High Flow Nasal Cannula Oxygen Therapy, work in progress in respiratory critical care

Abstract

After a planned extubation, the re-occurrence of acute respiratory distress needing the restoration of invasive mechanical support is a severe phenomenon associated with several important consequences, including increased morbidity, Intensive Care Unit mortality, and an enormous financial burden. So far, the most commonly used techniques to ameliorate gas exchange in the post-extubation period were low-flow oxygen therapy and non-invasive ventilation (NIV). High flows through nasal cannulae (HFNC) is a system which allows increased CO_2 wash-out of in anatomical dead space, positive nasopharyngeal pressure, a relatively constant FiO_2, and an improvement of mucociliary function. In a recently published paper by Hernandez et al. HFNC therapy, compared in the post-extubation period to standard oxygen in patients at low risk of re-intubation, was associated with a lower re-intubation rate within 72 hours of extubation, with no evidence of any delays in re-intubation which may prove fatal, as previously reported in the context of NIV. Despite yielding some useful starting points and positive results with HFNC, some discrepancies have emerged in the findings of the studies in this field. As we await further more homogeneous and enlightening studies, at present we can only affirm that HFNC seems to be a useful means to prevent and treat post-extubation hypoxemia. In fact no harmful or adverse effects related to HFNC emerged in any of the studies and globally, it was associated with better comfort and tolerance compared with NIV, which justifies its use as a first alternative to standard oxygen therapy.

INTRODUCTION

After a planned extubation, the re-occurrence of acute respiratory distress needing the restoration of invasive mechanical support through an endotracheal tube is a severe phenomenon associated with several important consequences, including increased morbidity, Intensive Care Unit (ICU) mortality, and an enormous financial burden. [Penuelas O, Frutos-Vivar F, Fernandez C, et al. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J Respir Crit Care Med 2011; 430-437. Esteban A, Alia I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish lung failure collaborative group. Am J Respir Crit Care Med 1999; 159:512-518. Torres A, Gatell JM, Aznar E, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 1995; 152:137-141]. A spontaneous breathing trial (SBT) passed with no signs of respiratory distress is a necessary step before extubation but may not be enough to predict extubation outcome, even in the short-term period. In fact, despite a successful SBT, 15-30% of extubated patients develop acute respiratory distress and require reintroduction of invasive mechanical ventilation (IMV) within 48 hours [Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J 2007; 29:1033-1056. Tobin MJ, Laghi F. Extubation. In: Tobin MJ, editor. Principles and practice of mechanical ventilation, third ed. New York Chicago San Francisco: McGraw-Hill Medical Publishing Division; 2006. p.1353-71]. In the post-extubation period, it is therefore crucial to prevent or identify early clinical deterioration, to limit the development of respiratory failure. It is equally important to understand which category of patient can benefit most, from which type of treatment, and when (i.e. immediately after extubation or later). In the past, the most commonly used techniques to ameliorate gas exchange in the post-extubation period were low-flow oxygen therapy and non-invasive ventilation (NIV). Standard low-flow oxygen was the first-line therapy and the only possible alternative in the case of inadequate hypoxemia correction, whilst non-invasive ventilation was mainly used in case of hypercapnia. [Boles J-M, Bion J, Connors A, et al. Weaning from mechanical ventilation. Eur Respir J. 2007; 29 (5):1033-1056. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):362-369. Guarracino F, Cabrini L, Ferro B, et al. Noninvasive ventilation practice in cardiac surgery patients: insights from a European survey. J Cardiothorac Vasc Anesth. 2013;27(5):e63-e65. Thille AW, Richard J-CM, Brochard L. The decision to extubate in the intensive care unit. Am J Respir Crit Care Med. 2013;187(12):1294-1302]. NIV was also successfully used as a preventive intervention in patients considered at high-risk of developing post-extubation respiratory failure. [Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, Beltrame F, Navalesi P. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005

Nov; 33(11):2465-70. Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. Eur Respir J. 2010;36(2):362-369].

HIGH-FLOW THROUGH NASAL CANNULA SYSTEM

Over the past two decades, a new device able to deliver heated and humidified oxygen at high flows through nasal cannulae (HFNC) has been proposed, first in preterm newborns and the pediatric setting, [Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med 2013;369:1425–1433.] and then in the care of adult patients with acute respiratory failure (ARF) [Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. Respir Care 2010;55:408–413]. Gas from an air/oxygen blender that can generate a total flow of up to 60 L/min is heated and humidified with an active humidifier and subsequently delivered through a heated circuit (Nishimura M. High-flow nasal cannula oxygen therapy in adults. Journal of Intensive Care (2015) 3:15 pp 2-8). High flow of adequately heated and humidified gas is considered to have a number of physiological effects: 1) high flow washes out carbon dioxide in anatomical dead space; 2) although delivered through an open system, high flow overcomes resistance against expiratory flow and creates positive nasopharyngeal pressure (Parke R, McGunness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth. 2009;103:886–90). While the pressure is relatively low compared with closed systems, it is considered adequate to increase lung volume or recruit collapsed alveoli; 3) the difference between the inspiratory flow of patients and delivered flow is small and FiO_2 remains relatively constant; 4) As gas is generally warmed to 37°C and completely humidified, mucociliary functions remain good and a limited level of discomfort is reported (Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med. 2011;37:1780–6).

EFFICACY OF HFNC IN PATIENTS WITH ACUTE RESPIRATORY FAILURE

Preliminary studies in patients suffering from acute respiratory failure, mainly due to pneumonia, a condition associated to a scarce efficacy of NIV, seemed to show efficacy of HFNC. HFNC was associated with less dyspnea and mouth dryness, and greater overall comfort. Dyspnea decrease was due to several factors: 1) the correction of hypoxemia, and the reduction in the respiratory rate; 2) the reduction of mouth dryness thanks to the effects of the heated humidification system; and 3) the comfort of the interface (Roca O., Riera J. Torres F. High-Flow Oxygen Therapy in Acute Respiratory Failure. Respiratory Care 2010; 55(4): 408-413). A more recent study reported effects not only on comfort and dyspnea but also on biologic parameters. In fact the use of HFNC enabled a significant reduction of respiratory rate and a significant increase in oxygen saturation as measured by pulse oximetry, with a mild increase of $PaCO_2$, without affecting pH. Six patients were secondarily intubated,

and 3 died in the ICU. This technique was well tolerated for several days probably avoiding invasive mechanical ventilation and its potential drawbacks in some of them (Sztrymf B., Messika J., Mayot J. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. Journal of Critical Care (2012) 27, 324.e9–e13). These promising results were confirmed by the Florali Study (Frat J.P., Thille A.W., Mercat A. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. N Engl J Med 2015;372:2185-96.): treatment with HFNC improved the survival rate among patients with acute hypoxemic respiratory failure (mainly related to pneumonia), even though no statistic difference but just a favorable trend in the primary outcome (i.e. intubation rate) was observed with HFNC, as compared with standard oxygen therapy or noninvasive ventilation. In this cohort the rate of intubation seemed to be lower in more hypoxiemic patients with PaO_2/FiO_2 ratio lower than 200.

EFFECT OF HFNC IN THE POST-EXTUABTION PERIOD

Maggiore et al. [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 (3): 282-288] compared HFNC with Venturi masks in 105 patients intubated for at least 24 hours with a PaO_2/FiO_2 ratio < 300 at the end of a SBT. After 24 hours, oxygen saturation (for the same FiO_2 level) and PaO_2/FiO_2 ratio were significantly higher in the HFNC group (287±74 *vs.* 247±81, p=0.03) with a lower arterial carbon dioxide and respiratory rate. Discomfort related to the interface and airways dryness was also lower in the HFNC group. Furthermore, high-flow oxygen was associated with fewer episodes of desaturation detected on bedside monitors, interface displacement and fewer patients in the HFNC group required escalation to NIV or re-intubation as compared with the Venturi mask group. Parke and coll. conducted a randomized controlled trial comparing HFNC *vs.* usual care (i.e. standard oxygen therapy) administered in the first 48 hours after the extubation of post-op cardiac surgery patients. [Parke R, McGuinness S, Dixon R. and Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. British Journal of Anaesthesia 111 (6): 925–31 (2013)]. The number of patients with a SpO_2/FiO_2 ratio ≥ 445 on day 3, which was the primary outcome, was not different between the two groups (46.4% in the HFNC group *vs.* 42.4% in the standard care group, p=0.45), whereas $PaCO_2$ at 4 hours post-extubation and escalation in respiratory support were slightly but significantly lower in the HFNC group *vs.* the standard care group. Similarly, in patients who had undergone cardiac surgery, with a BMI of ≥ 30 kg/m^2, Corley and coll. [Corley A, Bull T, Spooner AJ, Barnett AG, Fraser JF (2015) Direct extubation onto high-flow nasal cannulae post-cardiac surgery versus standard treatment in patients with a BMI C30: a randomised controlled trial. Intensive Care Med 41:887–894] assessed the effects of HFNC delivered immediately after extubation on post-operative atelectasis formation and respiratory

function, in comparison to standard oxygen therapy care. For the primary outcome of atelectasis, no evidence of any difference between treatment and control groups was found. Likewise, no difference was found in the PaO_2/FiO_2 ratio in the first 24 hours after extubation. However, when different time periods were analyzed separately, the mean PaO_2/FiO_2 ratio in the first 8 hours after extubation was significantly higher in the standard oxygen group. No difference was found in failure of allocated therapy and requirement of an escalation of respiratory support within the first 24 hours. There was statistically but not clinically less dyspnea in the standard group in comparison to the HFNC group. Tiruvoipati et al. [Tiruvoipati R, Lewis D, Haji K, Botha J. High-flow nasal oxygen vs. high-flow face mask: a randomized crossover trial in extubated patients. J Crit Care. 2010;25(3):463-468], conducted a small randomized crossover trial comparing short-term interventions (30-min HFNC *vs.* 30-min non rebreathing mask), and found no significant differences in gas exchange or respiratory rate between the two therapeutic strategies. However, greater comfort was associated with the high-flow nasal cannula. Another similar randomized crossover trial showed the same trend toward greater comfort with HFNC [Rittayamai N, Tscheikuna J, Rujiwit P. High-flow nasal oxygen versus conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study. Respir Care. 2014; 59(4):485-490] but, differently from the first one, it was able to show a significant reduction in patients' dyspnea scores, respiratory rates and heart rates with HFNC compared to standard oxygen delivered through a mask. In contrast to the studies cited so far testing mask oxygen or low-flow nasal cannulae therapy, in a large multicenter randomized study, Stephan and coworkers [Stephan 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; 313:2331–2339] compared the effect of bilevel positive airway pressure (BiPAP) to high-flow nasal cannula therapy. In this non-inferiority trial patients were randomized to receive HFNC or BiPAP for at least 4 hours per day if they developed acute respiratory failure during or after a SBT or if, even not developing it, they were deemed at risk due to preexisting risk factors. HFNC did not seem to be inferior to BiPAP in terms of re-intubation rate. No significant differences were found in ICU mortality, dyspnea, or comfort scores. pH and $PaCO_2$ values were slightly but significantly better in the HFNC group in the first hour after extubation, but this difference became irrelevant at 6 hours and onwards. Skin breakdown was significantly more common with BiPAP after 24 hours. The Authors concluded that the results supported the use of HFNC in this patient population.

In the recently published paper by Hernandez and coll. [Hernandez G, Vaquero C, Gonzalez P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L,Cuena R, Fernandez R. Effect of Postextubation High-FlowNasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients. A Randomized Clinical Trial. JAMA. 2016;315(13):1354-1361] once again HFNC therapy was compared in the post-extubation period to standard oxygen, but with at least one difference from all of the aforementioned papers. The authors recruited only patients who met the criteria of low risk of re-

intubation, according to previous literature definitions [Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006;173(2):164-170. 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(11):2465-2470.] Patients were randomized to receive either HFNC, preventively administrated immediately after extubation, or standard oxygen therapy, with the aim of highlighting differences in re-intubation rate, occurrence of post-extubation respiratory failure, time to re-intubation, hospital length of stay and mortality. HFNC oxygen was administered for the first 24 hours and then stopped; flow was initially set at 10 l/min and titrated upward in 5 l/min-steps until patients experienced discomfort; standard oxygen was applied continuously through nasal cannulae or non-rebreathing facemasks with the flow adjusted to maintain SpO_2 above a preset value. Re-intubation rate within 72 hours of extubation was lower in the HFNC group *versus* the standard therapy group (4.9% *vs.* 12.2% respectively, p=0.004) and similarly post-extubation respiratory failure was less common in the high-flow group (8.3% *vs.* 14.4% of the standard oxygen group, p=0.03). Differences in other secondary outcomes were not statistically significant. The absence of any dissimilarity in median time to re-intubation appears to be particularly relevant. In fact, this finding suggests that the application of HFNC was not associated with a delay in re-intubation which, in some cases, may prove fatal, as previously reported by other authors in the context of NIV [Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004; 350(24): 2452-2460] and also, more recently, HFNC [Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med. 2015; 41(4): 623-632]. The immediate implication of the results of the study of Hernandez and coll. is that at present, high-flow oxygen, for the category of patients with a low *a priori* risk of re-intubation, has probably to be considered not only a better choice in comparison to standard oxygen, but also the best currently available therapeutic option. In fact, when administrated preventively in the post-extubation period, NIV has failed to demonstrate an effect on post-extubation failure in the general population of critically ill patients, showing a protective effect only in specific categories of patients at high risk of re-intubation. [Glossop AJ, Shephard N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: ameta-analysis [published correction appears in Br J Anaesth. 2013; 110(1): 164] Br J Anaesth. 2012; 109(3): 305-314. FerrerM, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. Am J Respir Crit Care Med. 2006; 173(2): 164-170. 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(11):2465-2470.]

LIMITATION OF THE STUDIES FOCUSED ON THE EFFECT OF HFNC IN THE POST-EXTUABATION

PERIOD

Despite yielding some useful starting points and positive results with HFNC, some discrepancies have emerged in the findings of the aforementioned studies, prevalently in terms of efficacy in improving gas exchange and avoiding desaturations, preventing escalation of respiratory support and re-intubation and in promoting comfort and tolerance. These discrepancies could be explained by some of the differences and variability among the studies.

1. The first difference lies in patients' baseline characteristics. The comparability of patients of different studies and sometimes even within the same study may be questionable. In some cases, patients with preexisting chronic respiratory diseases, such as COPD, were excluded, whereas in others they were enrolled. Furthermore, some demographic and clinical parameters at enrollment, such as arterial blood gases, previous use of domiciliary oxygen and/or mechanical ventilation, are sometimes not available, precluding the possibility of evaluating the comparability of different patient populations. [Tiruvoipati R, Lewis D, Haji K, Botha J. High-flow nasal oxygen vs. high-flow face mask: a randomized crossover trial in extubated patients. J Crit Care. 2010; 25 (3): 463-468. Rittayamai N, Tscheikuna J, Rujiwit P. High-flow nasal oxygen versus conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study. Respir Care. 2014; 59 (4): 485-490. Scala R. High-Flow Nasal Oxygen Therapy: One More Chance for Extubation? Respiratory Care 2014; 59 (4): 609-612]

2. Other differences emerge in the protocols used. In the majority of the studies cited, treatments were allocated immediately after extubation [Maggiore, Parke, Corley, Rittayamai, Hernandez], whereas in the study by Tiruvoipati [Tiruvoipati R, Lewis D, Haji K, Botha J. High-flow nasal oxygen vs. high-flow face mask: a randomized crossover trial in extubated patients. J Crit Care. 2010; 25 (3): 463-468], patients were randomized to the first intervention 30 min after extubation and, finally, in the study by Stephan and coll. [Stephan F, Barrucand B, Petit P et al (2015) High-flow nasal oxygen vs. noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: A randomized clinical trial. JAMA 313:2331–2339] the therapeutic protocol was heterogeneous and it was applied at different times during the study period. In fact, in the latter study, some patients were eligible for randomization if they failed a SBT, others if a successful SBT was followed by failed extubation and others only in the presence of preexisting risk factors (without the need for any sign of respiratory failure during or after the SBT).

3. Even the studies in which the therapeutic device was applied at the same moment (i.e. immediately after extubation) show several important differences in patients' inclusion criteria. In fact, the

eligibility criterion was in one case a $PaO_2/FiO_2 \leq 300$ at the end of a SBT [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(3):282-288], the fulfillment of the criteria of high risk of reintubation in other two cases (i.e. postcardiac surgery in Parke, 2013, postcardiac surgery plus obesity in Corley, 2015), and in another one, the absence of *a prori* risks for re-intubation (i.e. patients at low risk) [Hernandez G, Vaquero C, Gonzalez P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L,Cuena R, Fernandez R. Effect of Postextubation High-FlowNasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients. A Randomized Clinical Trial. JAMA. 2016;315(13):1354-1361].

4. Variability also concerns device application time and time of the evaluation of the clinical effects and outcomes. In most cases, HFNC was applied for 48 consecutive hours [Maggiore, Parke], but sometimes until patients' discharge from the ICU [Maggiore], occasionally only for the first 24 hours due to planned ICU discharge and the impossibility of continuing HFNC in general wards [Hernandez], or even for a minimum of 8 hours (without specification of the maximum) [Corley]. In the trial by Stephan and coll. [Stephan F, Barrucand B, Petit P et al (2015) High-flow nasal oxygen vs. noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: A randomized clinical trial. JAMA 313:2331–2339], HFNC was discontinued not at a predetermined time but when SaO_2 was at least 95% at 6 l/min or the PaO_2/FiO_2 ratio was ≥ 300 and, finally, in the two crossover trials [Tiruvoipati and Riaayamai], NFNC was administered for only 30 minutes just before or just after standard oxygen. Concerning the primary clinical outcome and time of its evaluation, for Maggiore and coll. it was assessed at 24h when HFNC was still ongoing, for Parke at day 3 after surgery, when HFNC had already been stopped, and likewise in the study by Hernandez, as re-intubation was assessed at 72 hours after extubation while HFNC was stopped at 24.

5. HFNC flow rate also varied, ranging from 30 l/min [Tiruvoipati] to 50 l/min [Maggiore, Stéphan] and was sometimes started at an extremely low value (10 l/min), more typical of a low-flow device, and augmented until the occurrence of patient discomfort, but without a specified inferior limit [Hernandez]. This factor has probably played an important role in determining the different measurable effects of HFNC and the different outcomes. In fact, the well-known PEEP effect of HFNC strictly depends on and is directly proportional to the set flow rate [Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care. 2007; 20 (4):126-131. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care. 2011; 56 (8): 1151-1155]. Also, higher flow rates may have a greater effect on washout of nasopharyngeal dead space and in reducing the fraction of inspired CO_2 [Spence CJT, Buchmann NA, Jermy MC. Unsteady flow in the nasal cavity with high flow therapy measured by

stereoscopic PIV. Exp Fluids 2011; 52 (3): 569-579. Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated Humidified High-Flow Nasal Oxygen in Adults Mechanisms of Action and Clinical Implications. CHEST 2015; 148(1): 253-261], in minimizing the entrainment of room air with the supplemental oxygen [Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airways pressure. Anesth Intensive Care 2011: 39 (6): 1103-1110], and in assuring a higher delivered FiO_2. Furthermore, in the study by Parke and coll. an AIRVO™ humidifier (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) was used, whereas in the other studies an 850 Optiflow™ system was applied (RT202 delivery tubing and MR850 heated humidifier, Fisher and Paykel Healthcare, Auckland, New Zealand). This could represent an additional source of variability in terms of flow and oxygen delivered.

6. Similarly, all the studies mentioned did not consider the role of open-mouth breathing. Patients' attitude of prevalently maintaining the mouth open or closed while breathing may have further increased the variability among the studies. Open-mouth breathing during HFNC lowers delivered FiO_2 compared with closed-mouth nasal breathing due to mixing of the high-flow nasal oxygen with room air inhaled through the mouth, [Ritchie JE, Williams AB, Gerard C, Hockey H. Evaluation of humidified nasal high-flow oxygen system, using oxygraphy, capnography and measurement of upper airways pressure. Anesth Intensive Care 2011: 39 (6): 1103-1110] and significantly reduces the PEEP effect [Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care 2007; 20 (4): 126-131]. No data about this factor are provided in any of the studies reported herein. Incidentally, even the oxygen used in control groups was extremely heterogeneous, both in terms of the type of device and the flow set. Sometimes different devices were used in the same study and even in the same patients, as they could receive oxygen via face mask immediately after extubation and then be switched to nasal cannulae in the following 24 hours and sometimes the type of oxygen device and the flow was not recorded after 24 hours [Hernandez]. Consequently, in many cases FiO_2 was neither truly reliable nor known in the control groups.

7. There is evidence of discrepancies even in the definition and assessment of comfort of the different devices. Comfort is an extremely important issue as it may affect the final efficacy of a therapeutic device. In fact, even in the setting of NIV, intolerance related to interface discomfort was enumerated as one of the most common reasons for failure [Mehta S, Hill N. Noninvasive Ventilation State of the Art. Am J Respir Crit Care Med Vol 163. pp 540–577, 2001]. What Parke and coll. [Parke] affirm may well be true, namely, that the more critical the patients, the better they tolerate HFNC. In fact, patients suffering from acute respiratory failure with a high respiratory flow demand gain can benefit more from HFNC and consequently tolerate it better in comparison to less dyspnoeic patients. However, it is also true that some differences may be related to the fact that comfort and tolerance are not univocally

defined in the different studies. Sometimes discomfort is specified as related to interface and to symptoms of mouth and throat dryness, difficulty to swallow and throat pain [Maggiore], in some other cases it is not defined and it is assessed more generally. Sometimes it is reported by the patients themselves and in other cases it is assessed by a nurse by the means of a visual analogue scale.

CONCLUSIONS

A consolidated experience in the application of HFNC to prevent or treat post-extubation failure in adults is still lacking. As we await further more homogeneous and enlightening studies in this context, as proposed by Scala [Scala R. High-Flow Nasal Oxygen Therapy: One More Chance for Extubation? Respiratory Care 2014; 59 (4):609-612], HFNC may be seen as an additional step, a further chance in the available therapeutic options. As brilliantly highlighted in the editorial by Spoletini and coll. [Spoletini G, Garpestad E, Hill NS. High-FlowNasal Oxygen or Noninvasive Ventilation for Postextubation Hypoxemia Flow vs Pressure? JAMA April 5, 2016 Volume 315, Number 13], the existing studies on the topic, first of all the study by Hernandez and coll, raise more questions than answers. What are the optimal settings and the best durations of use of HFNC in the postoperative or post-extubation setting? When is the best time to apply it - preventively or after the occurrence of failure? Which could be the best alternation? Should we expect to see benefits in alternating between HFNC and NIV? When should we remove it? And many others. Presently, from the available literature in this specific setting, we can only affirm that HFNC seems to be a useful means to prevent and treat post-extubation hypoxemia. In fact, despite all of the aforementioned discrepancies, no harmful or adverse effects related to HFNC emerged in any of the studies and globally, it was associated with better comfort and tolerance compared with NIV, which justifies its use as a first alternative to standard oxygen therapy.