Task Force on Optimal Use of High flow nasal cannula oxygenation in ICU adults

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Abstract (241 words)

Oxygen therapy is the first-line treatment in hypoxemic patients. Oxygen can be delivered using low-flow, medium-flow (Venturi mask), or high-flow devices. Low/medium-flow oxygen devices have several drawbacks that cause patient discomfort and translate into sub-optimal clinical results. These include limitation of the FiO2, lack of humidification, or insufficient warming of the inspired gas. Also, in patients with respiratory failure, inspiratory flows are so high that FiO2 values are lower than needed. High-flow nasal cannula (HFNC) delivers oxygen flow rates of up to 60 L/min and has widely been evaluated over the last decade for its efficacy on clinical outcomes such as the improvement of respiratory distress, the need for intubation as well as mortality. This review has the major aim to guide clinicians towards evidence-based clinical practice guidelines. It summarises current knowledge about HFNC use in ICU patients and the potential areas of uncertainties. For instance, HFNC oxygen therapy has recently received resounding evidence of its efficacy in patients with hypoxemic acute respiratory failure. In other settings, research is ongoing and additional evidence is needed. For instance, if intubation is required, studies suggest that HFNC may help improve pre-oxygenation and be used for post-extubation. Likewise, HFNC might be used in obese patients, or to prevent respiratory deterioration in hypoxemic patients requiring bronchoscopy, or for the delivery of aerosol therapy. However, areas for which conclusive data exist are limited and interventions using standardized HFNC protocols, comparators and relevant clinical outcomes are warranted.

Introduction

Oxygen therapy is the first-line treatment in hypoxemic patients. Oxygen can be delivered using low-flow devices (up to 15 L/min) such as nasal cannulas, non-rebreathing masks, and bag valve masks (Figure 1). The fraction of inspired oxygen (FiO_2) obtained using these devices varies with the patient's breathing pattern, peak inspiratory flow rate, delivery system, and mask characteristics. Maximum flow rates are limited in part by the inability of these devices to heat and humidify gas at high flows. With conventional medium-flow systems, such as Venturi masks, pressurized oxygen is forced through a small orifice at a constant flow, and this draws in room air through entrainment ports, at a set air/oxygen ratio. Although, compared to conventional nasal systems the FiO_2 value thus obtained is more stable, tolerance is poorer, as the mask is cumbersome and the inspired gas may be inadequately heated and humidified. Also, if the patient has a high inspiratory flow rate, the amount of entrained room air is large and dilutes the oxygen, thereby lowering the FiO_2. Low/medium-flow oxygen is however the first-line treatment for hypoxemic patients and is generally provided via a face mask or nasal cannula. These delivery devices have several drawbacks in addition to ~~other than~~ the limitation of the FiO_2 that restrict~~restrain~~ their efficacy and tolerance. The usual lack of humidification often causes symptoms such as dry nose, dry throat, and nasal pain. Bubble humidifiers fail to eliminate all discomfort when absolute humidity is low. In addition to insufficient humidification, insufficient warming of the inspired gas causes patient discomfort. Symptom~~s~~ severity increases with flow. Thus, oxygen cannot be delivered at flows greater than 15 L/min. However, in patients with respiratory failure, inspiratory flows vary widely and are considerably higher, between 30 and more than 100 L/min. As a result FiO_2 values are variable and often lower than needed.

Twenty years ago, Dewan and Bell described their experience with 'high flow rates' delivered using a regular nasal cannula in patients with chronic obstructive pulmonary disease [1]. Over

the past two decades, devices that deliver heated and humidified oxygen at high flows through a nasal cannula were developed as an alternative to low/medium flow devices. High-flow nasal cannula (HFNC) delivers oxygen flow rates of up to 60 L/min. An air/oxygen blender is connected via an active heated humidifier to a nasal cannula and allows FiO_2 adjustment independently from the flow rate (Figure 2). Recently published studies suggested that HFNC is a valuable tool in enhancing patients' comfort, oxygenation and could be associated with better outcomes. We'll summarise here the current knowledge about HFNC use in ICU patients and the potential areas of uncertainties.

Principles and mechanisms of action of High Flow Nasal Cannula oxygen therapy

The main mechanisms of action are summarized in Table 1. HFNC oxygen therapy generates a flow-dependent FiO_2 [2]. The ~~M~~more the flow is increased, the more the FiO_2 augments. From 15 L/min to 45 L/min oxygen flow, tracheal FiO_2 increases from 60 to 90% [3]. HFNC maintains high FiO_2 values by delivering flow rates higher than the spontaneous inspiratory demand, thereby diminishing room-air entrainment, which occurs commonly with standard nasal cannulas and face masks. Among all other oxygen delivery devices, only the Venturi mask at its maximum flow rate can deliver stable FiO_2 values across a wide range of respiratory rates [4]. As the difference between the patients' inspiratory flow and the delivered flow is small with HFNC, FiO_2 remains relatively stable. However, the flow rate must be set to match the patient's inspiratory demand and/or the severity of respiratory distress. Two other important categories of mechanisms of action underpinning the ~~of the~~ reported clinical benefits of HFNC are proposed. The first category of mechanism is related to ~~an~~ optimal ~~gas~~ conditioning of the delivered gas because the nasal air/oxygen mixtures are warmed and humidified close~~ly~~ to physiological conditions [3, 5]. Then, oxygen flow delivery is better tolerated and provides greater respiratory comfort especially with flows up ~~higher~~ to 6 L/min [3, 5]. The second category of mechanism is related to high-flow delivery (>30 L/min). HFNC oxygen therapy generates a flow-dependent positive airway pressure [3, 6]. At 35 L/min, the mean pressure measured with a nasopharyngeal catheter was 1.2 ± 0.8 cmH2O, mouth open, increasing up to 2.7 ± 1.0 cmH2O, mouth closed and to 3.3 ± 1.0 cm H2O at 50 L/min [7, 8]. A physiological study demonstrated lower pressures with HNFC with the highest median value below 2.5 cm H20 at 45 L/min, mouth closed [3]. This difference between studies could be explained by airway pressure measurement inside the trachea [3], more distal from the device, rather than in the nasal-pharynx [7] and decreased airway pressure when patients breath with an open mouth [3, 9]. This should be taken into account

when HFNC is used in critically ill patients with acute respiratory failure (ARF) often breathing through an open mouth rather than through~~with~~ the nose. It has also been shown that HFNC is associated with an increased end-expiratory lung impedance in a cohort of post-cardiac surgical patients, suggestive of increased lung volumes and functional residual capacity [10]. In obese patients with higher body mass index (BMI), the increase in end-expiratory lung volume (EELV) was found to be significantly greater [10]. This increase in EELV might be interpreted by the recruitment of alveoli, and prevention of further alveolar collapse, as a result of the low-level positive pressure generated by HFNC. The higher PaO_2/FiO_2 ratio reported in patients using HFNC could be attributed in part to the observed increase in EELV and resultant increase in alveolar ventilation. An increase in lung compliance and functional residual capacity could be contributing factors in the trend towards an improvement in subjective dyspnoea and may also be partially responsible for the observed decrease in respiratory rate. This increase in end-expiratory lung impedance is also influenced by the position. In healthy subjects Riera et al. [11] reported that HFNC in supine position, the regional improvement in end-expiratory lung impedance of the lung ventral regions was significantly higher than in the dorsal regions. This observation was not documented when subjects were in prone position, in whom end-expiratory lung impedance distribution was more homogeneous. However, it is generally ~~admitted~~acknowledged that non-intubated patients look more comfortable when supine or semi-recumbent position than in prone position. Although the generated positive airway pressure by HNFC is moderate [3, 7, 8], it could partially counteract intrinsic-PEEP leading to decreased work of breathing and improved comfort [12].

HFNC oxygen therapy also allows a flushing~~rinsing~~ of airway dead space [13, 14]. The ability to continually flush out CO_2 from the upper airway is another potential benefit of HFNC. HNFC oxygen therapy allows a reduction of nasopharyngeal resistance [6]. It increases the

fraction of minute ventilation that penetrates into the alveoli and participates in gas exchange [1]. However, this effect reaches a plateau above a threshold flow rate corresponding to complete washout of the nasopharyngeal dead space. ~~It improves thoraco-abdominal synchrony.~~ In a study that used respiratory inductance plethysmography, thoraco-abdominal synchrony was better with HFNC than with facemask oxygen therapy [15]. Furthermore, HFNC was associated with a lower respiratory rate while tidal volume was maintained, indicating a decrease in minute ventilation [2, 10, 15, 16]. HFNC decreases the work of breathing by mechanically stenting the airway [17]. Also, the high flow of oxygen matches the patient's inspiratory flow and markedly decreases the inspiratory resistance associated with the nasopharynx and, therefore, the attendant work of breathing. This change in resistance ~~that~~ translates into a decrease in the resistive work of breathing and is as efficient as nasal continuous positive airway pressure set at 6 cmH_2O [1, 7]. Finally, available data suggest that HFNC is an effective method for delivering oxygen therapy. In comparison to conventional low-flow oxygen devices, HFNC allows an improvement of gas exchange, respiratory rate and comfort. HFNC seems safer than face mask, with less interface displacement and less oxygen desaturations.

Finally, unique features of HFNC lie in its simplicity of use [18]; its remarkable tolerance and comfort [2, 14, 16, 19-22] in comparison with other forms of oxygen delivery, including noninvasive ventilation (NIV) [19, 20, 23] and its practicality in terms of oxygen and ventilation equipment management.

High Flow Nasal Cannula for acute respiratory failure

Acute respiratory failure is one the leading reasons for ICU admission. HFNC oxygen therapy has recently received resounding evidence of its efficacy in patients with hypoxemic ARF [20]. The main studies related to the use of HFNC oxygen therapy in ARF are detailed in Table 2. Results from this study corroborate the beneficial effects of HFNC during ARF suggested by several observational studies [2, 16, 22, 24]. Based on limited numbers of patients and without control groups, these studies lacked strong primary outcomes such as avoidance of intubation and reduced mortality. They were nonetheless instrumental in forming the basis for a large multicenter randomized study such as FLORALI [20].

One striking effect observed in the early studies on HFNC is the rapid alleviation of dyspnoea experienced by patients with ARF under HFNC. Within 15 to 30 minutes, significant changes in respiratory rate [2, 14, 19] and clinical signs of distress, as use of accessory muscles, thoracoabdominal asynchrony [2, 20] are observed in patients with persistent respiratory distress under conventional facemask oxygen. These changes were reported to be more pronounced under HFNC as compared to non-invasive mechanical ventilation (NIV), which paradoxically provided better oxygenation, suggesting that improvement in oxygenation because of higher FiO_2 is not the sole mechanisms of action of HFNC [19, 20]. Indeed, early studies both in healthy volunteers [6, 9] and post-cardiac surgery patients [25] found that HFNC generated a certain amount of flow-dependent positive pressure, the higher the flow and the larger the cannula, the greater the pressure measured in the nasopharynx [9]. The principal indication for HFNC in the ICU is hypoxemic ARF whose main aetiology is community-acquired pneumonia, from bacterial or viral origin [2, 16, 20, 22, 24]. An important question is whether the severity of hypoxemia is a limitation to the use of HFNC. A recent study reporting the use of HFNC in severe ARDS patients [22] showed that failure (i.e., need for intubation) rate of HFNC was 40%, similar to the 35% reported in the subgroup

of patients with a severe hypoxemia (PaO_2/FiO_2 ≤200 mmHg) reported in the FLORALI study [20]. It therefore appears that in the absence of immediate intubation criteria, severity of hypoxemia is not a contraindication to HFNC.

Based on observational studies showing the improvement of many patients treated with HFNC, associated with the reported failure rates mentioned above, it was suggested that HFNC was able to prevent intubation in some patients. There was however no definite proof of intubation avoidance by HFNC until recently. Indeed, FLORALI study is therefore pivotal in demonstrating the superiority of HFNC over both conventional oxygenation and NIV [20]. The significant reduction in mortality in the group of patients treated with HFNC weakens the use of NIV in hypoxemic ARF and suggests that HFNC should be the first line strategy in these patients [20]. As for NIV use which was blamed for ~~of~~ delaying intubation and increasing mortality [26], a similar concern was raised with HFNC; one recent study reporting such an association [27]. A closer analysis of the literature indicates that this may not be the case if the decision to intubate is taken within 24-48h following HFNC initiation [28] and supported by pre-specified criteria for intubation [19, 20, 22]. The ensuing question is how to predict failure. Persistence of high respiratory rates [2, 19] and of distress (thoracoabdominal asynchrony), use of accessory muscles [2] are indicative of an unsatisfactory response to HFNC that should lead to discussions regarding intubation. Studies have suggested that more than the severity of the respiratory disease *per se*, presence of an additional organ failure such as hemodynamic instability places the patients at higher risk for failure [22, 24].

There is now solid evidence that HFNC has a central place in the armamentarium of ARF management. Its unique features allow it to be used from admission to discharge. If intubation is required, HFNC may help improve preoxygenation [29] and be used for post-extubation [21, 30].

The use of High Flow Nasal Cannula in immunocompromised patients

Because mortality in immunocompromised patients with hypoxemic ARF is significantly higher compared to unselected patients, respiratory management that aims to avoid intubation and invasive mechanical ventilation is of major interest. Five studies have reported feasibility and safety of HFNC in selected groups of immunocompromised patients with acute respiratory failure. In a retrospective single-center study, Lee et al. [31] reported the feasibility of HFNC for treating ARF in 45 patients with hematologic malignancies. The most common underlying hematologic diseases were acute myeloid leukaemia (46.7%), myelodysplastic syndrome (13.3%), and lymphoma (11.1%) [31]. Twenty-one patients (46.7%) underwent bone marrow transplantation, half received recent systemic chemotherapy, and 19 patients (42.2%) were neutropenic [31]. HFNC therapy was titrated at a FiO_2 sufficient to maintain the arterial O_2 saturation level at greater than 90% and a flow of up to 45 to 50 L/min [31]. Fifteen (33%) patients successfully recovered without intubation and their mortality was lower compared to intubated patients [31]. HFNC failure was associated with the diagnosis of bacterial pneumonia [31]. In another study of ARF patients outside the ICU, Epstein et al. [32] reported a 72% HFNC use among 183 patients with solid tumors. Among them, 41% improved, 44% stabilized, and 15% worsened. In a pilot randomized physiological trial, 30 patients with advanced cancer and persistent dyspnoea were assigned either to HFNC or BiPAP for two hours [33]. Dyspnoea (VAS and modified Borg scale), vital signs and adverse effects were measured before and after the intervention. Dyspnoea was significantly improved by both HFNC and BiPAP, with no difference between the two techniques [33]. Oxygen saturation was only improved by HFNC and there was a trend for a non-significant decrease in respiratory rate by both techniques. No significant adverse effects were observed [33]. In 37 critically ill lung transplant patients, Roca et al. reported that HFNC was feasible and safe to treat acute respiratory failure [34]. The absolute risk reduction for mechanical

ventilation with HFNC was 29.8%, and the number of patients needed to treat to prevent one intubation with HFNC was 3 [34]. Last, in a study of 50 do-not-intubate patients with hypoxemic respiratory distress, including mostly immunocompromised patients [35], HFNC allowed an improvement in oxygenation and decreased respiratory rate. In addition, three soon-published studies have assessed survival benefits from HFNC in different groups of immunocompromised patients. The first study analysed 178 cancer patients with ARF (O_2>9l/min), including 76 (43%) treated with NIV and HFNC, 74 (42%) with NIV and standard oxygen therapy, 20 (11%) with HFNC alone and 8 with standard oxygen therapy alone. Patients receiving combination of HFNC and NIV exhibited lower mortality rates (37% vs. 52%, P=0.04) [36]. In the propensity analysis, HFNC associated with NIV was independently associated with improved D-28 survival [36]. This is in sharp contrast with the results of the sub study from the FLORALI trial where HFNC allowed survival benefits but HFNC combined with NIV was associated with significant increased day-28 mortality [20]. Last, in a sub study from the iVNIctus trial [37] that investigated benefits from early NIV in immunocompromised patients with ARF, 141/374 (38%) patients received HFNC and other patients received either oxygen only or NIV. A propensity score using variables available at ICU admission was built to allow adjustments. Intubation rate and day-28 mortality were not significantly different in immunocompromised patients treated with HFNC as compared to NIV or standard oxygen [37].

All these studies and discrepant results confirm feasibility and safety of HFNC in immunocompromised patients and demonstrate at least equipoise between HFNC, NIV and standard oxygen therapy in this setting. They also warrant future trials to demonstrate that survival benefits reported in unselected patients with hypoxemic ARF extend to immunocompromised patients.

High Flow Nasal Cannula oxygen use preceding endotracheal intubation (Table 3)

Endotracheal intubation (ETI) is a routinely performed ICU procedure notably for patients with ARF [38]. ETI is frequently associated with morbidity, or even mortality. Almost 30% of ETI are associated with serious adverse events. The most frequently reported complication (26%) is severe desaturation under 80%, notably for hypoxemic patients [39]. Preoxygenation before ETI is a crucial stage permitting to delay desaturation. Oxygenation through high flow facial bag valve mask is usually recommended. However, in ICU, especially in severe ARF, efficiency of preoxygenation is lessened with a high prevalence of desaturations, due to patients' instability [40]. Even if NIV usefulness in preoxygenation has been reported, no large randomized multicentre study has confirmed this assumption [41]. Because this device has to be interrupted during laryngoscopy, NIV fails to totally prevent desaturation during ETI. Considering the encouraging results for ARF, there has been a great interest for HFNC during ETI preoxygenation. Indeed, HFNC exhibits seducing theoretical and clinical advantages. HFNC significantly increases PaO_2/FiO_2 ratio and end expiratory lung volume in hypoxemic patients [10]. Finally, HFNC is easy to implement, usually well tolerated and can be maintained during the entire ETI procedure allowing for apneic oxygenation. A recent single centre trial compared non-rebreathing bag reservoir facial mask to HFNC for preoxygenation before ETI [29]. This before–after study included incidental patients (n=101) regardless of the reasons for intubation. For most of them, respiratory failure was not the main issue. Notably, patients with severe hypoxemia were excluded from~~of~~ this study. Concerning the primary outcome, the median [IQR] lowest SpO_2 reached during ETI was ~~reached~~ 100% [95%-100%] in the HFNC group as compared to 94% [83%-98,5%] ($p<0.0001$) for the facial mask [29]. After adjustment for several relevant baseline covariables, this difference remained significant. The prevalence of desaturation events (<80%) decreased from 14% in the facial mask group to 2% in the HFNC group ($p=0.03$) [29]. This latter study suggests that HFNC

strongly improved oxygenation during ETI in ICU. These conclusions are however deeply in contrast with the first multicentre randomised controlled trial done on this topic. “Preoxyflow” study compared HFNC (n=62) to high flow facial bag valve mask (n=57) for preoxygenation (and apneic oxygenation) in severe hypoxemic patients [42]. This latter trial concluded that HFNC was not superior in preventing desaturation during ETI. HFNC and high flow facial bag valve mask exhibited the same median [IQR] lowest saturation respectively 91.5% [80%-96%] vs 89.5% [81%-95%]. There was no difference in desaturation events prevalence, respectively 25.8% and 22.8%. The discrepancy between these two studies could be explained by differences regarding both the reasons for intubation and the severity of hypoxemia at inclusion, and the methodology of each trial. The literature suggests that despite interesting properties, the place of HFNC for preoxygenation during ETI is still not clear. We are waiting for further large trials to ultimately conclude on its accuracy in ICU, in comparison with NIV or standard oxygen therapy, especially for severely hypoxemic patients.

High Flow Nasal Cannula use following extubation (Table 3)

In the ICU

Lung derecruitment and hypoxemia is not uncommon after extubation. Even in patients with healthy lung, atelectasis may persist up to 24-48 hours after extubation following anesthesia and paralysis [43]. In fact, oxygen therapy is almost invariably used after extubation to correct the residual oxygenation impairment. Because of its positive effects on the respiratory system, HFNC can be an appealing device to reverse post-extubation atelectasis and improve oxygenation after extubation [44]. Few studies have been published to date on the use of HFNC after extubation. HFNC after extubation decreased dyspnoea score (1.6±1.2 vs. 2.9±1.5), breathing frequency (19.8±3.2 vs. 23.1±4.4 breaths/min), and heart rate (89.5±9.5 vs. 95.4±10.4 beats/min) as compared with a non-rebreathing mask [45]. However, in a small randomized, crossover trial comparing high-flow delivered with nasal cannula or face mask after extubation, no difference regarding gas exchange, respiratory rate, or hemodynamic parameters was reported [46]. A retrospective study compared the clinical effects of HFNC and non-rebreathing mask in 67 critically-ill patients after extubation [47] [47]. The authors found a better oxygenation (measured as the PaO_2 to the nominal FiO_2 ratio) with HFNC, while $PaCO_2$, respiratory rate, mean arterial pressure and heart rate were not different among the two groups. In addition, the use of HFNC was associated with a higher number of ventilator-free days (4.14±2.2 vs. 3.0±2.0) and a lower reintubation rate (2.9% vs. 18.2%) [47]. A recent randomized controlled trial comparing the effects of the Venturi mask (52 patients) and HFNC (53 patients) in patients presenting a moderate hypoxemia (i.e., PaO_2/FiO_2 ≤300 immediately before extubation) [21] showed that HFNC improved oxygenation. In addition, HFNC decreased $PaCO_2$ and respiratory rate, suggesting a reduction in the upper airways dead-space. The use of HFNC improved patient's discomfort both related to the interface (from the 12th hour) and to symptoms of airway's dryness (from the

24th hour), and was associated with fewer episodes of interface's displacement and of oxygen desaturation [21]. Finally, fewer patients had post-extubation respiratory failure requiring any form of ventilator support (7.5% vs. 34.6%) with less need for NIV (3.8% vs. 15.4%) and endotracheal re-intubation (3.8% vs. 21.2%) with HFNC than with the Venturi mask [21]. This study, however, was not aimed at demonstrating the superiority of the HFNC over the Venturi mask in the weaning outcome [21]. These authors have therefore designed a multicenter, randomized, controlled trial (RINO trial) to assess whether, as compared with the Venturi mask, the use of HFNC may reduce the extubation failure rate in patients with moderate hypoxemia after extubation (ClinicalTrials.gov: NCT02107183). Few multicenter, randomized, controlled trials have been performed to evaluate the effectiveness of HFNC after extubation but are not still published. In summary, available evidence suggests that HFNC is an effective method for delivering oxygen therapy after extubation in the ICU. It can improve gas exchange, respiratory rate and patient's comfort better than conventional, low-flow oxygenation devices. Its use can also be associated with a better patient's compliance with treatment, allowing less interface displacement and less oxygen desaturation. Finally, HFNC may play a role in protecting extubation in moderately hypoxemic patients, although further studies are needed to better define which patients can benefit the most and the optimal timing of application. Findings of ongoing randomized trials will hopefully help to answer these questions.

Following surgery

Hypoxemia following surgery is frequent, as high as 52% of patients after cardio-thoracic surgery [48]. The first treatment of hypoxemia is to provide low flow oxygen therapy. When low-flow oxygen therapy is insufficient, NIV is therefore often used in the postoperative setting. Noninvasive ventilation fails in about 20% of patients after cardiothoracic surgery, who then require reintubation [49, 50]. As a curative strategy, a single randomized trial found

that NIV after lung resection decreased the rate of intubation, from 50.0% to 20.8%, and also decreased mortality [49]. Both reintubation and mortality rates decreased significantly with noninvasive ventilation in the single published randomized study after heart surgery [51]. As a preventive strategy, a randomized controlled trial after major lung resection in COPD patients did not improve the rate of acute respiratory failure, but decrease the rate of acute respiratory failure requiring NIV [52]. Following cardiac surgery, prophylactic use of NIV improved oxygenation and reduced incidence of pulmonary complications [53]. There are few published studies on the use of HFNC during postoperative period. In a pragmatic randomized controlled trial of routine HFNC in cardiac surgical patients, HFNC was not associated with an increase in oxygenation compared with usual oxygen therapy, but it was associated with a reduced requirement for escalation of therapy and a slightly lower $PaCO_2$ [54]. In the same way, prophylactic extubation using HFNC in post-cardiac surgery patients with a BMI≥30 kg/m^2 did not lead to improvement in respiratory function [55]. Recently, in a multicenter, randomized, non inferiority, open trial, including 830 patients, the use of continuous HFNC compared with intermittent NIV did not result in a worse rate of treatment failure (risk difference = 0.86% [95%-confidence interval -4.9 – 6.6]) [30]. The PaO_2/FiO_2 ratio improved in the two groups but to a lesser extent for HFNC. Both the $PaCO_2$ level and the respiratory rate decreased more rapidly in patients treated by HFNC [30]. Interestingly there was no difference for the dyspnoea or the comfort scores. Skin breakdown was significantly more common with NIV after 24 hours [30]. In a post-hoc analysis of this latter study [56], the authors reported that preventive postextubation bilevel positive airway pressure use was associated with a higher rate of failure in high-risk patients treated as compared with HFNC (12.6% vs. 5.7%, respectively). Finally, for many postoperative hypoxemic patients, HFNC appear to be a valuable alternative to NIV [30]. For patients with moderate to severe hypercapnia NIV is still the best choice in the absence of data. Finally, as NIV, HFNC should

be applied in a safe environment with a close monitoring. Indeed, as it has been reported with NIV [57], delaying intubation with HFNC could lead to a worse outcome [27].

The use of High Flow Nasal Cannula in specific conditions

Aerosol Delivery by High Flow Nasal Cannula

Aerosol therapy is largely used in ICU patients, especially in non-intubated patients. Some in vitro studies have been done regarding the performance of aerosol therapy during HFNC. When heliox (80% helium/20% oxygen) was compared with oxygen for aerosol delivery with a pediatric high flow nasal cannula, the inhaled dose was similar at 3 L/min (11.41 ± 1.54% and 10.65 ± 0.51%, respectively) [58]. At a flow of 6 L/min, drug deposition was more than 2-fold greater with heliox (5.42 ± 0.54%) than oxygen (1.95 ± 0.50%). With oxygen or heliox, there was an important decrease in the delivered dose with an increase in flow from 3 L/min to 6 L/min. It is important to note that flows commonly used for HFNC in adults are 30 to 50 L/min, which is much greater than that used in this study. Perry et al. [59] evaluated the in vitro albuterol delivery and particle size with a mesh nebulizer and HFNC. Albuterol was delivered by mesh nebulizer positioned between a nasal cannula and heated humidifier. The inspired dose (% of nominal dose) for each cannula size and flow was 2.5%, 0.8%, 0.4%, and 0.2% for the adult cannula at 5, 10, 20, and 40 L/min, respectively; 1.2%, 0.6%, 0.1%, and 0% for the pediatric cannula at 3, 5, 10, and 20 L/min, respectively; and 0.6%, 0.6%, and 0.5% for the infant cannula at 3, 5, and 8 L/min, respectively. For each cannula size, there was a significant decrease in inspired dose with increasing flow. The effects of nebulizer type, nebulizer position, flow (30, 45, and 60 L/min), breathing pattern (quiet and respiratory distress), and opened and closed mouth was also assessed in another in vitro study [60]. The most efficient placement of the nebulizer was upstream from the humidifier. Using a mesh nebulizer, the respirable mass ranged from 2% to 10% of the nebulizer charge. Higher flows and an open mouth were associated with a lower efficiency. Simulated respiratory distress did not hinder drug delivery. When simulating a mean inspiratory flow of 45 L/min with a HFNC flow of 60 L/min, and using a mesh nebulizer upstream of the humidifier, the average inhaled

mass of respirable aerosol was 5% of the nominal dose. A reasonable estimate of usual aerosol delivery by mouthpiece is 15% of the nominal dose, or 0.375 mg of a 2.5 mg nominal dose, which is much greater than that reported by Perry et al. [59]. But the benefit of albuterol delivery by HFNC might be for continuous aerosol bronchodilator (CAB) in the setting of severe acute asthma. Imagine that HFNC is used with a CAB set to deliver 15 mg albuterol per hour for an adult with HFNC set at 5 L/min. Using the results of Perry et al. [59], this would deliver 0.375 mg/h – exactly the same amount estimated for a single treatment by mouthpiece. Using the data of Renimiac et al. [60], the delivered dose would be 0.75 mg/h at HFNC flows, which is greater than that typically administered with a single treatment. HFNC for CAB might be more acceptable to the patient, and might more convenient for the healthcare provider, than hourly mouthpiece treatments. This is encouraging for the use of HFNC for aerosol delivery, but needs to be confirmed in clinical studies.

With HFNC, much aerosol is lost due to impaction in the circuit and into the ambient environment. One approach to this problem uses of separate streams of submicrometer aerosol and heated humidified air to the right and left nostrils [61]. Submicrometer aerosol is generated by evaporating the output of an aerosol generator. There is a subsequent increase to particle size when mixed with the heated and humidified gas beyond the nose. This co-administration of heated humidified gas, as used with the HFNC, causes the enhanced condensational growth of the aerosol to the respirable size range. Another approach delivers a submicrometer aerosol in combination with a hygroscopic excipient [61]. With the combination of drug and hygroscopic excipient particles, when the aerosol is exposed to the natural humidity of the respiratory system, excipient-enhanced growth occurs, producing droplets of a size suitable for deposition in the lungs. Longest et al. [62] used in vitro experiments and simulations to evaluate the feasibility of enhanced condensational growth with a nasal cannula. They found that it might be possible to use a nasal cannula with delivery

efficiencies of 80 to 90%. Submicrometer particles with enhanced condensational growth delivery resulted in lower depositional losses. Using an in vitro model, Golshahi et al. [61] found that aerosol delivery using realistic breathing profiles of submicrometer condensational growth aerosols was efficient in delivering nasally administered drugs. These approaches might allow high aerosol dose delivery by HFNC. The available in vitro evidence is not sufficiently robust to recommend for or against aerosol delivery with HFNC. At high flows, the amount of aerosol delivery might be low. Enhanced condensational growth and excipient-enhanced growth have the potential to improve the feasibility of aerosol delivery with HFNC. Clinical studies are necessary to inform the use of HFNC for aerosol delivery as part of patient care.

Bronchoscopy during High Flow Nasal Cannula use

While being regarded as a safe procedure, bronchoscopy is associated with temporary alterations of gas exchange, lung mechanics and hemodynamics caused by a variety of mechanisms, such as reduction of alveolar ventilation, increase of ventilation/perfusion mismatch, increase of cardiac output and oxygen consumption [63]. The bronchoscope occupies approximately 10% of the cross-sectional area of the trachea, and this leads to a 10 to 30% decrease in arterial oxygen tension despite low flow oxygen administration, as compared to its baseline value [64, 65]}. In patients with hypoxemia, the risks associated with bronchoscopy, especially during a BAL, are significantly enhanced, worsening of gas exchange and cardiovascular events [66]. A number of randomized trials demonstrated that continuous positive airway pressure (CPAP) and NIV are better means of preventing deterioration of gas exchange than conventional sources of oxygen in patients with respiratory failure undergoing bronchoscopy [65, 67]. The success of these methods depend however on the tolerance of the interface that is some patients may be poor, and also by the difficulty for the operator to insert and direct the instrument, passing through an orifice of the

interface that is not necessarily in the proximity of the nose or mouth of the patient [65, 67]. Given its capacity of ameliorating hypoxemia in patients with acute respiratory failure, HFNC is, theoretically, a new potential and simpler means of preventing the worsening of hypoxemia during bronchoscopy [68]. In a randomized trial, Lucangelo et al. [69] evaluated the effect on gas exchange and cardiovascular variables of bronchoscopy with BAL in 45 patients receiving 40 L/min of oxygen through Venturi mask, 40L/min through HFNC or 60 L/min through HFNC. Being a pilot study the inclusion criteria (*i.e*,, SpO2≥90% and absence of respiratory or cardiac failure) were quite conservative. The procedures were completed in a standard endoscopy suite, and conscious sedation was achieved in all patients with a low dose of midazolam. Patients receiving HFNC at 60 L/min through HFNC had better PaO2, PaO2/FiO2 and SpO2 than those receiving 40 L/min through Venturi mask or HFNC. No differences were seen in the above variables among patients receiving 40 L/min through Venturi mask or HFNC. Simon et al. [70] evaluated the effect of HFNC in a small cohort of patients with a more severe respiratory involvement (PaO_2/FiO_2 ratio <165 in all patients) during bronchoscopy with BAL. In this study, 40 critically ill patients with hypoxemic respiratory failure were randomised to receive either NIV or HFNC (set at an oxygen flow of 50 L/min). The procedures were completed in the ICU and the amount of sedation given (96 mg and 74 mg of propofol in the HFNC and NIV group, respectively) was significantly higher than that in the study by Lucangelo et al. [69].The lowest oxygen saturation recorded by pulse oxymetry during bronchoscopy was the primary outcome measure. Oxygen levels were significantly higher in the NIV group than in the HFNC group both during and after bronchoscopy, but 19/20 patients in the HFNC group completed successfully the procedure with no complications.

In conclusion, the limited available data do not allow to establish decision-making pathways to guide use of the HFNC therapy to prevent gas exchange deterioration in hypoxemic

patients requiring bronchoscopy. Further research is required to assess the predictors of success and failure of NHFC during bronchoscopy, and to identify the patient population to whom it is most beneficial. A large prospective, observational multicenter trial (NCT02523573) is currently being conducted to evaluate efficacy and tolerance of HFNC in ICU patients admitted for acute respiratory failure requiring BAL.

The use of High Flow Nasal Cannula in obese patients

Global obesity levels, having doubled since the 80s, now exceed 600 million sufferers [71]. Respiratory alterations specifically associated with obesity include a reduced functional residual capacity (FRC) which exponentially decreases as body mass indices (BMI) increase [72, 73]. Therefore, the majority of respiration occurs on the less compliant part of the pressure-volume curve, encroaching on closing volume. Ventilation-perfusion mismatch and hypoxemia ensues with increased ventilatory requirements necessitating higher inspiratory flows [74]. An increased upper airway resistance and collapsibility due to the mechanical load imposed particularly by central obesity is also seen [73]. Finally, increased work of breathing due to pressure exerted by the abdomen, reduced respiratory compliance and increased metabolic demands of the respiratory muscle result in respiratory muscle inefficiency have also been reported [75]. Considering the physiologic rationale for HFNC and understanding the aetiology of obesity-induced respiratory dysfunction, it seems reasonable that HFNC might provide this cohort some clinical benefit. Obesity-induced FRC reductions may be partially reversed by the combination of both positive end-expiratory pressure (PEEP) generated by HFNC [10, 25] and increased EELV [10]. Hence, respiration returns to the more compliant part of the pressure-volume curve leading to improvements in respiratory efficiency, compliance, and ventilation-perfusion mismatch. PEEP may also assist in upper airway splinting thereby reducing the airway collapsibility of central obesity. Through a constant high flow of oxygen-rich gas, HFNC reduces anatomical dead-space leading to

improved respiratory efficiency due to a larger proportion of minute ventilation participating in gas exchange [44]. Moreover, HFNC more accurately match the inspiratory flow demands of the obese patient by providing flows of up to 60 L/min. This may result in a reduction in inspiratory resistance and, consequently, work of breathing [17]. Less entrainment of room air results in higher delivered FiO_2 thereby meeting the increased oxygen requirements of the morbidly obese patient in particular.

Whilst we can postulate on how the mechanisms of action of HFNC may benefit the obese patient, data specific to HFNC use in this cohort is very limited. In a post-cardiac surgery observational study comparing HFNC with low flow oxygen, higher BMI was associated with larger increases in end-expiratory lung volume (EELV) [10]. At a BMI of 25kg/m^2, a mean increase in EELV of 13.3% was seen with HFNC use however, at a BMI of 40kg/m^2, EELV increase by 24.4%. This finding led to a randomised controlled trial investigating the efficacy of HFNC in reducing the higher incidence of post-operative atelectasis seen in the obese patient [55]. Direct extubation onto HFNC was compared with standard oxygen therapy in post-cardiac surgical patients with a BMI≥30kg/m^2. One hundred and fifty-five patients were randomised to receive either HFNC up to 50L/min or standard oxygen therapy (2–6 L/min) for at least eight hours post-extubation. HFNC did not improve atelectasis, oxygenation, respiratory rate, patient-rated dyspnoea or failure of allocated therapy when tested in a randomised controlled fashion. Heinrich et al. [76] conducted a randomised controlled trial in 33 patients investigating three pre-oxygenation techniques prior to rapid sequence induction in morbidly obese patients undergoing bariatric surgery. HFNC (50L/min at FiO_2 1.0) was compared with continuous positive airway pressure (CPAP; 7cmH_2O at FiO_2 1.0) and standard treatment (12L/min via anaesthetic facemask at FiO_2 1.0), and the primary outcome was PaO_2. HFNC significantly improved PaO_2 at 5 and 7 minutes of the pre-oxygenation/induction period compared with standard treatment and provided comparable

oxygenation to CPAP. The authors concluded that HFNC was a feasible and safe method of pre-oxygenation in this cohort. However, given the paucity of data, targeted investigation of the clinical utility of HFNC in obese patients must take place before their efficacy in this cohort can be determined.

Uncertainties about high flow nasal cannula oxygen therapy

A growing body of evidence suggests that HFNC therapy may be effective for the early treatment of adults with respiratory failure. However, the areas for which conclusive data exist and those requiring further investigation need to be stressed. At least five points deserve attention. First, the wide variability in inclusion criteria creates considerable heterogeneity among published studies. For instance, studies of patients with hypoxaemia included all patients with hypoxaemia, patients with hypoxaemia and respiratory distress, or patients with a PaO_2/FiO_2 ratio <300. Second, the primary endpoints used in some studies were improvements in physiological variables (oxygenation or lung volumes), which do not always translate into better clinical outcomes (less respiratory distress, less intubation, or better survival). Third, the HFNC parameters (flow rate, FiO_2, time of HFNC exposure) varied in most studies, precluding an assessment of a possible dose-response effect. Fourth, the magnitude of the benefits from HFNC (odds ratio) on the various endpoints (oxygenation, comfort, intubation, or survival), varied markedly across studies. This point is related to the previous one, as dose may influence the effect size. Furthermore, the time of endpoint evaluation also varied. Finally, and importantly, a variety of comparators have been used, including low-flow oxygen, Venturi mask, and NIV. This last point is a major source of bias and reflects the current uncertainty about what should be the reference or "standard" for oxygen therapy in patients with acute hypoxaemia.

The beneficial effects of HFNC may be related to the humidification and/or warming of the inspired gas, high flow, high FiO_2, continuous use (as opposed to intermittent use with NIV), maintenance of a positive pressure all around the clock, or any combination thereof. Usual care generally involves oxygen delivery via a face mask or nasal cannula, at flows no higher than 15 L/min. Therefore, the improved oxygenation (higher SpO_2 or PaO_2 values) seen with HFNC may be simply a pharmacological effect of the high flow of oxygen. Moreover, when

there are large differences between the patient's inspiratory flow and the delivered flow, FiO_2 values are difficult to control and usually lower than predicted. HFNC, however, effectively delivers high flows with actual FiO_2 values that are usually close to those delivered by the device. These considerations emphasise the importance of using clinical endpoints such as the intubation rate or mortality, rather than physiological endpoints such as SpO_2 or PaO_2/ FiO_2.

A fundamental difference between HFNC and NIV is that HFNC systems maintain a fixed flow and generate variable pressures, whereas many NIV systems use a variable flow to generate a fixed pressure, precluding the manipulation of alveolar ventilation. Another major difference is that the anatomical dead space is increased by NIV interfaces and decreased by HFNC interfaces. With the open HFNC circuit tidal volume cannot be actively increased. Nevertheless, HFNC helps patients by improving alveolar ventilation and decreasing the anatomical dead space.

HFNC may play a role in protecting against extubation and might improve clinical outcomes in patients with hypoxemic respiratory failure or to prevent the occurrence of hypoxemia in selected patients at high-risk. There is however the need for additional trials in order to target the patients who should be treated with HFNC, either in preventing intubation and following extubation.

In summary (Table 4), HFNC oxygen therapy improves the outcome of patients with hypoxemic acute respiratory failure. In other settings, research is ongoing and additional evidence is needed. For instance, if intubation is required, studies suggest that HFNC may help improve pre-oxygenation and be used for post-extubation. Likewise, HFNC might be used in obese patients, or to prevent respiratory deterioration in hypoxemic patients requiring bronchoscopy, or for the delivery of aerosol therapy. However, areas for which conclusive data exist are limited and interventions using standardized HFNC protocols, comparators and relevant clinical outcomes are warranted.

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Table 1: Physiological benefits of HFNO compared to conventional oxygen therapy

FiO_2 values are higher and more stable because the delivered flow rate is higher than the spontaneous inspiratory demand and because the difference between the delivered flow rate and the patient's inspiratory flow rate is smaller. ☞ The flow rate must be set to match the patient's inspiratory demand and/or the severity of the respiratory distress.
The anatomical dead space is decreased, via washout of the nasopharyngeal space Consequently, a larger fraction of the minute ventilation reaches the alveoli, where it can participate in gas exchange. Respiratory efforts become more efficient. Thoraco-abdominal synchrony improves.
The work of breathing is decreased because HFNO mechanically stents the airway, provides flow rates that match the patient's inspiratory flow, and markedly attenuates the inspiratory resistance associated with the nasopharynx, thereby eliminating the attendant work of breathing.
The gas delivered is heated and humidified Warm humid gas reduces the work of breathing and improves muco-ciliary function, thereby facilitating secretion clearance, decreasing the risk of atelectasis, and improving the ventilation/perfusion ratio and oxygenation. The body is spared the energy cost of warming and humidifying the inspired gas. Warm humid gas is associated with better conductance and pulmonary compliance compared to dry, cooler gas. ☞ HFNO delivers adequately warmed and humidified gas only when the flow rate is >40 L/min.
Positive airway pressures are increased The nasal cannula generates continuous positive pressures in the pharynx of up to 8 cm H_2O. The positive pressure distends the lungs, ensuring lung recruitment and decreasing the ventilation-perfusion mismatch in the lungs. End-expiratory lung volume is greater with HFNO than with low-flow oxygen therapy. ☞ Minimising leaks around the cannula prongs is of the utmost importance.

Table 2: Main clinical studies on HFNC oxygen therapy in adults with hypoxemic acute respiratory failure

Reference	Study design	Population	N patients	Main results
Hypoxemic acute respiratory failure in the ICU				
[2]	Cohort, unselected patients. HFNC 50 L/min vs. face mask oxygen	Hypoxemic ARF	38	Improved oxygenation Decreased respiratory rate
[16]	Cohort, unselected patients. HFNC 20-30 L/min vs. face mask oxygen	Hypoxemic ARF	20	Improved oxygenation Decrease in respiratory/heart rates, dyspnoea, respiratory distress, and thoraco-abdominal asynchrony
[8]	HFNC vs. face mask oxygen	Hypoxemic ARF	60	Decreased treatment failure (defined as need for non-invasive ventilation) from 30% to 10%. Fewer desaturation episodes
[14]	Cohort study, HFNC 20-30 L/min vs. face mask oxygen	Hypoxemic ARF	20	Improved comfort; Improved oxygenation
[24]	Cohort study (post hoc)	Hypoxemic ARF (2009 A/H1N1v outbreak)	20	9/20 (45%) success (no intubation). All 8 patients on vasopressors required intubation within 24 hours. After 6 hours of HFNC, non-responders had lower PaO_2/FiO_2 values
[22]	Observational, single-centre study	ARDS	45	40% intubation rate. HFNC failure associated with higher SAPSII, development of additional organ failure, and trends toward lower PaO_2/FiO_2 values and higher respiratory rate
[20]	Multicentre, open-label RCT with 3 groups: HFNC, usual oxygen therapy (face mask), or non-invasive ventilation.	Hypoxemic ARF, $PaO_2/FiO_2 \leq 300$	310	Intubation rate was 38% with HFNC, 47% with standard oxygen, and 50% with non-invasive ventilation. Decreased day-90 mortality with HFNC
[77]	Retrospective before/after study of HFNC	Hypoxemic ARF	172	Reduced need for intubation (100% vs 63%, $P<0.01$)
[27]	Patients intubated after HFNC	Hypoxemic ARF	175	In patients intubated early, lower mortality (39.2 vs. 66.7 %), higher extubation success (37.7% vs. 15.6 %) and more ventilator-free days. Early intubation was associated with decreased ICU mortality.
Hypoxemic acute respiratory failure in the emergency department				
[18]	Patients with ARF (>9 L/min oxygen or clinical signs of respiratory distress)	Hypoxemic ARF	17	Decreased dyspnoea and respiratory rate and improved oxygenation
[78]	RCT of HFNC vs. standard oxygen for 1 h	Hypoxemic ARF	40	Decreased dyspnoea and improved comfort

ARF, acute respiratory failure; HFNC, high-flow nasal cannula; RCT: randomised controlled trial

Table 3: Clinical studies of HFNC in adults before intubation, and after extubation

Reference	Study design	Population	N patients	Main results
After surgery				
[30]	Multicentre RCT of HFNC vs. BiPAP for at least 4 hours per day	Prevention or treatment of ARF after cardio-thoracic surgery	830	HFNC was not inferior to BiPAP. No difference in ICU mortality Skin breakdown more common with BiPAP after 24 hours
[55]	Cohort	Patients with ARF after cardiac surgery	20	Lower respiratory rate and less dyspnoea Improved oxygenation
After extubation [to avoid re-intubation]				
[21]	Single-centre RCT Venturi mask vs. HFNC for 48 h	Patients with PaO_2/FiO_2 ≤300 immediately before extubation	105	Improved oxygenation and comfort Fewer patients had interface displacements. Fewer patients required re-intubation or NIV.
[8]	RCT of HFNC until day-2 vs. face mask oxygen	Heart surgery patients ready for extubation	340	Fewer patients needed escalation of respiratory support to NIV.
[46]	Randomised cross-over study of HFNC vs. Venturi	Patients ready for extubation	50	Tolerance was better with HFNC.
[78]	Randomised cross-over study of HFNC vs. non-rebreather mask	Patients ready for extubation	17	Less dyspnoea Lower respiratory and heart rates
[55]	RCT of HFNC vs. usual care	Patients with a BMI≥30 ready for extubation after heart surgery	155	No difference in atelectasis scores on Day 1 or 5, mean PaO_2/FiO_2 ratio, respiratory rate, or re-intubation
[47]	Retrospective study of HFNC vs. non-rebreather face mask	Patients ready for extubation	67	Improved oxygenation Fewer patients required re-intubation. No difference in mortality
Before intubation [for oxygenation]				
[29]	Before-(non-rebreather bag-reservoir mask) after (HFNC) study	Adults with acute hypoxemia requiring intubation	101	Higher lowest SpO_2 value during intubation (100% vs. 94%) Higher SpO_2 value at the end of pre-oxygenation
[42]	Multicentre RCT of HFNC throughout the procedure vs. O_2 mask	Adults with acute hypoxemia requiring intubation, PaO_2/FiO_2<30, and respiratory rate ≥30/min	124	No difference in lowest SpO_2 (91.5 % vs. 89.5%, p=0.44). No difference in intubation-related adverse events including desaturation <80%, and mortality

ARF, acute respiratory failure; HFNC, high-flow nasal cannula; RCT: randomised controlled trial

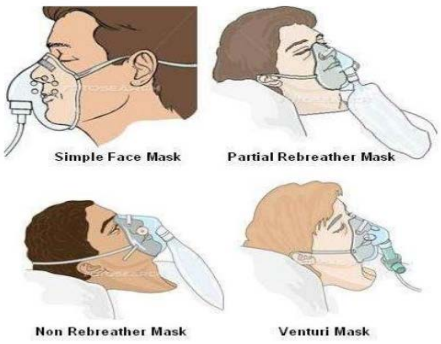
Table 4 Recommendations of the task force regarding the use of HFNC

Indication	Acute respiratory failure	In obese patients	Prior intubation	Following extubation	During bronchoscopy	For the delivery of aerosol therapy
Level of evidence	High *To be confirmed*	Low *Additional trials are needed*	Low to Moderate *Additional trials are needed*	Moderate *Additional trials are needed*	Moderate *Additional trials are needed*	Low to Moderate *Additional trials are needed*

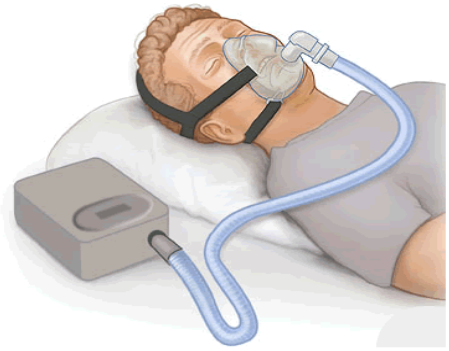
Figure 1: Low-flow and high-flow oxygen delivery devices

Low-flow nasal catheter

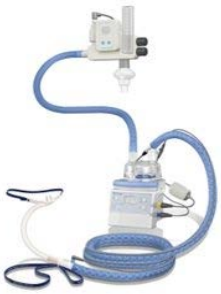
Low-flow nasal cannula



Low-flow and medium-flow masks



Non-invasive ventilation



High-flow nasal cannula

Figure 2: High-flow nasal oxygen [HFNO] device. An air/oxygen blender, allowing FiO_2 values ranging from 0.21 to 1.0, generates flow rates of up to 60 L/min. The gas is heated and humidified by an active heated humidifier and delivered via a single limb.