Editorial

Nasal high flow oxygen therapy after extubation: the road is open but don't drive too fast!

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Provenance: This is an invited Editorial commissioned by the Section Editor Zhongheng Zhang (Department of Emergency Medicine, Sir Run-Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China).

Comment on: Hernández G, Vaquero C, Colinas L, *et al.* Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA 2016;316:1565-1574.

Submitted Oct 26, 2016. Accepted for publication Nov 02, 2016.

doi: 10.21037/jtd.2016.12.08

View this article at: http://dx.doi.org/10.21037/jtd.2016.12.08

Mechanical ventilation (MV) is necessary for many patients admitted in intensive care unit (ICU). In intubated patients, weaning from invasive MV is a major event during their ICU stay (1,2). Delayed extubation increases the risks associated with IMV and extubation failure is associated with prolonged ICU and hospital stays and increased mortality, particularly attributable to nosocomial infection (3-5). Hopefully a large majority of intubated patients will be successfully and definitely disconnected from the ventilator after a simple weaning process including a spontaneous breathing trial either with a "T" piece tube or with a low level of pressure support (2,6-8). After interruption of the ventilator support and removal of the endotracheal tube, oxygen therapy is used to correct residual impairment in oxygenation.

For some other patients, weaning may be a more difficult task. Medical background and failure of the first attempt of spontaneous breathing trial may easily screen the patients at high risk of extubation failure (2,6-8). Nevertheless, despite having successfully passed a weaning readiness test, 15% of patients on average and up to 20–25% of those at high-risk may need re-intubation (1,2,6-8). Any intervention aimed to improve patient's care and outcome after extubation such as Hernández et al study is therefore welcome (9).

After removal of the endotracheal tube, non-invasive ventilation (NIV) has been proposed as a tool to improve weaning but with controversial results (2,6,10-19). According to the first situation, applying curative NIV to avoid re-intubation in case of ARF occurring after extubation (10-12), seems efficient mainly in surgical patients either lung resection surgery (11) or major abdominal surgery (12). Several studies have suggested that prophylactic NIV could help to prevent post-extubation respiratory failure in patients at high-risk for extubation failure (13-19). Among the six randomized controlled studies of prophylactic NIV, two studies found a reduction in re-intubation rate (14,15), whereas the others found no significant difference (16-19). In postoperative patients, studies of preventive post-extubation NIV have also produced discordant results, for example no benefit of prophylactic NIV against standard oxygen therapy on re intubation rates after lung resection surgery was found in a randomized multicenter controlled study (20). In the third situation of patients failing spontaneous breathing trial, NIV may also hasten extubation in hypercapnic COPD (21,22).

Several devices for oxygen delivery are available in critically ill patients, such as high-concentration reservoir mask, simple face mask, Venturi mask, nasal cannula and more recently available nasal high flow oxygen devices (NHFO). NHFO delivers fully humidified, high-flow oxygen (up to 60 L/min) through a nasal cannula (Optiflow; Fisher and Paykel Healthcare, Auckland, New Zealand). By delivering the gas at flow rates that exceed the patient's peak inspiratory flow rate, this high-flow system provides a constant FiO_2. With this device, the final concentration of oxygen truly delivered to the patient is equivalent to the FiO_2 set. In addition, a flow-dependent effect of continuous

positive airway pressure has been documented in healthy subjects (23) and in patients (24,25). Last, the high gas flow may generate an upper airways dead-space washout effect and may create an oxygen reservoir within the upper airways. Through these mechanisms, the NHFO device has the potential to improve oxygenation as compared with conventional low-flow systems for oxygen therapy, such as the Venturi mask (26).

A recent study suggests that HFNO may be as effective as NIV to avoid intubation in patients with hypoxemic ARF (27). In this multicenter, randomized, open-label trial, neither NIV nor high-flow oxygen decreased the rate of intubation (the primary outcome) among patients with acute hypoxemic respiratory failure. High-flow oxygen therapy, as compared with standard oxygen therapy or NIV resulted in reduced mortality in the ICU and at 90 days.

Clinical studies have also investigated NHFO devices against other oxygen devices during the weaning period (28-30). In a randomized, controlled trial conducted in two Italian ICUs, comparing NHFO with the Venturi mask in critically ill patients requiring oxygen therapy after extubation, Maggiore *et al.* demonstrated that as compared with Venturi mask, the use of NHFO therapy resulted in better oxygenation for the same set FiO_2 (28). In addition, discomfort related to the interface and to airways dryness improved, whereas the breathing frequency and the rate of interface displacement and of oxygen desaturation decreased. In this same study, not designed to evaluate this particular point, the authors found that fewer patients in the NHFO group required re-intubation during the study period, suggesting a potential role of this device in protecting extubation. Hernández *et al.* examined the role of high-flow nasal oxygen in reducing 72-h intubation rate after extubation (29). This multicenter trial recruited 527 patients deemed at low risk for extubation failure. The included patients having successfully passed a spontaneous breathing trial and not having risk factors such as age older than 65 years or obesity, or inability to manage secretions, and having received more than 7 days of MV. Patients randomized to receive high-flow nasal oxygen had a lower re-intubation rate at 72 h compared with those receiving standard oxygen therapy (4.9% *vs.* 12.2%; P=0.004). Time to re-intubation, ICU length of stay, and mortality rates were not significantly different between the 2 groups, and there were no major adverse effects. This high-quality study also attempted to account for the effects of potential confounders, by performing post hoc sensitivity analyses. It should be noticed that this study included a large number of patients with postsurgical and neurologic conditions that may have posed secretion clearance challenges that may have favored better outcomes in the high-flow nasal oxygen group. Concerning exclusively post-operative abdominal surgery patients, a multicenter randomized controlled trial, carried out in France, included 220 patients at moderate to high risk of postoperative pulmonary complications who had undergone major abdominal surgery using lung-protective ventilation (30). Patients were randomly assigned to receive either NHFO (n=108) or standard oxygen therapy (n=112). In this study, early preventive application of NHFO after extubation did not result in improved pulmonary outcomes compared with standard oxygen therapy.

Regarding first the conflicting results concerning post-extubation NIV as a tool to improve weaning and prevent re-intubation, and second the fact that patients often tolerate NIV poorly because of mask discomfort or claustrophobia, limiting the number of hours per day this device can be applied, recent studies were conducted to compare NIV and NHFO.

The first study was conducted in cardiothoracic patients. In a large multicenter, randomized, non-inferiority trial (BiPOP study) conducted in 6 French ICUs and including a total of 830 cardiothoracic surgery patients with or at risk for respiratory failure, the use of NHFO therapy compared with intermittent bi-level positive airway pressure did not result in a worse rate of treatment failure defined as re-intubation, switch to the other study treatment, or premature treatment discontinuation (31). Bi-level positive airway pressure was associated with a higher PaO_2:FiO_2 ratio; high-flow nasal oxygen therapy, with lower values for $PaCO_2$ and respiratory rate. NHFO therapy had no effect on frequencies of adverse events or stay lengths in the ICU or hospital. There were no significant differences for comfort, tolerance of the therapy, or ICU mortality. The main limitation of this study is the fact that they included patients in various situations and applied NHFO therapy *vs.* NIV either for patients with ARF after successful spontaneous breathing weaning trial (curative situation) or patients considered at risk of ARF despite a successful spontaneous breathing weaning trial (preventive situation) or even in patients failing the spontaneous breathing weaning trial.

The second study, recently published by Hernández *et al.* is a multicenter randomized non-inferiority clinical trial that included 604 adults considered as high risk patients for re-intubation after a successful spontaneous breathing trial to determine whether NHFO therapy is superior to NIV

for preventing re-intubation in mechanically ventilated patients (9). Patients included in this study were considered at high-risk of extubation failure if they fulfilled at least one of the following criteria: age older than 65, heart failure as the primary indication for MV, moderate to severe COPD, APACHEII score higher than 12 on extubation day, BMI of more than 30, airway patency problems inability to clear airway secretions, patients failing the first attempt at disconnection from MV, 2 or more comorbidities and MV more than 7 days. Patients were randomized to undergo either NHO therapy or NIV for 24 h after extubation. Primary outcomes were re-intubation and respiratory failure within 72 h. Non-inferiority was 10% margin points. The proportion of patients requiring re-intubation within 72 h was 22.8% with NHFO therapy *vs* 19.1% with NIV, reaching the non-inferiority threshold. Post extubation respiratory failure was less common In the NHFO therapy group 26.9% experienced post extubation respiratory failure *vs*. 39.8% in the NIV group Median time to re-intubation was similar in both groups respectively 26.5 h in the NHFO therapy group and 21.5 h in the NIV group. Median post randomization ICU length of care was lower in the NHFO group [3 (IQR, 2–7) *vs*. 4 (IQR, 2–9) days; P=0.048]. Other secondary outcomes were similar in both groups. Also, well balanced between the two groups, one third of the patients were surgical patients and only 20% were COPD and hypercapnia in this study was rarely the reason for re-intubation (respectively 2% in the NHFO therapy group and 2.5% in the NIV group). Adverse effects requiring withdrawal of the device was observed in none of the NHFO therapy group and in 42.9% of the NIV patients (P<0.001) and the median time under NIV was 14 h intolerance to NIV was the main adverse event reflecting the poor tolerance of NIV in this study. Despite these few limitations, this well-designed study indicates that NHFO therapy is not inferior to NIV to prevent re-intubation and post-extubation respiratory failure in a well-defined population of high risk patients.

Clearly NHFO therapy and NIV have fundamental differences, each device having some advantages and limitations. So, what are the main findings of all these clinical studies evaluating post-extubation NHFO therapy?

First the significantly better comfort and better tolerance of NHFO therapy compared with NIV, permitting nearly 24 h of daily use, are significant advantages and justify using NHFO therapy as the first alternative to standard oxygen therapy.

Second NIV or NHFO therapy may be as effective to prevent post-extubation re-intubation in at risk patients. The results of these studies performed in centers of excellence should be confirmed in other studies before generalizing the results.

Third, we need some more studies to compare NIV and NHFO therapy during the weaning period. More homogenous population should be studied as post-extubation NIV may provide different results according to the population included in the studies. Even if NHFO therapy provides a continuous flow, pressure is low and not continuous. The ability of NHFOT therapy to reduce work of breathing in patients with COPD and high level of auto-PEEP is questionable. Specific studies on COPD patients or hypercapnic patients at the end of the spontaneous breathing trial and on patients with prolonged weaning failure are mandatory. In hypoxemic patients, NIV may promote lung volo-trauma by delivering uncontrolled high tidal volumes (32-34). NHFO therapy could be preferred in hypoxemic ARF after extubation.

Fourth, both devices should not delay re-intubation in case of hypoxemic ARF following extubation. In patients with hypoxemic ARF, the overall effects of NIV with respect to the prevention of intubation and improvements in outcome are conflicting and around 50% of the patients will need intubation (35-38). In real life setting, failure of NIV in patients with hypoxemic ARF is associated with a worse outcome (39-41). We should better define the limits of NHFO therapy to avoid the risk of increased mortality in case of severe hypoxemic ARF. Whether escalation to NIV is desirable in some patients as opposed to prompt re-intubation? This is a still pending question.

Fifth, we should keep in mind that universal problem with these kinds of studies is the near impossibility of blinding, introducing a major bias.

Also, Hernández *et al.'s* study is an important contribution to the evaluation of post-extubation NFHO therapy in the weaning process of at high-risk patients (9); we still need some more large randomized controlled studies to confirm these results. We should also evaluate post-extubation NHFO therapy in real life situation, before throwing away NIV during the weaning period.

The road is open but work is still going on, so don't drive too fast!

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Thille AW, Richard JC, Brochard L. The decision to extubate in the intensive care unit. Am J Respir Crit Care Med 2013;187:1294-302.
2. Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007;29:1033-56.
3. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. Chest 1997;112:186-92.
4. Frutos-Vivar F, Esteban A, Apezteguia C, et al. Outcome of reintubated patients after scheduled extubation. J Crit Care 2011;26:502-9.
5. Thille AW, Harrois A, Schortgen F, et al. Outcomes of extubation failure in medical intensive care unit patients. Crit Care Med 2011;39:2612-8.
6. Thille AW, Cortés-Puch I, Esteban A. Weaning from the ventilator and extubation in ICU. Curr Opin Crit Care 2013;19:57-64.
7. Vallverdú I, Calaf N, Subirana M, et al. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. Am J Respir Crit Care Med 1998;158:1855-62.
8. Esteban A, Alía I, Gordo F, et al. Extubation outcome after spontaneous breathing trials with T-tube or pressure support ventilation. The Spanish Lung Failure Collaborative Group. Am J Respir Crit Care Med 1997;156:459-65.
9. Hernández G, Vaquero C, Colinas L, et al. Effect of Postextubation High-Flow Nasal Cannula vs Noninvasive Ventilation on Reintubation and Postextubation Respiratory Failure in High-Risk Patients: A Randomized Clinical Trial. JAMA 2016;316:1565-74.
10. Keenan SP, Powers C, McCormack DG, et al. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. JAMA 2002;287:3238-44.
11. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350:2452-60.
12. Auriant I, Jallot A, Hervé P, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. Am J Respir Crit Care Med 2001;164:1231-5.
13. Jaber S, Lescot T, Futier E, et al. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. JAMA 2016;315:1345-53.
14. Burns KE, Meade MO, Premji A, et al. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. CMAJ 2014;186:E112-22.
15. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 2005;33:2465-70.
16. Ferrer M, Valencia M, Nicolas JM, et al. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med 2006;173:164-70.
17. Ornico SR, Lobo SM, Sanches HS, et al. Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. Crit Care 2013;17:R39.
18. Su CL, Chiang LL, Yang SH, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. Respir Care 2012;57:204-10.
19. Khilnani GC, Galle AD, Hadda V, et al. Non-invasive ventilation after extubation in patients with chronic obstructive airways disease: a randomised controlled trial. Anaesth Intensive Care 2011;39:217-23.
20. Ferrer M, Sellarés J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. Lancet 2009;374:1082-8.
21. Lorut C, Lefebvre A, Planquette B, et al. Early postoperative prophylactic noninvasive ventilation after major lung resection in COPD patients: a randomized controlled trial. Intensive Care Med 2014;40:220-7.
22. Ferrer M, Esquinas A, Arancibia F, et al. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. Am J Respir Crit Care Med 2003;168:70-6.
23. Girault C, Bubenheim M, Abroug F, et al. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. Am J Respir Crit Care Med 2011;184:672-9.
24. Spoletini G, Alotaibi M, Blasi F, et al. Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. Chest 2015;148:253-61.
25. Parke RL, Eccleston ML, McGuinness SP. The effects

of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care 2011;56:1151-5.
26. Corley A, Caruana LR, Barnett AG, et al. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107:998-1004.
27. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-96.
28. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 2014;190:282-8.
29. Hernández G, Vaquero C, González P, et al. Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. JAMA 2016;315:1354-61.
30. Futier E, Paugam-Burtz C, Godet T, et al. Effect of early postextubation high-flow nasal cannula vs conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). Intensive Care Med 2016;42:1888-1898.
31. Stéphan F, Barrucand B, Petit P, et al. High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery: A Randomized Clinical Trial. JAMA 2015;313:2331-9.
32. Dreyfuss D, Saumon G. Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 1993;148:1194-203.
33. de Prost N, Ricard JD, Saumon G, et al. Ventilator-induced lung injury: historical perspectives and clinical implications. Ann Intensive Care 2011;1:28.
34. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2014;370:980.
35. Confalonieri M, Potena A, Carbone G, et al. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 1999;160:1585-91.
36. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. JAMA 2000;284:2352-60.
37. Martin TJ, Hovis JD, Costantino JP, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med 2000;161:807-13.
38. Ferrer M, Esquinas A, Leon M, et al. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 2003;168:1438-44.
39. Demoule A, Girou E, Richard JC, et al. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med 2006;32:1756-65.
40. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: experience at the Massachusetts General Hospital. Crit Care Med 2008;36:441-7.
41. Thille AW, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care 2013;17:R269.

Cite this article as: Rabbat A, Blanc K, Lefebvre A, Lorut C. Nasal high flow oxygen therapy after extubation: the road is open but don't drive too fast! J Thorac Dis 2016;8(12):E1620-E1624. doi: 10.21037/jtd.2016.12.08

