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

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**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.


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

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

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

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