

Preventive post-extubation high-flow nasal oxygen therapy versus non-invasive ventilation: a substitutive or a complementary ventilatory strategy?

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Endotracheal mechanical ventilation (MV) is a major treatment of life-threatening conditions, but weaning from MV remains a great challenge, and time of extubation a critical issue in the intensive care unit (ICU) management (1,2). ICU clinicians have to clearly distinguish the weaning phase from extubation period to best identify their respective mechanisms and risk factors for failure. Indeed, weaning difficulties [failure of one or more spontaneous breathing trial (SBT)] occur in 19% of ICU patients according to a recent new definition of weaning outcome, and ICU mortality can reach up to 21% in these patients (3). Despite a SBT success, extubation failure can occur in 10% to 20% of cases with a higher ICU mortality rate in reintubated patients ranging from 25% to 50% (2). Hence, ICU physicians should consider the potential issue of the weaning/extubation process as early as possible according to the underlying status for optimizing the weaning/extubation conditions, limit the risk of reintubation and eventually propose alternative techniques for post-extubation management (1).

In addition to standard oxygen therapy (O₂), two other non-invasive techniques have been proposed for the weaning/post-extubation management: non-invasive ventilation (NIV) and high-flow nasal oxygen therapy (HFNO). Apart from NIV used as a weaning strategy (4,5), preventive post-extubation NIV appears to be of clinical benefit mainly in medical population considered at risk for

extubation failure (6-8), whereas curative post-extubation NIV seems more beneficial in surgical (post-operative) than in non-selected medical population (4,9,10). HFNO is a new technique of oxygenation with extending indications in the management of ICU adults (11,12). HFNO enables delivery of high-flows (up to 70 L/min) of heated and humidified air-oxygen mixture (37 °C, 44 mg/L) at a controlled and adjustable (21% to 100%) inspired fraction of oxygen (FiO₂). Consequently, HFNO exhibits several physiological mechanisms of potential clinical benefit: a moderate positive end-expiratory pressure (PEEP) effect with increased end-expiratory lung volume, a nasopharyngeal dead-space CO₂ washout, and preservation of mucosal function contributing to improve oxygenation, adequate secretion removal, decrease airways resistance, intrinsic PEEP and work of breathing, while improving patient comfort (11,12). Hence, HFNO has been recently demonstrated to be beneficial on clinical outcome in severe hypoxemic ARF patients (13). HFNO has also been recently assessed as a preventive post-extubation ventilatory support. Compared to conventional O₂, HFNO has been shown to improve oxygenation and respiratory comfort, decrease the need for reintubation and post-extubation NIV in a general ICU population (14). In patients at low-risk for extubation failure, HFNO has also been demonstrated to decrease post-extubation ARF and reintubation rate within 72 hours (15). As yet, nevertheless,

no study has applied post-extubation HFNO in high-risk patients for extubation failure nor compared HFNO with NIV in this setting.

In a recent issue of the *Journal of American Medical Association*, Hernández *et al.* (16) compared, in a large multicenter non-inferiority randomized trial, HFNO with NIV immediately after planned extubation in patients considered at high-risk for reintubation based on criteria previously described (6-8). Primary outcomes were reintubation and occurrence of post-extubation ARF within 72 hours after planned extubation. FiO₂ with HFNO and NIV was adjusted to maintain a transcutaneous oxygen saturation >92%. HFNO and NIV were applied for only 24 hours and, afterwards, patients received standard O₂ if needed. Rescue NIV was not allowed in the HFNO group in cases of post-extubation ARF. The reintubation rate was assumed to be of 20% to 25% for each group with a non-inferiority margin of 10%. Among 1,211 patients who successfully passed a SBT, 604 were randomized, 314 in the NIV group and 290 in the HFNO group. HFNO was found to be non-inferior to NIV for preventing reintubation (19.1% *vs.* 22.8% of patients, respectively; risk difference, -3.7%; 95% CI, -9.1% to ∞) and more patients experienced post-extubation ARF in the NIV than in the HFNO group (39.8% *vs.* 26.9%, respectively; risk difference, 12.9%; 95% CI, 6.6% to ∞). Delay for reintubation was similar (21.5 *vs.* 26.5 hours, respectively) as well as causes of reintubation and post-extubation ARF. The ICU stay was lower in the HFNO group (4 *vs.* 3 days, respectively; P=0.048) and HFNO was never withdrawn for adverse events as compared to 42.9% of patients in the NIV group (P<0.001). Other secondary outcomes (sepsis, multiorgan failure, respiratory infections, hospital stay, ICU and hospital mortality) were similar in both groups. These promising results raise the question, therefore, of whether preventive HFNO can substitute for NIV in the post-extubation management, particularly in high-risk patients for reintubation?

As stated above, studies have previously suggested a potential benefit of HFNO compared to standard O₂ in the post-extubation management (14,15). The last trial (15) was, in fact, performed by the same investigators who enrolled 1,131 patients into two studies assessing the role of preventive post-extubation HFNO according to their risk for reintubation. Logically, HFNO was compared to conventional O₂ in the low-risk study (15), whereas it was compared to NIV in the high-risk study (16), this choice being justified by evidence showing a clinical benefit of NIV in high-risk patients

(6-8). Both trials demonstrated a decrease in post-extubation ARF and reintubation rates within 72 hours with HFNO as compared to the control group (15,16). Nevertheless, before considering we have to extubate all ICU patients (low and high-risk) under preventive HFNO, some considerations should be taken into account.

First of all as stated by the authors (15,16), risk factors for extubation failure can be difficult to determine, since numerous factors can influence simultaneously the extubation outcome. These factors, including weak cough, abundant tracheo-bronchial secretions, and swallowing disorders, can also be difficult to objectively assess by caregivers at bedside (17). Moreover, the post-extubation ventilatory management should be able to potentially reverse the risk factors for reintubation which can be questionable according to the risks considered such as age or APACHE II score. In addition, it has been recently demonstrated that physiological parameters could be not associated with the risk for extubation failure (17). Therefore, the impact of post-extubation management on the risk for reintubation may highly depend on the selected population and criteria considered at risk for extubation failure. Recently, easily identified at-risk patients for extubation failure have been demonstrated to benefit from post-extubation NIV (8). Risk factors considered in Hernández *et al.* trials (15,16) were mainly those used in previous studies regarding preventive post-extubation NIV (6-8). In high-risk study, they excluded, however, hypercapnic patients during the SBT arguing that physicians preferred using preventive NIV in this situation and the uncertain role of HFNO in managing hypercapnia (16). Indeed, preventive post-extubation NIV seems particularly effective in selected medical population with chronic pulmonary diseases and underlying hypercapnia during SBT (6,7). Such a benefit has also been demonstrated with NIV used as a weaning technique in chronic obstructive pulmonary disease (COPD) patients (5). Among the numerous factors considered at risk for extubation failure which may affect a very large population in ICU, hypercapnia during SBT appears to be, in fact, one of the most objective and discriminant criterion to propose preventive post-extubation NIV (7). Therefore, to not have allowed rescue NIV in the HFNO group in cases of post-extubation ARF with hypercapnia can be debatable (16). Regarding the effect of HFNO in cases of hypercapnia, it has been recently demonstrated that the dead-space CO₂ washout can limit or decrease hypercapnia and improve ventilation in stable COPD patients, providing to use a sufficient gas-flow (≥ 30 L/min) with HFNO (18).

Despite the lack of current clinical evidence on outcome in acute setting, this flow-dependent reduction in CO₂ rebreathing with HFNO could, therefore, be useful in the management of hypercapnia, particularly to extubate chronic respiratory diseases. In this condition, the gas-flow tolerated by high-risk patients could not only be considered as a marker of severity (16), but also the gas-flow which is necessary to decrease the partial pressure of CO₂.

Another concern in interpreting the study results (16) is that it included medical as well as surgical patients (38.4%). Indeed, the effect of preventive post-extubation NIV remains controversial on outcome in post-operative population (4,9,10). Furthermore in a recent randomized study, early preventive application of HFNO after extubation did not result in improved pulmonary outcomes compared with standard O₂ in patients undergoing major abdominal surgery (19), which can be considered as a potential risk factor for extubation failure.

From a methodological point of view, it can also be debatable to assess the main end-points at 72 hours post-extubation and to apply the ventilatory strategies allocated (NIV and HFNO) for only 24 hours (16). In addition, having restricted the duration of ventilatory support in both groups to the first 24 hours post-extubation may limit the interpretation of results. Indeed, the time from extubation to reintubation Kaplan-Meier curve clearly showed a dramatic increase in the reintubation rate for the HFNO group shortly after switching to standard O₂ (16). This could have led to the trend toward increased hospital mortality rate observed after 7 days in this group. Moreover despite a preventive approach, numerous patients at risk for reintubation may require non-invasive ventilatory support for a longer duration than 24 hours after extubation, more particularly in high-risk patients. The main studies evaluating preventive post-extubation NIV applied it, intermittently or continuously, for more than 24 hours (6,7) and a pragmatic approach is probably to continue NIV afterwards according to clinical response (8). Also, one previous study found a persistent improvement in oxygenation, respiratory comfort and a significant decrease in the reintubation rate by using post-extubation HFNO for 48 hours (14). In fact, it has been recently proposed that assessment of weaning/extubation outcome should be prolonged up to 7 days when applying post-extubation NIV (2,8).

Whatever it may be, the two recent studies by Hernández *et al.* (15,16) provide new insights in the post-extubation management by implementing preventive HFNO. Using

preventive HFNO in all low-risk patients for extubation failure (15) could be, however, unreasonable since HFNO is more expansive than standard O₂ and can be still unavailable in all adults ICU. Furthermore, weaning from HFNO being not well established (11), such a strategy could unnecessarily increase the ICU stay in low-risk patients, the use of HFNO being not recommended on general wards because of its potential risk to mask undertreated ARF (20). By contrast based on its characteristics and physiological mechanisms, applying preventive HFNO in high-risk patients for extubation failure could be relevant and of potential clinical interest (16). Indeed, HFNO has the advantages over NIV to be a simpler technique better tolerated and more comfortable. Nevertheless, whether HFNO can substitute for NIV to prevent reintubation (15,16), or even to treat post-extubation ARF (21), need further randomized controlled studies. Additional physiological studies are also required to better understand the mechanisms of extubation failure and the potential effects of HFNO on these factors, including hypercapnia, as well as to select patients most likely to benefit from the different available techniques for post-extubation management (standard O₂, NIV or HFNO). Finally, results of the current trial (16) suggest that HFNO could be used, at least, in a complementary way with preventive post-extubation NIV in high-risk patients for reintubation, even potentially associated (NIV with HFNO) as previously shown in acute ARF (22). Despite a secured environment, ICU clinicians have to keep in mind, however, that such a complementary use of preventive post-extubation HFNO and/or NIV should never delay the reintubation time (20).

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Footnote

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