Editorial

Noninvasive respiratory support for acute respiratory failure—high flow nasal cannula oxygen or non-invasive ventilation?

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Submitted Jun 30, 2015. Accepted for publication Jul 09, 2015.
doi: 10.3978/j.issn.2072-1439.2015.07.18
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.07.18

For patients with acute respiratory failure there may be advantages to the avoidance of invasive mechanical ventilation, i.e., ventilation via endotracheal intubation. Indeed, soon after the introduction of invasive mechanical ventilation many complications of positive pressure ventilation were identified (1,2). Some are directly related to the intubation procedure, such as cardiac arrest following endotracheal intubation, and laryngeal or tracheal injury leading to long-term sequelae. Others are related to the fact that the endotracheal tube adversely affects pulmonary host defenses (e.g., cough, mucociliary transport) setting the stage for ventilator-associated pneumonia, that carries its own risk of morbidity and mortality (3). Invasive mechanical ventilation generally requires sedation, which itself is often a cause of prolonged weaning and prolonged mechanical ventilation.

These major safety considerations prompted the development of non-invasive methods for delivering respiratory support without the need for intubation. Convincing evidence that non-invasive ventilation (NIV) diminishes the risk of infectious complications has been obtained from randomized controlled trials and Meta-analyses, as well as from large cohort studies and case-control studies, which have demonstrated substantial decreases in all categories of nosocomial infection (3-7). With NIV, sedation is usually not required or, if necessary, it is administered at low doses (6). By averting airway intubation, non-invasive methods of respiratory support leaves the upper airway intact, preserves airway defenses, and allows patients to eat, vocalize normally, and clear secretions more effectively.

Strengthening the rationale for the use of non-invasive respiratory support is evidence that has accumulated over the past decade that NIV lowers morbidity and mortality rates of selected patients with acute respiratory failure and may shorten hospital length of stay (8), thus reducing costs. NIV is now considered the ventilatory mode of choice in acute respiratory failure due to chronic obstructive pulmonary disease (COPD) exacerbations (9-11), acute cardiogenic pulmonary edema (12,13), and hypoxemic failure in immunocompromised patients (6,14), and for facilitating extubation in patients with COPD who fail spontaneous breathing trials (15). NIV use in these conditions is underpinned by a sound physiologic rationale—in COPD, NIV can address several of the major abnormalities in respiratory mechanics, allowing the patient to generate larger tidal volumes with less effort; in cardiogenic pulmonary edema, NIV decreases left ventricular afterload, and reduces left and right ventricular preload. By contrast, the beneficial effects of NIV remain unclear in patients with *de novo* acute hypoxemic respiratory failure, that is, non-hypercapnic patients having acute respiratory failure in the absence of a cardiac origin or underlying chronic pulmonary disease. NIV is more likely to fail in hypoxemic patients (16), and NIV failure could be associated with increased mortality (17). In unselected patients admitted to ICUs for acute hypoxemic respiratory failure, the rate of intubation is particularly high, reaching

60% (17,18), and their in-ICU mortality after intubation may exceed 60% (17,18). Thus, NIV may improve outcome of patients who succeed in NIV by avoiding intubation, but may worsen outcome by delaying intubation in those having failed NIV.

Over the past 2 decades, systems to deliver heated and humidified oxygen at high flows through nasal cannulae have been developed as an alternative to standard oxygen delivery systems and NIV. Not withstanding the success of NIV for certain indications, high-flow nasal cannula (HFNC) oxygen delivery has been gaining attention as an alternative means of respiratory support from several clinical research groups and has been proposed as a supportive therapy in critically ill patients with acute respiratory failure (19), including post-operative respiratory failure (20), during bronchoscopy (21), or to prevent severe desaturation during intubation of patients with mild-to-moderate hypoxemia (22). The apparatus comprises an air/oxygen blender, an active heated humidifier, a single heated circuit, and a nasal cannula. At the air/oxygen blender, the inspiratory fraction of oxygen (FiO_2) is set from 0.21 to 1.0 at a flow of up to 60 L/min. The gas is heated and humidified with the active humidifier and delivered through the heated circuit.

Theoretically, HFNC has a number of advantages over other respiratory support systems, including conventional nasal cannula, face masks, or NIV. First, because gas is generally warmed to 37 ℃ and completely humidified in HFNC circuits, mucociliary function remain intact and patients report minimal discomfort (23). This is often in contrast to the delivery of low flow oxygen which is generally not humidified, leading to patient complaints such as dry nose, dry throat, and nasal pain (24,25). Insufficient heating and humidification leads to poor tolerance to oxygen therapy. Second, with HFNC the flow demands of patients are better met, maintaining the inspired FiO_2 relatively constant (26). HFNC generates a higher flow rate compared to other oxygen delivery systems, exceeding the patient's peak inspiratory flow rate in most cases. For example, during hypopharyngeal oxygraphy studies (26), during nose breathing at rest, above a flow rate of 30 L/min using HFNC the measured FiO_2 was close to the delivered FiO_2. Using conventional devices, oxygen flow is usually <15 L/min. However, the inspiratory flow of patients with respiratory failure varies widely in a range from 30 to more than 100 L/min. The difference between patient inspiratory flow and delivered flow is large, leading to entrainment of room air with the delivered gas, thus resulting in variable and lower than expected FiO_2 (27). Third, although delivered through an open system, high flow overcomes resistance against expiratory flow and creates positive nasopharyngeal pressure (28). While the pressure is relatively low compared with closed systems, it is considered adequate to increase lung volume or recruit collapsed alveoli (29,30). A further advantage of HFNC is the wash out of carbon dioxide in anatomical dead space. Breathing frequency is lower with HFNC, while $PaCO_2$ and tidal volume remain relatively constant indicating that dead space is reduced (19,31,32). These results suggest effective carbon dioxide washout with HFNC. Finally, another major difference between NIV and HFNC is the interface. While interfaces for NIV increase anatomical dead space, those for HFNC actually decrease dead space.

Until now, only anecdotal case reports, case series and some preliminary controlled trials have provided an evidence base to guide the use of HFNC in adults with respiratory failure. The recently published FLORALI (high flow oxygen therapy for resuscitation of patients with acute lung injury) study (33), provides much needed randomized controlled trial data on the types and severities of hypoxemic respiratory failure that are most likely to benefit from HFNC. This multicenter 310 patient trial was designed to assess the rate of endotracheal intubation and other clinical outcomes among three groups: high-flow oxygen (heated and humidified air/oxygen mixture at a gas flow rate of 50 L/min applied via large-bore binasal prongs), standard oxygen therapy, and noninvasive ventilation for patients with acute, nonhypercapnic, hypoxemic respiratory failure [ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2), ≤300 mmHg]. The trial excluded patients with a history of chronic respiratory disease, including COPD, as well as patients with cardiogenic pulmonary edema, severe neutropenia and hypercapnic patients ($PaCO_2$ >45 mmHg), as NIV has already demonstrated a reduction in the intubation rate and mortality in these patients.

The primary outcome, the rate of endotracheal intubation, did not differ significantly among the groups (high flow 38% *vs.* standard 47% and NIV 50%) (P=0.18). However, in a post hoc adjusted analysis that included the 238 patients with severe initial hypoxemia (PaO_2:FiO_2, ≤200 mmHg), the intubation rate was significantly lower among patients who received high-flow oxygen than among patients in the other two groups (P=0.009).

In the entire cohort of 310 patients, the high-flow oxygen significantly increased the number of ventilator-free days and also reduced 90-day mortality, compared with

standard oxygen therapy (P=0.046) or NIV (P=0.006). As compared with the other strategies, high-flow oxygen was associated with less respiratory discomfort and a reduction in dyspnea, as measured by validated assessments of patient comfort. Because there was a lower respiratory rate than was observed with the other strategies at the same partial pressure of arterial carbon dioxide, it appears that the system for delivering high-flow oxygen through a nasal cannula also decreased the pulmonary dead space.

What conclusions can we draw from this study? The safety and efficacy of HFNC in non-hypercapnic respiratory failure appears to be superior to NIV or conventional facemask oxygen. However, the study does have some limitations including population itself, the use of NIV therein, the relatively small sample size, and the failure of the study to meet its primary endpoint. Just over 3/4 of the patients in each group had pneumonia, while the same proportion of patients had bilateral infiltrates on chest radiograph, thus fulfilling the criteria for acute respiratory distress syndrome (ARDS). The use of NIV in this patient population is open to question.

The pathophysiologic rationale for NIV use in pneumonia and ARDS is less sound. Unlike exacerbations of COPD, hypoxemic respiratory failure is frequently not associated with frank ventilatory failure, at least in the initial phase. NIV does not address the key pathophysiologic abnormalities of the disease, and in fact a beneficial effect on gas exchange and dyspnea may mask disease deterioration. This could lead to life threatening respiratory failure in case NIV is subsequently interrupted. Therefore, there is likely a severity window for delivering NIV as a preventive support beyond which its use may contribute to harm (34).

Robust large randomized controlled trials of NIV for acute respiratory failure (non-COPD, non-hypercapnic) are relatively scarce, and because of the heterogeneity of causes, studies fail to show that all patient subgroups with hypoxemic respiratory failure benefit equally from NIV. For example, acute pneumonia has long been considered a risk factor for NIV failure (35). A trial evaluating NIV use in heterogeneous respiratory failure showed very poor outcome in the group of patients with pneumonia, with all such patients requiring intubation (36). Another study evaluated NIV use in patients with hypoxemic respiratory failure and identified community acquired pneumonia as a subcategory with a high NIV failure rate (50% intubation rate) (35). A randomized trial showed benefit of NIV in patients with severe community acquired pneumonia, but only in the subgroup with underlying COPD (37). Other studies (7,38), with more rigorous patient selection (such as no alteration in the state of consciousness, absence of organ dysfunction, abundant secretions, cardiac arrhythmias or ischemia) have shown some benefit in patients with acute respiratory failure (including pneumonia) treated with NIV. However, large observational studies describing the use of NIV in pneumonia have often shown high rates of failure (17,35).

Observational studies and subgroup analysis of randomized controlled trials have also identified ARDS as a strong predictor of NIV failure (35,39,40). A multicenter survey (41) evaluated NIV as first-line therapy in early ARDS patients and found that a higher severity score and a PaO_2:FiO_2 less than or equal to 175 mmHg 1 hour after initiation of NPPV were independently associated with NIV failure. This survey showed that, with NIV use, intubation was avoided in no more than 50% of patients, even in experienced centers. The recent Berlin definition of ARDS suggested that NIV may be indicated only in mild ARDS, and not in severe and moderate ARDS, but also emphasized that the role of NIV in ARDS has to be further evaluated (42). NIV failure in ARDS patients is highly predictable in case of shock, metabolic acidosis, high severity scores of illness, and a greater degree of hypoxemia (40).

Moreover, many patients with ARDS may not be favorable candidates for NIV due to the need to deliver lung protective ventilation. During NIV, high transpulmonary pressure swings and large tidal volumes may be generated, which could lead to the development of ventilator-induced lung injury (VILI) and contribute to the poor outcome observed in intubated patients who fail NIV. Most patients with hypoxemic ARF have a high respiratory drive, and it has been shown experimentally that the increased drive caused by a severe metabolic acidosis may cause lung injury (43). In the study by Frat *et al.*, NIV pressure support levels of 8±3 cm of water, and a PEEP of 5±1 of water resulted in a tidal volume of 9.2±3 mL/kg.

In the FLORALI study (33), it is interesting to note that there were numerically more ICU deaths in the NIV group (27 *vs.* 12 in the HFNC group and 18 in the standard oxygen group). The unadjusted hazard ratio for ICU death in the three groups was significant only in the NIV *vs.* HFNC group (HR: 2.55, 95% CI, 1.21-5.35). At 90 days, both the standard oxygen group and the NIV group had increased risk of death, but for the standard oxygen group the confidence interval almost crosses unity (HR: 2.01, 95 CI, 1.01-3.99 for standard oxygen *vs.* HFNC, HR: 2.5, 95 CI, 1.31-4.78 for NIV *vs.* HFNC). Importantly, the authors provide some information on why those patients

died. Eighteen patients died from refractory shock in the NIV group, *vs.* six in the HFNC group and twelve in the standard oxygen group. Three died from cardiac arrest in the NIV group, *vs.* one in each of the other two groups. While the authors state, and the data indicates, that there was no significant difference among the groups in terms of the time until intubation (median 27 hrs in both HFNC and NIV groups *vs.* 15hrs in standard oxygen groups) or the reasons for intubation, it is clear that NIV can mask deterioration in patients with respiratory failure, while HFNC may simply be a more effective treatment in this patient population. At the very least, this data highlights the importance of careful patient selection for NIV in acute respiratory failure resulting from pneumonia and ARDS.

In conclusion, a growing body of evidence suggests that HFNC oxygen therapy is an innovative and effective modality for the early treatment of adults with respiratory failure associated with diverse underlying diseases. However, there is no therapy that is efficient in every patient and in every type of acute respiratory failure. The study by Frat *et al.* (33) has improved our knowledge regarding the right indication for HFNC–conscious, cooperative, non-hypercapnic patients, without chronic respiratory failure. While more randomized studies are needed to confirm the clinical advantages of HFNC over other methods in specific adult populations, HFNC should be considered for the treatment of early acute respiratory failure.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Ming Zhong (Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Curley GF, Laffey JG, Zhang H, Slutsky AS. Noninvasive respiratory support for acute respiratory failure—high flow nasal cannula oxygen or non-invasive ventilation? J Thorac Dis 2015;7(7):1092-1097. doi: 10.3978/j.issn.2072-1439.2015.07.18

