Editorial

High flow nasal cannula—coming to a hypoxic patient near you!

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Acute hypoxemic failure and need for mechanical ventilation is one of the most common indications for admission to the intensive care unit (ICU) (1). While some patients will require emergent intubation and mechanical ventilation, the majority of patients may be supported with noninvasive ventilation. Monitoring for clinical deterioration so that escalation of respiratory support can be instituted in a timely fashion is imperative for safe patient management. These noninvasive modes of respiratory support include oxygen therapy via face mask (FM), high flow nasal cannula (HFNC) oxygen and noninvasive positive pressure ventilation (NPPV) [continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP)].

In adult patients, HFNC was first utilized to support those with chronic obstructive pulmonary disease (2), but has expanded to be used in a variety of applications including the post-extubation period in both medical and surgical patients (e.g., after cardiac surgery, abdominal surgery) (3-5).

In a report in *The New England Journal of Medicine* (June 2015), on behalf of the FLORALI Study Group and the REVA Network, Frat *et al.* described the results of a multicentre, prospective, open-label, 3-armed trial that compared clinical outcomes of critically ill patients with acute hypoxemic respiratory failure supported with FM, HFNC, or NPPV (6). This study was powered to show an absolute difference of 20% reduction in the primary outcome of intubation and need for mechanical ventilation at day 28. Secondary outcomes in this study included ICU mortality, 90-day mortality, 28-day ventilator free days (VFD) and duration of ICU stay.

The study included a total of 310 patients recruited in 23 ICUs. More than three quarters (238/310, 77%) of patients had an arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) of less than 200 on admission, indicating severe hypoxemia. The most common cause of acute respiratory failure in this study was community-acquired pneumonia (197/310, 64%).

For the primary outcome of intubation rate, there was no statistical significant difference between the patients assigned to the three groups [HFNC *vs.* FM *vs.* NPPV: 40/106 (38%) *vs.* 44/94 (47%) *vs.* 55/110 (50%) respectively, P=0.18]. However, in a pre-specified subgroup analysis of patients with PaO_2:FiO_2 ratio ≤200 mmHg, there was a difference in intubation rates across the three groups [HFNC *vs.* FM *vs.* NPPV: 29.83 (35%) *vs.* 39/74 (53%) *vs.* 47/81 (58%) respectively, P=0.01]. Even after controlling for the presence of bilateral pulmonary infiltrates, respiratory rate and past medical history of cardiac insufficiency, patients supported on HFNC had lower odds of requiring intubation compared to FM [adjusted odds ratio (OR): 2.14, 95% confidence interval (CI): 1.08-4.22] and NPPV [adjusted OR: 2.60, 95% CI: 1.36-4.96]. This does not necessarily indicate that HFNC is the optimal noninvasive respiratory support in patients who are most hypoxemic. Further clinical data and information in this subgroup of patients such as repeat measurements of arterial blood gas after 1 hour of respiratory support may be helpful to provide further explanation for this observation. Indeed, it is interesting to postulate reasons why HFNC seems to confer a "protection" against the need for intubation in the subgroup of patients who are more hypoxemic at enrolment. Another important finding was the intensity of respiratory discomfort in the patients was reduced and the dyspnea score was improved with HFNC, as compared with FM and NPPV at 1 hour after enrolment. Could these findings

be related to the matching of peak inspiratory flow rates in patients with tachypnea and/or washing of pharyngeal dead space with HFNC (7)?

The investigators also demonstrated that 28-day VFD was significantly higher in patients supported with HFNC (24±8 days) compared to patients with FM (22±10 days) and those supported with NIV (19±12 days). In addition, a significant difference in both ICU and 90-day mortality was reported in patients supported with HFNC as compared to those supported on FM or NPPV. Whilst this impressive clinical outcome data, there are certain considerations that should be taken into account before concluding that HFNC reduces morbidity and mortality of critically ill patients. What is not known from the description of the study is that clinical management of patients after mechanical ventilation was started. Are patients across the three groups comparable in terms of management that impacts of duration of mechanical ventilation and mortality? Daily clinical management such as ventilator strategies, use of neuro-muscular blockade, prone positioning, and fluid balance potentially have an impact on VFD and mortality rates of critically ill patients. To make an association between the choices of initial noninvasive support to the subsequent clinical outcome of reduced duration of mechanical ventilation and mortality may be not be appropriate in this case.

This study has several strengths. Although it is not the first adult randomized controlled study investigating the use of HFNC against other forms of oxygen delivery or noninvasive respiratory support, it is certainly one of the largest to date. The investigators should be congratulated on the vigorous conduct and completion of this multi-center study. The study had clearly-defined inclusion and exclusion criteria. Specifically, the investigators were cognizant to exclude patients with hypercapnic respiratory failure (arterial partial pressure of carbon dioxide >45 mmHg) and cardiogenic pulmonary edema. In these two groups of patients, NPPV has been conclusively demonstrated to be an effective respiratory support and it may be of ethical question that we subject patients to randomization to receive alternative treatments such as HFNC (8,9). In addition, the investigators put in place pre-specified criteria for endotracheal intubation so as to ensure uniformity across sites and minimize subjective clinical judgement for the need for escalation to mechanical ventilation.

The findings of this study must be interpreted in the context of its limitations. As previously eluded to, further description of clinical management strategies that potentially impacts duration of mechanical ventilation and mortality can provide readers with more information to determine the strength of the association between HFNC and reduction in morbidity and mortality of patients with acute hypoxemic respiratory failure.

Is HFNC ready for the "opening weekend" in the clinical area near you? Focusing on the primary aim of this study, investigators did not demonstrate any difference in intubation rates in patients with acute hypoxemic respiratory failure supported on FM, HFNC or NPPV. With the increasing awareness of HFNC and number of studies that are currently conducted using this modality of oxygen delivery, HFNC should be considered part of the armamentarium of noninvasive respiratory support for critically ill patients. Appropriate patient selection and timely escalation of care to mechanical ventilation remains the most important clinical decision making aspect of noninvasive respiratory support.

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Footnote

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