_2 ≤300, $PaCO_2$ <45 mm Hg and respiratory rate >25 breaths/min) were included in the study and randomized into three arms: HFNO, SO, and NIV.

Although the primary outcome variable, intubation rate, did not reach statistical significance, there was a trend toward a favorable effect of HFNO over the other 2 therapies (38%, 47%, and 50% for HFNO, SO, and NIV, respectively, $P = 0.18$). A *post hoc* subgroup analysis on only the subjects with a PaO_2/FiO_2 <200 showed a significantly lower intubation rate among the patients treated with HFNO. Furthermore, the secondary outcomes were all in favor of the HFNO. Remarkably, both the ICU and 90 days mortality rates were significantly lower in the study group (13%, 22%, and 31% 90 days mortality rates in the HFNO, SO, and NIV groups, respectively, $P = 0.02$) regardless of whether subjects were intubated or not. In addition, the HFNO group had an average of 5 more ventilator-free days at day 28 than the NIV group, $P = 0.02$. In addition, subjects on HFNO reported significantly more improvement in respiratory comfort and dyspnea after 1 h of therapy than the other two groups and respiratory rate was slightly, but significantly, lower with HFNO than NIV after 1 h of therapy (28 vs. 31/min, $P < 0.01$).

Strengths of the Frat trial include intubation criteria that were prespecified, reducing variability due to differing clinicians' choices. In addition, possible overestimation of NIV efficacy was addressed by exclusion of patients with hypercapnia, chronic respiratory diseases or ACPE, and stratification of patients based on past cardiac history.

However, there were a number of weaknesses including the fact that the study was underpowered and it was, in truth, a negative trial, considering that the main outcome variable, intubation rate, did not differ significantly between groups. Furthermore, patients randomized to the NIV arm actually received NIV for only 8 h/day on the first 2 consecutive days (interquartile range 4–12 h on day 1 and 4–13 h on day 2). They received HFNO for the remaining 16 h/day. Thus, this was a trial of mainly HFNO supplemented by NIV, and it is difficult to fathom how 8 h/day of NIV on 2 initial days had such a large effect on mortality at 90 days. Perhaps, the average tidal volume on NIV of 9.2 ml/kg of predicted body weight, well above the 6 ml/kg tidal volumes associated with better outcomes in the ARDSnet tidal volume trial,[20] contributed to ventilator-induced lung injury, thus increasing mortality. In addition, patients randomized to NIV had more septic shock, which could have been a consequence of the trend for more time spent intubated, but could also have signified sicker patients in that group with a concomitant greater risk for death. By their nature, these trials cannot be blinded and are subject to bias, and the use of a crossover from SO or HFNO to NIV "at the discretion" of the treating physician could have altered outcomes, even though it did not result in avoidance of intubation in many patients.

Two other recent RCTs are relevant to this discussion. Almost simultaneously with the Frat trial, Stéphan *et al*.[14] published a trial of HFNO versus NIV in the Journal of the American Medical Association in postcardiac surgery patients. Patients were eligible if they failed a T-piece trial or succeeded a T-piece trial but had risk factors for respiratory failure or failed extubation (as evidenced by a PaO_2/FiO_2 <300 and a respiratory rate >25/min for >2 h). They were randomized to HFNO (50 L/min and 50% FiO_2) or NIV (pressure support 8 cmH_2O and PEEP 4 cmH_2O) used 1 out of 4 h (or more if needed for respiratory stability) and SO was used during NIV breaks. The major outcome variable was treatment failure, defined as the need for intubation, crossover to the other therapy, or early discontinuation, usually due to intolerance. The rate of treatment failure was virtually identical between the groups (roughly 22%), and intubation and mortality rates were also very similar (roughly 14% and 5–6% in both groups, respectively, P = ns). The only statistically significant differences were better oxygenation with NIV and lower respiratory rate with HFNO. Surprisingly, comfort and dyspnea scores did not differ between the groups, indices that have generally favored HFNO in earlier studies.

This study had larger numbers than any previous trials and a well-defined protocol using SO supplementation techniques for NIV breaks, the more usual practice. However, with their lower baseline respiratory rate (low 20 s/min vs. low 30 s/min) and lower rates of intubation and mortality than in the Frat trial, the patients enrolled in the Stephan trial were clearly considerably less ill than those in the Frat trial. The authors concluded that their study found that HFNO was not inferior to NIV and, therefore, could be used in substitution for NIV in postcardiac surgery patients. However, in the absence of a SO control group (not included because NIV was considered to be a standard of care in postoperative patients), it cannot be concluded that either arm of the trial had a significant effect

on the rate of treatment failure compared to SO and this may explain why the study, in contrast to the Frat trial, failed to show any substantial advantages of HFNO over NIV.

Finally, the study by Maggiore *et al.*[16] published in the American Journal of Respiratory and Critical Care Medicine a year ago, compared HFNO (50 L/min) to oxygen supplied via a Venturi mask, with FiO_2 adjusted in both groups to maintain oxygen saturation >92%, in the postextubation setting. Although patients in both groups had mild oxygenation defects and respiratory distress (PaO_2/FiO_2 nearly 240 and respiratory rates in low 20 s/min in both groups), HFNO achieved better oxygenation, lower respiratory rate, improved comfort related to the interface and dryness, and a lower intubation rate (4% vs. 21%, $P = 0.005$). HFNO appeared to be clearly advantageous in this study, but the concern was raised that entrainment of room air with the Venturi mask led to an underestimation of the PaO_2/FiO_2 and could have biased results in favor of HFNO.

Although these studies have quite different designs, methodologies, and patient populations, they are consistent in supporting the idea that HFNO is at least as good as NIV in the treatment of hypoxemic respiratory failure and even appears to have some advantages. First, with the exception of the Stephan study which enrolled quite mildly afflicted patients, HFNO consistently offered greater comfort than both SO and NIV and appears to be better tolerated. Second, HFNO is sometimes more effective in alleviating dyspnea and usually lowers respiratory rate more than either SO or NIV. It is effective at supporting oxygenation better than SO, but may not improve PaO_2/FiO_2 as effectively as NIV in more hypoxemic patients, perhaps related to the higher positive pressure of NIV. Effects on intubation and mortality rates have been inconsistent between studies but some, such as the Frat trial, suggest advantages here as well. An issue of concern with regard to NIV has been adverse effects on work load of nurses and respiratory therapists.[21,22] This has not yet been examined in any of the HFNO studies, but because of ease of application and enhanced tolerance, is likely to be less problematic with HFNO than NIV.

Based on the accumulating evidence, our current view is that once oxygenation becomes moderately impaired, particularly when accompanied by dyspnea and tachypnea, HFNO is preferable to SO due to its greater comfort and tolerability and ability to more reliably deliver a targeted FiO_2, reduce dyspnea, and lower respiratory rate. Although the recent studies support the idea that HFNO can be safely used in place of NIV in patients with hypoxemic respiratory failure, we are not yet convinced that it is superior to NIV in all AHRF settings, other than with regard to comfort. It remains to be seen whether some subgroups, such as those with higher work of breathing (and hence perhaps more likely to benefit from higher pressure support and PEEP levels), may actually benefit more from NIV. We would like to see more studies comparing HFNO and NIV in different patient groups and severities of AHRF (avoiding delay of needed intubation) to see whether HFNO, if initiated early, can more effectively forestall the progression to severe ARDS and avert the need for intubation, as suggested by the Frat trial. In addition, it is important to emphasize that equivalence of HFNO and NIV has not been demonstrated in acute hypercapnic respiratory failure, and HFNO should be used cautiously in such patients until it has been more thoroughly studied.

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