High-flow nasal cannula oxygen therapy: more than a higher amount of oxygen delivery

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The process of disconnecting critically ill patients from the respirator is a crucial step of patients care (1). Weaning can be initiated when stable patients have recovered enough to tolerate a spontaneous breathing trial (SBT). This requires daily identification of patients with an acceptable P/F ratio obtained with no more than 40–50% of inspiratory of oxygen, a low level of PEP (no more than 5 cm of water), hemodynamic stability (no or minimal regimen of intravenous vasopressors, no more than 5 µg/kg·min of dobutamine), and a neurologic status likely to allow spontaneous breathing (no or minimal sedation, ability to cough, absence of copious secretion) (2,3). The necessity to start SBT only in patients with a low temperature (<38 ℃) is less consensual. In patients with these criteria, a SBT of variable duration (30 to 120 min) is performed, with different modalities (T tube, low level pressure support with or without additional low level of PEP). Some practical advantages of using pressure support in this situation (accurate monitoring of tidal volume, respiratory rate and prevention of tube occlusion) may explain why some intensivists favor this modality. At the end of a successful SBT, airways patency could be assessed by the qualitative or quantitative detection of a leak around the tube whose cuff has been deflated. When no or minimal leak is observed, extubation is postponed, and prophylactic intravenous steroids administered for no more than 24 hours could decrease the risk of post extubation stridor (1). Following this strategy the patient is extubated.

Extubation failure is defined by the necessity to reintubate a patient during the 48–72 hours following extubation. The increasing use of non-invasive ventilation (NIV) in the post extubation period has made this definition less reproducible. Extubation failure is observed in about 15% to 20% of extubated patients (1). These patients are at high risk of complications including pneumonia with an overall mortality reaching 50% (4). It remains unclear whether extubation failure is a marker of severity or whether this event precipitates *per se* worsening evolution (5). Extubation failure is associated with several conditions including age more than 65 years, chronic obstructive pulmonary disease (COPD) and cardiopathy (LVEF <45%, valvulopathy, coronaropathy, hypertension) (6). Several studies have investigated strategies to improve the fate of this population. Prophylactic NIV (6,7) has been demonstrated to improve the prognosis of this population. High-flow nasal cannula oxygen (HFNCO) therapy could also be beneficial in this setting.

HFNCO is a recently available oxygen supply modality which has recently received considerable attention (8-13). HFNCO therapy delivers air/oxygen mixture from a blender and is connected via a heated humidifier to a nasal cannula. It allows to deliver flow as up as 60 L/min. The FiO_2 is adjusted independently from the flow. The flow delivered is equivalent or superior to patient demand. Therefore, the risk of room air entrainment is minimal and the fraction of oxygen in the trachea is equivalent to the fraction chosen on the blender. The fixation system is well accepted and has been proved to be superior to those of Venturi mask bag (14). Another valuable characteristic of HFNCO therapy is that it generates mild levels of PEP

between 1 and 5 cm of water (according to flow magnitude and to whether mouth is open or not). Roughly, a 10 L/min flow generates a 1-cm of water of positive pressure. This translates into an increase in end-expiratory lung volume compared to low flow oxygen therapy. Due to high-flow, the clearance of CO_2 in anatomic dead space might also contribute to the decrease in $PaCO_2$ and in perceived dyspnea producing decrease in respiratory rate. Compared to NIV, HFNCO is more comfortable for the patient allowing 24 hours a day therapy and allowing the patient to eat, drink and speech. Last, delivery of humidified heated gas could improve muco-ciliary function, making secretion clearance easier.

HFNCO has been evaluated in various populations of critically ill patients with promising results.

In 20 patients with acute respiratory failure (ARF) mainly related to pneumonia, HFNCO (FiO_2 100% flow 40 L/min) compared with face mask oxygen decreased respiratory rate, increased pulse oximetry and PaO_2 (10) confirming previous data of the same group using flow of 50 L/min in 38 patients (9). In a recent multicenter randomized controlled trial (RCT) conducted among 310 patients with ARF (PaO_2/FiO_2 <200) receiving supplemental oxygen delivered via a facial mask (n=94), NIV (n=110) and HFNCO (n=106), intubation rate didn't differ between the three groups (50%, 38%, 47%, respectively, P=0.18). Nevertheless, HFNCO was associated with a greater number of ventilator free days (22, 19, 24, respectively, P=0.02). Furthermore, the hazard ratio for 90 days mortality was 2.01 [95% confidence interval (CI), 1.01–3.99] with standard oxygen versus high-flow oxygen (P=0.046) and 2.50 (95% CI, 1.31–4.78) with NIV versus high-flow oxygen (P=0.006) suggesting the superiority of HFNCO over conventional oxygenotherapy and NIV (15).

HFNCO has also been tested during intubation of critically ill patients. HFNCO was compared to supplemental oxygen delivered via a non-rebreathing bag reservoir in a before after study including 101 patients with mild to moderate hypoxemia (median oximetry of 100% while receiving nasal oxygen 3.5 to 5 L/min) and requiring tracheal intubation. The lowest median SpO_2 during intubation was 94% with the facemask versus 100% [95–100] with HFNCO (P<0.0001) (16). In a before after study performed in critically ill patients requiring intubation, 13 patients receiving HFNCO were compared to 39 patients receiving NIV (17). The lowest SaO_2 observed during the procedure were similar in the two groups. However, a life threatening SaO_2, defined by a value less than 70%,

was more frequent in the NIV group than in patients receiving HFNCO (n=5 vs. n=0 respectively, P=0.31). These promising results were however not confirmed in a recent multicenter randomized controlled study (18) which compared HFNCO (n=62) and conventional oxygen supply (n=57) in hypoxemic patients (PaO_2/FiO_2 ratio <300 mmHg, respiratory rate >30/min, FiO_2 superior to 50% to obtain a SaO_2 more than 92%) requiring intubation. Authors found no difference between the two strategies regarding mortality or intubation-related adverse events including desaturation less than 80% (P=0.46).

HFNCO interest has also been investigated to avoid reintubation in extubated patients (19-22). Reintubation is a robust criterion to evaluate the impact of strategies applied in the post extubation period. However the switch from supplemental oxygen to HFNCO or use of NIV as rescue therapy in the post extubation period makes the analysis of some studies difficult (22). A recent meta-analysis assessing the effect of HFNCO on intubation found that HFNCO was superior to conventional oxygen therapy alone but not to NIV (23).

In 340 patients ready for extubation after heart surgery (21), Parke et al. found no difference in term of oxygenation between HFNCO (n=169) and oxygen therapy via nasal prong or facial mask (n=171). Use of NIV was required in five patients in the control group vs. nine in the HFNCO group (NS). Reintubation was reported only in two patients allocated to HFNCO group but there were cross over therapy and NIV use which impedes an accurate analysis of the data.

After cardiac surgery, Corley et al. (22) randomized 155 obese patients (BMI >30) to supplemental oxygen (n=74) or HFNCO (n=81). NIV was used in two patients in the control group and in three patients initially treated with HFNCO. Reintubation was required in only one patient in the control group.

HFNCO was compared to BiPAP in a large RCT including 840 patients after cardiac surgery (20). HFNCO appeared not inferior to BiPAP with 21% and 21.9% of treatment failure. Reintubation was required in 58 patients in the BiPAP group vs. 57 in the HFNCO group and mortality was similar in the two groups.

A recent RCT has compared Venturi mask (n=52) and HFNCO (n=53) applied for at least 48 hours in patients extubated after successful SBT and not requiring prophylactic NIV (19). Respiratory rate was lower in patients treated with HFNCO. Interestingly, oxygenation was improved among patients receiving HFNCO for the

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same level of FiO_2. Patients treated with Venturi mask required more frequently NIV (15.8% *vs.* 3.4%, P=0.04) and tracheal intubation (21.2% *vs.* 3.8%, P=0.005). Intubation was required for inability to clear secretion and severe hypoxemia. Moreover, the use of the HFNCO was associated with significantly less discomfort (mouth dryness, throat dryness, difficulty to swallow and throat pain). Owing to the significant difference on the rate of reintubation observed in the control arm, it was suggested that HFNCO benefitted to the group of patients with a high risk of intubation extubation failure, questioning on the interest of HFNCO to prevent reintubation in patients with low risk of extubation failure.

Hernández *et al.* recently reported the results of a trial aimed at assess this issue (24). In a multicenter randomized controlled study, the impact of HFNCO was assessed in the post extubation period of patients deemed to be at low risk of extubation failure. The authors should be congratulated for the design of the study. This was a large multicenter study with no treatment cross over possibility. Patients included were less than 65 years, ventilated for less than 1 week, without moderate to severe COPD, heart failure, had an APACHE score less than 12 on extubation day, a body mass index less than 30, and had neither airway patency problem nor inadequate secretions management. Patients were therefore randomized to 24 hours of HFNCO (n=264) or conventional oxygen therapy (n=263). A cuff leak test was performed in patients considered at risk of post extubation stridor and those with no or minimal leak received prophylactic steroids. Reintubation within 72 hours following extubation was less frequent in the HFNCO group (4.9% *vs.* 12.2%, P=0.004) and was mainly related to respiratory causes. It was calculated that the number needed to treat to prevent one reintubation with HFNCO was 14. Post extubation respiratory failure was less frequent among patients receiving HFNCO (8.3% *vs.* 14.4%, P=0.03). Patients requiring reintubation had longer mechanical ventilation duration (3 *vs.* 1 day; P<0.01) and significantly longer ICU and hospital stay. In-ICU and in-hospital mortality were however less than 5% and similar in the two groups. These results are promising and could support an unrestricted use of HFNCO after all extubation but they also raise several issues about its impact in a generalized use.

First, the rate of reintubation in the control group was significant in a highly selected population of patients expected to have a low risk of extubation failure. Whereas patients with heart failure were excluded, arterial hypertension was not uncommon among the two groups.

We do not know which modalities of SBT was used (T-tube or pressure support). SBT performed with low level of pressure support could mask latent pulmonary edema which could be patent after extubation as soon as positive pressure is removed (25,26). Second, while a cuff leak test was performed in patients at risk of post extubation stridor and prophylactic steroids given in case of no or weak leak, the rate of immediate post extubation stridor as well as the rate of stridor requiring reintubation were lower in the HFNCO group. It could be stressed that the cuff leak test was not performed in all patients but only in patients with risks factor of stridor which discriminative value is debated. HFNCO could have impeded respiratory failure occurrence in case of stridor, but stridor rate was lower in HFNCO group. A possible explanation is the important neurologic cause of respiratory failure in the two groups at admission [medical neurologic disease (HFNCO: 26.1% *vs.* control: 32.7%) and traumatic brain injury (HFNCO: 11.7%; control: 6.5%)]. Little is known about consciousness of patients at the time of extubation. Patients with altered level of consciousness are at increased risk of extubation failure (27). The unusual rate of immediate stridor could be explained by the occurrence of respiratory bruits due to lingual ptosis among neurologic patients with incapacity to maintain airway patency. The ability of HFNCO to produce a small but significant level PEP resulting in a stenting effect of the airway (14) could explain in part the reduction of stridor and post extubation respiratory failure observed in the HFNCO group. Third, the important part of surgical patients (HFNCO: 49.6% *vs.* control: 45.6%) raises several issues. Did the surgical patients undergo peripheral (orthopedic surgery) or thoraco-abdominal surgery which have very different impact on postoperative respiratory function and could affect the ability to clear secretions? While patients with inadequate secretions management were excluded from the study, the type of surgery could have been described. The authors performed a post hoc analysis after excluding surgical and neurocritical patients and found therefore a low reintubation rate (1.5%). The effect of HFNCO observed in this trial could therefore be due to the case mix.

It should also be bear in mind that in the study by Hernández and in most of the studies assessing HFNCO, flow used in patients receiving HFNCO was set at very high levels (40 or 50 L/min) whereas FiO_2 set was rather limited (0.40). HFNCO acts therefore more as a continuous positive airway pressure. In the study by Hernández, flow was started at 10 L/min and increased by 5 L/min step

until patients experienced discomfort. A last positive effect of HFNCO seems to be the ability to improve secretions clearance by a possible effect of mucociliary function due to delivery of heated and humidified gas flow. This resulted in less respiratory failure related to inability to clear secretions (13.6% *vs.* 36.8%). Nevertheless, while HFNCO was applied during only 24 hours, the protective effect of this therapy was observed even during the following days.

Finally, the study by Hernández suggests that HFNCO has a positive impact on extubation outcome even in patients with moderate hypoxemia (PaO_2/FiO_2 >200 mmHg) and decreases post extubation respiratory failure and reintubation rate. However, the significant proportion of surgical and neurocritical patients included in this trial impedes the generalization of the conclusion reported. The significant effect on stridor occurrence observed in this study suggests that HFNCO works not only as oxygen supply but also as a possible stenting of the airway. These promising data should be investigated and confirmed on unselected population of critically ill patients at low risk of extubation failure.

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Footnote

Comment on: 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.

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