Physiopathological rationale of using high-flow nasal therapy in the acute and chronic setting: a narrative review

Giulia Spoletini [a, b], Andrea Cortegiani A[c], Cesare Gregoretti C[c]

[a] Respiratory Department, Gledhow Wing, St James's University Hospital, Leeds Teaching Hospital NHS Trust, Beckett Street LS9 7TF Leeds UK. Email: giulia.spoletini@nhs.net

[b] Leeds Institute for Medical Research, Clinical Science Building, St James's University Hospital Campus, University of Leeds, Leeds, UK. Email: giulia.spoletini@nhs.net

[c] Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.). Section of Anesthesia, Analgesia, Intensive Care and Emergency. Policlinico Paolo Giaccone, University of Palermo, Via del vespro 129, 90127 Palermo, Italy. Email: andrea.cortegiani@unipa.it

[c] Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.). Section of Anesthesia, Analgesia, Intensive Care and Emergency. Policlinico Paolo Giaccone, University of Palermo, Via del vespro 129, 90127 Palermo, Italy. Email: c.gregoretti@gmail.com

Corresponding author

Andrea Cortegiani, MD

Department of Surgical, Oncological and Oral Science (Di.Chir.On.S.)

Section of Anesthesia, Analgesia, Intensive Care and Emergency

Policlinico Paolo Giaccone, University of Palermo

Via del vespro 129, 90127 Palermo, Italy

Email: andrea.cortegiani@unipa.it

Conflict of interest: Dr Spoletini and Dr Cortegiani declare no conflict of interest. Dr Gregoretti received fees for consultancies or lectures from Orion Pharma, ResMed, Medtronic, Philips, Air Liquide and EOVE.

Abstract

Chronic lung disease and admissions due to acute respiratory failure (ARF) are becoming increasingly common. Consequently, there is a growing focus on optimizing respiratory support, particularly non-invasive respiratory support, to manage these conditions. High flow nasal therapy (HFNT) is a noninvasive technique where humidified and heated gas is delivered through the nose to the airways via small dedicated nasal prongs at flows that are higher than the rates usually applied during conventional oxygen therapy. HFNT enables to deliver different inspired oxygen fractions ranging from 0.21 to 1. Despite having only recently become available, the use of HFNT in the adult population is quite widespread in several clinical settings. The respiratory effects of HNFT in patients with respiratory failure may be particularly relevant for clinicians. In this narrative review, we discuss the main pathophysiological mechanism and rationale for using HFNT in the acute and chronic setting**.**

Keywords: acute respiratory failure; high flow nasal therapy; noninvasive ventilation; high flow nasal cannula; chronic obstructive pulmonary disease

Abbreviations

Acute respiratory failure, ARF

High flow nasal therapy, HFNT

Conventional oxygen therapy, COT

Long-term oxygen therapy, LTOT

Acute hypercapnic respiratory failure, AHRF

Chronic obstructive pulmonary disease, COPD

Noninvasive ventilation, NIV

Positive airways pressure, PAP

Tidal volume, TV

Respiratory rate, RR

1. Introduction

The incidence of acute respiratory failure (ARF) among hospitalized patients and the prevalence of chronic lung conditions in the general population have been increasing steadily in the last decades [1, 2]. As result, in recent years there has been a growing interest in optimizing techniques to provide adequate respiratory support, particularly by using non-invasive means.

Conventional oxygen therapy (COT) includes systems to deliver oxygen such as standard nasal cannulae, face masks, and Venturi masks. Traditionally, COT has been the first-line treatment in patients with hypoxemia in both the acute and chronic settings [3–5]. In patients with mild acute hypoxemia, COT can to improve oxygenation and outcomes [102]. Similarly, long-term oxygen therapy (LTOT) is the only treatment proven to reduce mortality in patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory failure [6, 7].

Non-invasive ventilation (NIV) is a ventilation delivery mode used routinely in the treatment of acute hypercapnic respiratory failure (AHRF) secondary to exacerbation of COPD [8], in ARF in immunocompromised patients [9] and ARF secondary to cardiogenic pulmonary edema [10]. NIV has been shown to reduce intubation rate and improve outcomes [10]. Conversely, its role in *de novo* hypoxemic ARF is still controversial, with conflicting results on its efficacy and poorer outcomes in this group of patients [11–13]. In the chronic setting, there is good evidence to support the long-term domiciliary use of NIV in both neuromuscular and extra-pulmonary restrictive disease [14, 15]. More recently, a growing body of evidence has become available to support the already widespread use of long term NIV in patients with COPD and chronic ventilatory failure [14, 16]. In these patients, NIV has been shown to improve gas exchange, quality of life, and reduce exacerbation and readmission rate [17–21].

Both COT and NIV suffer from known limitations. In particular, COT is unable to deliver accurate FIO_2, while NIV is associated with poor tolerability, patient-ventilator asynchrony due mainly to air leaks, and skin damage [8]. It is not unexpected, therefore, that new devices which could overcome some of these drawbacks are gaining increasing attention as an alternative form of respiratory support.

Among these is high flow nasal therapy (HFNT). This was initially developed for and extensively studied in the pediatric population [22], and recently has also been shown to be advantageous in adults, initially in the acute setting and more recently for long-term domiciliary use [23, 24]. HFNT devices generate and deliver high flows (up to 60 L/min) of oxygen-enriched gas, at varying FIO_2 between 21% and 100%, through large non-occlusive nasal prongs. The delivered gas mixture is actively heated to core temperature and humidified to full saturation, via a heated humidifier connected to the interface through a single-limb non-condensing insulated circuit. Despite having only recently become available, the use of HFNT in the adult population is becoming more widespread. Several studies have shown the possible application of HFNT in *de novo* hypoxemic ARF [13, 25–30], in immunocompromised patients [31], in the treatment and prevention of post-extubation respiratory failure [32, 33], and in peri-operative medicine [34–38].

In these diverse clinical scenarios, HFNT has been studied in comparison to COT [25, 33] or NIV [13], and more recently as a complementary therapy to NIV [39]. A small number of studies has focused on the role of HFNT in patients with stable COPD, showing a reduction in exacerbation rate and improvement in gas exchange [40–42].

Despite the need for further trials to confirm these results, the data available so far on HFNT, in both the acute and chronic settings, paint a very promising picture, and its use is anchored on a strong physiological rationale. In this narrative review, we discuss the main

pathophysiological mechanisms and the rationale for the use of HFNT in both the acute and chronic setting.

2. Physiological mechanisms in acute respiratory failure

By delivering a gas mixture heated to body temperature and fully humidified at high flow rates, HFNT is beneficial to patients with acute respiratory failure, irrespective of the underlying cause. This is owing to its effects on muco-ciliary clearance, respiratory mechanics and work of breathing, and comfort (Table 1).

2.1 Effects of HFNT on muco-ciliary clearance

Muco-ciliary clearance is the first-line defense mechanism of the bronchial tree and depends on synchronous cilia movement and adequate water content in the mucus [43, 44]. In physiological conditions, the upper airways are responsible for heating and humidifying the inspired air, in part by extracting humidity from the expired gas [45]. This process ensures that in the main bronchi and peripheral parts of the bronchial system the inspired air reaches a temperature of 37 C, an absolute humidity of 44 mg/L and a relative humidity of 100%. These are optimal conditions for the functioning of cilia, and to maintain mucus hydration [45, 46]. Deviating from these conditions both with under- or over-humidification has been shown to negatively affect lung muco-ciliary clearance [46, 47].

In ARF the elevated respiratory rate (RR) and patients' mouth breathing can affect proper airway humification. This can cause mucus dehydration, impaired muco-ciliary clearance and eventually mucus retention [48]. In addition, medical gases, normally delivered through various forms of conventional respiratory support, contain only 6 parts per million of water vapour, contributing to airways dehydration [46]. Furthermore, the delivery of high flows of gases in tachypneic mouth-breathing patients under COT or NIV causes unidirectional nasal flows which lead the nasal mucosa to recover less moisture during expiration [49]. Therefore,

even if not bypassed, the upper airways cannot exert their heating and moisturizing effect and the lower airways mucosa become involved in the heating and humidification process, leading to increased mucosal inflammation, mucus dehydration with subsequent impaired cilia function and bronchial hyper-reactivity [46].

While cold air humidification with COT cannot significantly prevent these adverse events, the use of humidification during NIV treatment either via in-line heater humidifier or heat and moisture exchanger can [50]. Unfortunately, the absolute humidity that these systems deliver ranges between 5 and 30 mg/L, below the optimal conditions outlined above [51]. Conversely, HFNT provides the same level of absolute humidity found in the alveoli (44 mg/L) and it has been shown *in vitro* to be associated with lower level of inflammation and injury compared to conditions of under-humidification [46]. It is conceivable that this leads to restoration of the rheological properties of mucus, reducing the retention of secretions and the occurrence of atelectasis.

2.2 Effects on respiratory mechanics and oxygenation

Patients with acute respiratory failure present with increased work of breathing secondary to augmented inspiratory effort, respiratory rate(RR) and increased respiratory impedance. HFNT has been shown to reduce inspiratory effort compared to COT in patients with ARF, which translates clinically in improved outcomes on HFNT compared to both COT and NIV. These benefits can be explained by four key characteristics of HFNT: positive airway pressure, wash out of dead space, reduction in airway resistance and heating and humidification of the delivered gas.

2.2.1 Positive airway pressure

In the pediatric population, HFNT is known to be associated to reduced respiratory effort due to the positive pressure generated in the upper airways [22]. Similarly, in adults, HFNT

generates a variable level of positive airways pressure (PAP) throughout the respiratory cycle. The PAP generated by HFNT depends on flow-rate and is higher at the end of expiration. During expiration, the PAP also depends on the volume of air leaked through the mouth, being higher when patients breathe with their mouth closed. During inspiration, the PAP does not however depend on the level of mouth closure [52–60]. It has been estimated that mean expiratory PAP can increase by 0.69 cmH_2O for every 10 L/min of flow rate [56].

The PAP generated by HFNT can be approximated to a low-level PEEP, being higher during expiration. This has been suggested to be the mechanism by which HFNT exerts a recruitment effect as shown by the increase in end-expiratory lung volume (EELV) in patients with acute and post-surgical respiratory failure [36, 61, 62]. In ARF, HFNT has not been associated with a significant increase in tidal volume (TV) [61, 63], unlike to what observed in stable patients. Therefore, HFNT could reduce the risk of ventilation-induced lung injury possibly by reducing transpulmonary pressure. This is in contrast to NIV which is often associated with high tidal volume in *de novo* hypoxemic ARF [61, 64].

HFNT has also been shown to reduce patients' inspiratory effort as observed clinically through a reduction in respiratory distress and use of accessory muscles [25–28]. Physiological studies [61, 63, 65] have shown, on HFNT compared to COT, a reduction of approximately 25% in the esophageal pressure swing, a measure of the inspiratory effort, and a decreased metabolic work of breathing as measured by trans-diaphragmatic pressure (**P**di) time product (PTPdi). PTPdi is the area under the **P**di signal from the onset of its positive deflection to its return to baseline [66]. These effects on respiratory mechanics, reported by one study to be most significant for flows of 60 L/min, do not show a clear dose-response with flow rates [61, 63, 65]. Current data seems to suggest that a tailored approach for each patient, consisting in bedside titration of the flows, could lead to optimal outcomes [62].

2.2.2 Increased inspiratory oxygen fraction and dead space wash out

HFNT delivers flow rates which match or are closer to patient peak inspiratory flow rate, usually between 30 and 120 L/min in ARF. Conversely, COT cannot meet the peak inspiratory flow rate, leading to the set FIO_2 not being delivered due to dilution with entrainment of room air in the gas mixture. HFNT not only reduces this effect [52, 67, 68], but by delivering high flow rates, washes out the upper airways dead space. This increases the FIO_2 and reduces the $FICO_2$, minimizing the risk of re-breathing [69, 70]. As a result, the FIO_2 delivered by HFNT is closer to the desired one, with mild discrepancies for flows lower than 40 L/min or in case of high peak inspiratory flow rates [71]. As an effect of this, alveolar pO_2 is increased, and oxygenation is improved. Similarly, CO_2 is cleared more efficiently on HFNT than on COT with reduced work of breathing to ensure adequate ventilation.

Finally, it is conceivable that dead-space wash-out can improve work of breathing in patients on HFNT as increasing dead-space, such as the instrumental one related to HME, has been associated with worsening work of breathing in patients treated with NIV [72].

2.2.3 Airway resistance

Due to their distensibility, the upper airways, and especially the nasopharynx, create resistance to the air flow. This becomes particularly relevant in situations that lead to a contraction of the upper airways, such as with the increase of peak inspiratory flow rate in ARF. Noninvasive continuous positive pressure ventilation (CPAP) and intermittent positive pressure ventilation (NIPPV), through a splinting effect and by delivering an inspiratory pressure respectively, can overcome this resistance. HFNT reduces inspiratory resistance and the resistive component of the work of breathing by matching the peak inspiratory flow rate and possibly by triggering the activation of the alae nasae muscle, thereby stiffening the airway [73–75].

2.2.4 Humidification

The energy expenditure for the human body to heat and humidify the inspired gas in physiological conditions (TV 500 ml and RR 12/min) has been estimated to be 156 calories/min [75]. This increases significantly when patients are in ARF, tachypneic and breathing with their mouth open. HFNT provides a pre-conditioned gas mixture, reducing therefore the metabolic component of work of breathing.

2.3 Effects on respiratory pattern

As a consequence of the mechanisms described above, HFNT can affect the respiratory pattern in patients in various clinical scenarios, including healthy people [74]. HFNT in ARF tends to reduce respiratory rate, relieving patients' distress, and to increase tidal volume with reduction in dead space [61].

2.4 Effects on comfort

2.4.1 Heating and humidification

Patients treated with low-flow oxygen report minimal or no discomfort on treatment, hence clinical guidelines do not recommend the routine use of humidification in such circumstances [3, 76]. However, critically ill patients in ARF, who are often treated with higher flows of oxygen via face mask, are known to report discomfort on oxygen therapy, including airway dryness, despite the use of humidification [77]. Similarly, critically ill patients on NIV often report mucosal dryness in the nose, mouth and throat and this limits their comfort , leading to a higher risk of treatment failure [78, 79]. The use of humidification appears to reduce the perceived dryness on NIV, although in a fashion not necessarily correlated with the level of delivered absolute humidity [48, 80].

HFNT has been consistently shown to provide greater overall comfort to patients compared to both COT and NIV, including to patients with *de novo* ARF or post-extubation respiratory failure. This has mostly been attributed to the delivery of warmed and humidified gas through an in-line heated humidifier, which reduces airway dryness. However, only a handful of studies directly assessed subjective or objective measures of airway dryness using numeric rating scales or specialist assessment by otorhinolaryngologists. While most studies show a noticeable reduction in the perceived or measured dryness in the nose, mouth and throat, results are not consistent across the studies. Studies comparing HFNT to NIV or COT with added in-line humidification show that a similar fraction of patients reported airway dryness [39]. This would suggest that the greater overall comfort consistently observed on HFNT is associated with factors other than humidification, such as comfort of the interface.

2.4.2 Interface

Critically ill patients usually receive COT via face masks or NIV via oronasal masks, full-face masks, or helmets, depending on patients' characteristics and needs [81, 82]. The interface plays a central role in the improvement of comfort of HFNT compared to NIV.

The interfaces used for NIV in ARF suffer from several problems. One of them is the high instrumental dead space introduced by masks or helmets in NIV, which is almost negligible for nasal prongs used in HFNT. NIV interfaces suffer also from air leaks, which – in an attempt to be compensated by the clinician – cause the development of pressure sores, skin damage, and overall lead to poor tolerance. This, in turn, leads to the need for rotational strategies to be applied [50, 82, 83]. The nasal cannulae used on HFNT confer significant advantages to both COT and NIV. Not only the loose-fitting nasal prongs are reported to be more comfortable than those used for COT, but they are also associated with less displacement episodes, diminished eye irritation and greater ease eating [32, 39].

Finally, it is conceivable that improving patient's comfort by optimizing airway humidification and interfaces may in turn lead to reduced need for sedation thus decreasing the risk for delirium [84, 85].

3. Physiological mechanisms in long term chronic setting

Over the last few years, a small number of case reports and studies have started looking at the potential role of HFNT in patients with sleep-disordered breathing, COPD and bronchiectasis. While the clinical evidence for the use of HFNT in the chronic setting is still very limited, more convincing data are available on its physiological rationale. The main effects by which HFNT could confer any advantages over COT or NIV in long-term domiciliary use are the same as in the acute setting, including its role on muco-ciliary clearance, improvement of respiratory mechanics and gas exchange and comfort (Table 2).

3.1 Effects of HFNT on muco-ciliary clearance

Impaired muco-ciliary clearance in chronic respiratory conditions can be caused by various mechanisms, including decreased water content (i.e. Cystic Fibrosis), increased airways inflammation (i.e. COPD) or structural cilia damage (i.e. primary ciliary dyskinesia), and feeds into a vicious cycle leading to recurrent infections [43, 44].

The central role of temperature and humidification in optimizing cilia function and mucus hydration [46], discussed previously, has been validated *in vivo* by showing that patients with bronchiectasis in treatment with HFNT (20-25 L/min, FIO_2 21% 3 hours/day for 6 days) had improved, but not normalized, lung clearance with no significant changes in cough frequency [86]. This improvement in the clearance index could explain how HFNT can reduce the rate of exacerbations in patients with bronchiectasis and COPD [42, 87].

3.2 Effects on respiratory mechanics

In COPD, structural changes and airflow obstruction with subsequent increased respiratory resistance lead to dynamic hyperinflation. Elastic and resistive loads are responsible for the increased work of breathing, which tends to be particularly evident during exacerbations and exercise [88]. However, this can evolve to be apparent during rest as well, and patients develop chronic respiratory failure.

3.2.1 Positive airway pressure

In stable COPD, NIV improves alveolar ventilation altering the breathing pattern, and offloads the respiratory effort providing inspiratory pressure and counterbalancing the intrinsic PEEP [89]. The low-level PEEP effect exerted by HFNT has been described in stable patients with COPD and interstitial lung disease [54]. HFNT, used at relatively low flow rates in patients with stable COPD, leads to a reduction in Pdi swing, PTPdi and dynamic intrinsic PEEP compared to baseline, but in a lesser measure than NIV [90, 91]. These effects have been observed during wakefulness and in non-REM sleep [92]. This, together with the observed increase in TV [74, 92] and end-expiratory lung volume, suggest an increase in the residual functional capacity. Finally, the use of HFNT improves the I:E compared to COT, due to an increase in expiratory time. These effects have been observed for flow rates at 20 and 30 L/min with patients breathing with their mouth closed, but were more pronounce for higher flows.

Patients with COPD often adopt strategies as pursued-lips breathing to increase the expiratory resistances as this can increase the expiratory time, reduce the respiratory rate and dynamic hyperinflation [93]. However, pursued-lips breathing may lead to an increased effort that the patient is not able to maintain over time. HFNT, by resembling the breathing pattern of pursued-lips breathing [74], may be a therapeutic tool for patients with COPD slowing respiratory rate and improving breathing pattern. Finally, the adoption of a deep and slow

breathing pattern may reduce atelectasis [74].

In stabilized patients with Cystic Fibrosis, no differences in work of breathing as measured by diaphragmatic activity were observed while patients were at baseline, on HFNT or on NIV. However, HFNT resulted in mild improvement in VT compared to NIV and reduced RR compared to COT [94].

3.2.2 Dead space wash out

Studies on animal models suggested that the improved ventilation on HFNT is a consequence of flow rather than pressure [95]. Higher flow rates, by washing out the dead space in the upper and lower airways, improve pCO_2 or $tcCO_2$ clearance, reduce rebreathing and work of breathing in a flow-dependent manner with better results for flows greater than 30 L/min. Furthermore, recent *in vivo* studies have confirmed that the reduction in pCO_2 in patients with stable hypercapnia is flow-dependent, and this effect could be more relevant than that of the generated pressure. In a small physiological study, pCO_2 dropped more significantly with higher flow rather than in those conditions where highest mean PAP was achieved [96].

3.2.3 Airway resistance

HFNT can reduce inspiratory resistance, leading to a reduction in dyspnea and respiratory rate. As aforementioned the effect on respiratory resistance exerted by HFNT is mainly due by meeting or exceeding the patient's peak inspiratory flow rate by supplying gas at a high flow. In addition, HFNT can also reduce bronchoconstriction by reducing the muscarinic effect [97] resulting from nasal inhalation of cold air in patients undergoing oxygen therapy [98].

This could have significant clinical implications during exercise and in symptomatic patients [89, 99]. Alongside attenuating the inspiratory resistance, HFNT can increase the expiratory resistance through pressure effects and via the provision of continuous flow.

3.3 Effects on gas exchange

COT and NIV are used in the treatment of chronic respiratory failure to improve several significant outcomes, including quality of life, exacerbation rate, hospital readmission and mortality, through normalization or improvement in the gas exchange.

In most chronic respiratory conditions, this requires correcting both hypoxemia and hypercapnia. However, the studies available so far are limited to stable COPD with mild-moderate hypercapnia. In this setting, HFNT was consistently shown to decrease pCO_2, as a consequence of the mechanisms above described, in both sleep and wakefulness. It has been suggested that changes in pulmonary mechanics, breathing pattern, flow rate, and higher baseline pCO_2 can affect the response to HFNT, with an average fall in pCO_2 by 10% for baseline values greater than 50 mmHg [100]. Conversely, results on oxygenation mostly show no changes in oxygen saturation, although a non-clinically-significant reduction in oxygenation has been observed during sleep and in short term physiological studies [92]. This could be because HFNT provides a more reliable delivery of a FIO2 than COT which could lead to a higher FIO2 being provided to patients.

3.4 Effects on comfort

Contrary to studies and results on ARF, results on comfort and dyspnea are inconsistent in patients with chronic respiratory failure who could be potential candidate for the domiciliary use of HFNT.

Interestingly long-term studies have shown that HFNT is well tolerated, and reduces dyspnea compared to LTOT [41, 42], but when used in the short-term HFNT does not provide similar results in patients with COPD or CF [90, 91, 94]. Despite the lack of side effects, patients have reported overall comfort to be better or similar on LTOT and NIV compared to HFNT

[90, 91, 101]. On this treatment the highest level of tolerability appeared to be achieved when the delivered flow was 30 L/min [101].

4. Summary and conclusion

In conclusion, HFNT entails several physiopathological mechanisms which can lead to improve patient's clinical condition both in acute and in chronic setting. Although these mechanisms have been demonstrated to improve patients' outcomes in some clinical scenarios, other applications, particularly in the chronic setting, require important issues to be resolved, such as timing of treatment and escalation plan to more invasive tools. Further studies are warranted to investigate these important issues.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgement

The authors would like to thank Laura Caley for assistance in language editing and proof-reading.

References

1. Stefan MS, Shieh M-S, Pekow PS, Rothberg MB, Steingrub JS, Lagu T, Lindenauer PK, Stefan MS (2013) Epidemiology and outcomes of acute respiratory failure in the United States, 2001 to 2009: A national survey. J Hosp Med 8:76–82

2. GBD 2015 Chronic Respiratory Disease Collaborators (2017) Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 5:691–706

3. Kallstrom TJ, American Association for Respiratory Care (AARC) (2002) AARC Clinical Practice Guideline: oxygen therapy for adults in the acute care facility--2002 revision & update. Respir Care 47:717–20

4. Hardinge M, Annandale J, Bourne S, Cooper B, Evans A, Freeman D, Green A, Hippolyte S, Knwoles V, MacNee W, McDonnell L, Pye K, Suntharlingam J, Vora V, Wilkinson T (2015) British Thoracic Society guidelines for Home Oxygen use in adults. Thorax 70:i1–i43

5. O'Driscoll BR, Howard LS, Earis J, Mak V, British Thoracic Society Emergency Oxygen Guideline Group, BTS Emergency Oxygen Guideline Development Group (2017) BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 72:ii1-ii90

6. NOTT Study group (1980) Is 12-hour oxygen as effective as 24-hour oxygen in advanced chronic obstructive pulmonary disease with hypoxemia? (The nocturnal oxygen therapy trial--NOTT). Chest 78:419–20

7. NOTT study group (1980) Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 93:391–8

8. Gregoretti C, Pisani L, Cortegiani A, Ranieri VM (2015) Noninvasive ventilation in critically ill patients. Crit Care Clin 31:435–57

9. Cortegiani A, Madotto F, Gregoretti C, Bellani G, Laffey JG, Pham T, Van Haren F, Giarratano A, Antonelli M, Pesenti A, Grasselli G, LUNG SAFE Invesitgators and the ESICM Trials Group (2018) Immunocompromised patients with acute respiratory distress syndrome: secondary analysis of the LUNG SAFE database. Crit Care 22:157

10. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, Navalesi P, Antonelli M, Brozek J, Conti G, Ferrer M, Guntupalli K, Jaber S, Keenan S, Mancebo J, Metha S, Raoof S (2017) Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 50:1602426

11. Hill NS, Garpestad E, Schumaker G, Spoletini G (2018) Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure/ARDS – is There a Role? Turkish J Anesth Reanim 45:332–334

12. Cortegiani A, Russotto V, Antonelli M, Azoulay E, Carlucci A, Conti G, Demoule A, Ferrer M, Hill NS, Jaber S, Navalesi P, Pelosi P, Scala R, Gregoretti C (2017) Ten important articles on noninvasive ventilation in critically ill patients and insights for the future: A report of expert opinions. BMC Anesthesiol 17:122

13. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, Prat G, Boulain T, Morawiec E, Cottareau A, Devaquet J, Nseir S, Razazi K, Mira JP, Argaud L, Chakarian JC, Ricard JD, Wittebole X, Chevalier S, Herbland A, Fartoukh M,

Constantin JM, Tonnelier JM, Pierrot M, Mathonnet A, Beduneau G, Deletage-Metreau C, Richard JC, Brochard L, Robert F, FLORALI study group; REVA network (2015) High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 372:2185–96

14. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, Escarabill J, Farre R, Fauroux B, Robert D, Schoenhofer B, Simonds AK, Wedzicha JA (2005) Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J 25:1025–31

15. Robert D, Argaud L (2007) Clinical review: Long-term noninvasive ventilation. Crit Care 11:210

16. Crimi C, Noto A, Princi P, Cuvelier A, Masa JF, Simonds A, Elliott M, Wijkstra P, Windisch W, Nava S (2014) Domiciliary noninvasive ventilation (NIV) in severe COPD patients: A European survey about indications and practices. ERS Journals

17. Elliott MW, Mulvey DA, Moxham J, Green M, Branthwaite MA (1991) Domiciliary nocturnal nasal intermittent positive pressure ventilation in COPD: mechanisms underlying changes in arterial blood gas tensions. Eur Respir J 4:1044–52

18. Meecham Jones DJ, Paul EA, Jones PW, Wedzicha JA (1995) Nasal pressure support ventilation plus oxygen compared with oxygen therapy alone in hypercapnic COPD. Am J Respir Crit Care Med 152:538–44

19. Nickol A, Hart N, Hopkinson NS, Hamnegård C-H, Moxham J, Simonds A, Polkey MI (2008) Mechanisms of improvement of respiratory failure in patients with COPD treated with NIV. Int J Chron Obstruct Pulmon Dis Volume 3:453–462

20. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, Karg O, Laier-

Groeneveld G, Nava S, Schonhofer B, Wegscheider K, Criee CP, Welte T (2014) Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med 2:698–705

21. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, Dowson L, Duffy N, Gibson GJ, Hughes PD, Hurst JR, Mukherjee R, Nickol A, Oscroft N, Patout M, Pepperell J, Smith I, Stradling JR, Wedzicha JA, Polkey MI, Elliott MW, Hart N (2017) Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation. JAMA 317:2177

22. Franklin, Schibler A (2018) Nasal high-flow therapy in infants and children. Pediatr Respirol Crit Care Med 2:2

23. Spoletini G, Alotaibi M, Blasi F, Hill NS (2015) Heated Humidified High-Flow Nasal Oxygen in Adults: Mechanisms of Action and Clinical Implications. Chest 138: 253-261

24. Pisani L, Vega ML (2017) Use of Nasal High Flow in Stable COPD: Rationale and Physiology. COPD J Chronic Obstr Pulm Dis 14:346–350

25. Roca O, Riera J, Torres F, Masclans JR (2010) High-flow oxygen therapy in acute respiratory failure. Respir Care 55:408–413

26. Sztrymf B, Messika J, Mayot T, Lenglet H, Dreyfuss D, Ricard J-D (2012) Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. J Crit Care 27:324.e9-13

27. Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, Ricard J-DD (2011)

Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med 37:1780–6

28. Lenglet H, Sztrymf B, Leroy C, Brun P, Dreyfuss D, Ricard J-D (2012) Humidified high flow nasal oxygen during respiratory failure in the emergency department: feasibility and efficacy. Respir Care 57:1873–8

29. Messika J, Ben Ahmed K, Gaudry S, Miguel-Montanes R, Rafat C, Sztrymf B, Dreyfuss D, Ricard J-D (2015) Use of High-Flow Nasal Cannula Oxygen Therapy in Subjects With ARDS: A 1-Year Observational Study. Respir Care 60:162–9

30. Helviz Y, Einav S (2018) A Systematic Review of the High-flow Nasal Cannula for Adult Patients. Crit Care 22:71

31. Cortegiani A, Crimi C, Sanfilippo F, Noto A, Di Falco D, Grasselli G, Gregoretti C, Giarratano A (2019) High flow nasal therapy in immunocompromised patients with acute respiratory failure: A systematic review and meta-analysis. J Crit Care. 50:250-6

32. Maggiore SM, Idone FA, Vaschetto R, Festa R, Cataldo A, Antonicelli F, Montini L, De Gaetano A, Navalesi P, Antonelli M (2014) Nasal high-flow versus Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 190:282–8

33. Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuena R, Fernández R (2016) Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients. JAMA 315:1354–61

34. Ansari BM, Hogan MP, Collier TJ, Baddeley RA, Scarci M, Coonar AS, Bottrill FE, Martinez GC, Klein AA (2015) A Randomized Controlled Trial of High-Flow Nasal

Oxygen (Optiflow) as Part of an Enhanced Recovery Program After Lung Resection Surgery. Ann Thorac Surg 101:459–64

35. Stéphan F, Barrucand B, Petit P, et al (2015) High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery. JAMA 313:2331–9

36. 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 ≥30: a randomised controlled trial. Intensive Care Med 41:887–94

37. Cortegiani A, Accurso G, Mercadante S, Giarratano A, Gregoretti C (2018) High flow nasal therapy in perioperative medicine: from operating room to general ward. BMC Anesthesiol 18:166

38. Russotto V, Cortegiani A, Raineri SM, Gregoretti C, Giarratano A (2017) Respiratory support techniques to avoid desaturation in critically ill patients requiring endotracheal intubation: A systematic review and meta-analysis. J Crit Care 41:98–106

39. Spoletini G, Mega C, Pisani L, Alotaibi M, Khoja A, Price LL, Blasi F, Nava S, Hill NS (2018) High-flow nasal therapy vs standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: A pilot randomized controlled trial. J Crit Care 48:418–425

40. Bräunlich J, Köhler M, Wirtz H (2016) Nasal highflow improves ventilation in patients with COPD. Int J Chron Obstruct Pulmon Dis 11:1077

41. Nagata K, Kikuchi T, Horie T, Shiraki A, Kitajima T, Kadowaki T, Tokioka F, Chohnabayashi Nm Watanabe A, Sato S, Tomii K (2018) Domiciliary High-Flow Nasal Cannula Oxygen Therapy for Patients with Stable Hypercapnic Chronic

Obstructive Pulmonary Disease. A Multicenter Randomized Crossover Trial. Ann Am Thorac Soc 15:432–439

42. Storgaard LH, Hockey H, Laursen BS, Weinreich UM (2018) Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. Int J Chron Obstruct Pulmon Dis Volume 13:1195–1205

43. Wanner A, Salathé M, O'Riordan TG (1996) Mucociliary clearance in the airways. Am J Respir Crit Care Med 154:1868–902

44. Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M (1999) Regulation of mucociliary clearance in health and disease. Eur Respir J 13:1177–88

45. Sahin-Yilmaz A, Naclerio RM (2011) Anatomy and Physiology of the Upper Airway. Proc Am Thorac Soc 8:31–39

46. Chidekel A, Zhu Y, Wang J, Mosko JJ, Rodriguez E, Shaffer TH (2012) The effects of gas humidification with high-flow nasal cannula on cultured human airway epithelial cells. Pulm Med 2012:380686

47. Kilgour E, Rankin N, Ryan S, Pack R (2004) Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. Intensive Care Med 30:1491–4

48. Lellouche F, L'Her E, Abroug F, et al (2014) Impact of the humidification device on intubation rate during noninvasive ventilation with ICU ventilators: results of a multicenter randomized controlled trial. Intensive Care Med 40:211–219

49. Richards GN, Cistulli PA, Ungar RG, Berthon-Jones M, Sullivan CE (1996) Mouth leak with nasal continuous positive airway pressure increases nasal airway resistance. Am J Respir Crit Care Med 154:182–6

50. Nava S, Navalesi P, Gregoretti C (2009) Interfaces and humidification for noninvasive mechanical ventilation. Respir Care 54:71–84

51. Lellouche F, Maggiore SM, Lyazidi A, Deye N, Taillé S, Brochard L (2009) Water content of delivered gases during non-invasive ventilation in healthy subjects. Intensive Care Med 35:987–995

52. Sim MAB, Dean P, Kinsella J, Black R, Carter R, Hughes M (2008) Performance of oxygen delivery devices when the breathing pattern of respiratory failure is simulated. Anaesthesia 63:938–40

53. Groves N, Tobin A (2007) High flow nasal oxygen generates positive airway pressure in adult volunteers. Aust Crit Care 20:126–131

54. Braunlich J, Beyer D, Mai D, Hammerschimdt S, Seyfarth HJ, Wirtz H (2012) Effects of Nasal High Flow in Ventilation in Volunteers, COPD and Idiopathic Pulmonary Fibrosis Patients. Respiration 85:319–25

55. Parke R, McGuinness S, Eccleston M (2009) Nasal high-flow therapy delivers low level positive airway pressure. Br J Anaesth 103:886–90

56. Parke RL, Eccleston ML, McGuinness SP (2011) The effects of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care 56:1151–5

57. Parke RL, McGuinness SP (2013) Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. Respir Care 58:1621–4

58. Parke R, McGuinness S, Dixon R, Jull A (2013) Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. Br J Anaesth 111:925–31

59. Parke RL, Bloch A, McGuinness SP (2015) Effect of Very-High-Flow Nasal Therapy

on Airway Pressure and End-Expiratory Lung Impedance in Healthy Volunteers. Respir Care 60:1397–403

60. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF (2011) Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 107:998–1004

61. Mauri T, Turrini C, Eronia N, Grasselli G, Volta CA, Bellani G, Pesenti A (2017) Physiologic Effects of High-Flow Nasal Cannula in Acute Hypoxemic Respiratory Failure. Am J Respir Crit Care Med 195:1207–1215

62. Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, Bottino N, Lissoni A, Spadaro S, Volta CA, Gattinoni L, Pesenti A, Grasselli G (2017) Optimum support by high-flow nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med 43:1453–1463

63. Delorme M, Bouchard, Pierre-alexandre Simon S, Simard M, Lellouche F (2017) Effects of High-flow Nasal Cannula on the Work of Breathing in Patients Recovering From Acute Respiratory Failure*. Crit Care Med 45:1981–1988

64. Carteaux G, Millán-Guilarte T, De Prost N, Razazi K, Abid S, Thille AW, Schortgen F, Brochard L, Brun-Buisson C, Mekontso Dessap A (2016) Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure. Crit Care Med 44:282–290

65. Vargas F, Saint-Leger M, Boyer A, Bui NH, Hilbert G (2015) Physiologic Effects of High-Flow Nasal Cannula Oxygen in Critical Care Subjects. Respir Care 60:1369–76

66. Vivier E, Mekontso Dessap A, Dimassi S, Vargas F, Lyazidi A, Thille AW, Brochard L (2012) Diaphragm ultrasonography to estimate the work of breathing during non-

invasive ventilation. Intensive Care Med 38:796–803

67. Wagstaff TAJ, Soni N (2007) Performance of six types of oxygen delivery devices at varying respiratory rates. Anaesthesia 62:492–503

68. Ritchie JEE, Williams AB, Gerard C, Hockey H (2011) Evaluation of humidified nasal high flow oxygen system, using oxygraphy, capnography and measurement of upper airway pressures. Anaesth Intensive Care 39:1103–10

69. Möller W, Celik G, Feng S, Bartenstein P, Meyer G, Oliver E, Schmid O, Tatkov S (2015) Nasal high flow clears anatomical dead space in upper airway models. J Appl Physiol 118:1525–32

70. Möller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, Becker S, Meyer G, Schmid O, Eickelberg O, Tatkov S, Nilius G (2017) Nasal high flow reduces dead space. J Appl Physiol 122:191–197

71. Chikata Y, Onodera M, Oto J, Nishimura M (2017) FIO2 in an Adult Model Simulating High-Flow Nasal Cannula Therapy. Respir Care 62:193–198

72. Campbell RS, Davis K, Johannigman JA, Branson RD (2000) The effects of passive humidifier dead space on respiratory variables in paralyzed and spontaneously breathing patients. Respir Care 45:306–12

73. Gold AR, Smith PL, Schwartz AR (1998) Effect of alae nasi activation on maximal nasal inspiratory airflow in humans. J Appl Physiol 84:2115–2122

74. Mundel T, Feng S, Tatkov S, Schneider H, Mündel T, Feng S, Tatkov S, Schneider H (2013) Mechanisms of nasal high flow on ventilation during wakefulness and sleep. J Appl Physiol 114:1058–1065

75. Dysart K, Miller TL, Wolfson MR, Shaffer TH (2009) Research in high flow therapy: mechanisms of action. Respir Med 103:1400–5

76. Campbell EJ, Baker MD, Crites-Silver P (1988) Subjective Effects of Humidification of Oxygen for Delivery By Nasal Cannula: A Prospective Study. Chest 93:289–293

77. Chanques G, Constantin J-M, Sauter M, Jung B, Sebbane M, Verzilli D, Lefrant J-Y, Jaber S (2009) Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. Intensive Care Med 35:996–1003

78. Ozyilmaz E, Ugurlu AO, Nava S (2014) Timing of noninvasive ventilation failure: causes, risk factors, and potential remedies. BMC Pulm Med 14:19

79. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L, SRLF Collaborative Group on Mechanical Ventilation (2001) Noninvasive Versus Conventional Mechanical Ventilation. Am J Respir Crit Care Med 163:874–880

80. Oto J, Nakataki E, Okuda N, Onodera M, Imanaka H, Nishimura M (2014) Hygrometric properties of inspired gas and oral dryness in patients with acute respiratory failure during noninvasive ventilation. Respir Care 59:39–45

81. Crimi C, Noto A, Princi P, Esquinas A, Nava S (2010) A European survey of noninvasive ventilation practices. Eur Respir J 36:362–9

82. Racca F, Appendini L, Berta G, Barberis L, Vittone F, Gregoretti C, Ferreyra G, Urbino R, Ranieri VM (2009) Helmet ventilation for acute respiratory failure and nasal skin breakdown in neuromuscular disorders. Anesth Analg 109:164–7

83. Gregoretti C, Foti G, Beltrame F, Giugaro P, Biolino P, Burbi L, Turello M, Agostini F, Berardino M, Musto P (1995) Pressure control ventilation and minitracheotomy in treating severe flail chest trauma. Intensive Care Med 21:1054–1056

84. Mistraletti G, Mantovani ES, Berardino M (2012) Delirium: Clinical approach and prevention. Best Pract Res Clin Anaesthesiol 26:311–326

85. Bellelli G, Morandi A, Zanetti E, Bozzini M, Lucchi E, Terrasi M, Trabucchi M (2014) Recognition and management of delirium among doctors, nurses, physiotherapists, and psychologists: an Italian survey. Int Psychogeriatrics 26:2093–2102

86. Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE (2008) Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. Chron Respir Dis 5:81–6

87. Rea H, McAuley S, Jayaram L, Garrett J, Hockey H, Storey L, O'Donnell G, Haru L, Payton M, O'Donnell K (2010) The clinical utility of long-term humidification therapy in chronic airway disease. Respir Med 104:525–33

88. Laveneziana P, Guenette JA, Webb KA, O'Donnell DE (2012) New physiological insights into dyspnea and exercise intolerance in chronic obstructive pulmonary disease patients. Expert Rev Respir Med 6:651–662

89. Chatila W, Nugent T, Vance G, Gaughan J, Criner GJ (2004) The Effects of High-Flow vs Low-Flow Oxygen on Exercise in Advanced Obstructive Airways Disease. Chest 126:1108–1115

90. Fraser JF, Spooner AJ, Dunster KR, Anstey CM, Corley A (2016) Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. Thorax 71:759–61

91. Pisani L, Fasano L, Corcione N, Comellini V, Musti MA, Brandao M, Bottone D,

Calderini E, Navalesi P, Nava S (2017) Change in pulmonary mechanics and the effect on breathing pattern of high flow oxygen therapy in stable hypercapnic COPD. Thorax 72:373–375

92. Biselli PJC, Kirkness JP, Grote L, Fricke K, Schwartz AR, Smith P, Schneider H (2017) Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study. J Appl Physiol 122:82–88

93. Spahija J, de Marchie M, Grassino A (2005) Effects of Imposed Pursed-Lips Breathing on Respiratory Mechanics and Dyspnea at Rest and During Exercise in COPD. Chest 128:640–650

94. Sklar MC, Dres M, Rittayamai N, West B, Grieco DL, Telias I, Junhasavasdikul D, Rauseo M, Pham T, Madotto F, Cambpell C, Tullis E, Brochard L (2018) High-flow nasal oxygen versus noninvasive ventilation in adult patients with cystic fibrosis: a randomized crossover physiological study. Ann Intensive Care 8:85

95. Frizzola M, Miller TL, Rodriguez ME, Zhu Y, Rojas J, Hesek A, Stump A, Shaffer TH, Dysart K (2011) High-flow nasal cannula: impact on oxygenation and ventilation in an acute lung injury model. Pediatr Pulmonol 46:67–74

96. Bräunlich J, Mauersberger F, Wirtz H (2018) Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent. BMC Pulm Med 18:14

97. On LS, Boonyongsunchai P, Webb S, Davies L, Calverley PMA, Costello RW (2001) Functinon of Pulmonary Neuronal M_2 Muscarinic Receptors in Stable Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 163:1320–1325

98. Fontanari P, Burnet H, Zattara-Hartmann MC, Jammes Y (1996) Changes in airway

resistance induced by nasal inhalation of cold dry, dry, or moist air in normal individuals. J Appl Physiol 81:1739–1743

99. Cirio S, Piran M, Vitacca M, Piaggi G, Ceriana P, Prazzoli M, Paneroni M, Carlucci A (2016) Effects of heated and humidified high flow gases during high-intensity constant-load exercise on severe COPD patients with ventilatory limitation. Respir Med 118:128–132

100. Bräunlich J, Wirtz H (2017) NHF and hypercapnia: How brief can you look? Respirology 22:1049–1050

101. McKinstry S, Pilcher J, Bardsley G, Berry J, Van de Hei S, Braithwaite I, Fingleton J, Weatherall M, Beasley R (2018) Nasal high flow therapy and $PtCO_2$ in stable COPD: A randomized controlled cross-over trial. Respirology 23:378–384

102. O'Driscoll BR, Howard LS, Earis J, Mak V (2017) BTS guideline for oxygen use in adults in healthcare and emergency settings. Thorax 72:ii1-ii90.

103. Riera J, Perez P, Cortez J, Roca O, Masclan JR, Rello J (2013) Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. Respiratory Care 58:589-596.

Table 1. Potential mechanisms of benefit of HFNT in the acute setting

Heating	**Effects on muco-ciliary clearance** **Reduced metabolic cost of work of breathing** **Increased comfort**
Humidification	Effects muco-ciliary clearance Reduced metabolic cost of work of breathing Reduced inflammation *in vitro* Increased comfort
High-flow	Positive airway pressure • Recruitment effect • Increase dynamic lung compliance • Reduced work of breathing Matching patients' PIFR • Reliable delivery of FIO2 • Reduced inspiratory resistance • Reduced resistive component of WOB Dead-space wash-out • Reliable delivery of FIO2 • Reduced re-breathing
Interface	Minimal instrumental dead-space Increased comfort

Table 2. Potential mechanisms of benefit of HFNT in the chronic setting

Heating	**Effects on muco-ciliary clearance** **Increased comfort** **Reduced bronchoconstriction secondary to muscarinic activation**
Humidification	Effects muco-ciliary clearance Reduced inflammation *in vitro* Increased comfort
High-flow	Positive airway pressure • Recruitment effect • Increased tidal volume • Reduced work of breathing • Increased expiratory resistance Matching patients' PIFR • Reduced inspiratory resistance • Reduced resistive component of WOB Dead-space wash-out • Reliable delivery of FIO2 • Reduced re-breathing
Interface	Increased comfort