



High-flow nasal cannula therapy for adult patients

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Abstract

High-flow nasal cannula (HFNC) oxygen therapy has several physiological advantages over traditional oxygen therapy devices, including decreased nasopharyngeal resistance, washing out of the nasopharyngeal dead space, generation of positive pressure in the pharynx, increasing alveolar recruitment in the lungs, humidification of the airways, increased fraction of inspired oxygen and improved mucociliary clearance. Recently, the use of HFNC in treating adult critical illness patients has significantly increased, and it is now being used in many patients with a range of different disease conditions. However, there are no established guidelines to direct the safe and effective use of HFNC for these patients. This review article summarizes the available published literature on the positive physiological effects, mechanisms of action, and the clinical applications of HFNC, compared with traditional oxygen therapy devices. The available literature suggests that HFNC oxygen therapy is an effective modality for the early treatment of critically adult patients.

Keywords

Oxygen therapy, nasal cannula, positive airway pressure, respiratory failure

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Introduction

The nasal cannula has become the device of choice in modern medicine for the delivery of supplemental oxygen to patients with non-hypercarbic hypoxaemic diseases. Such patients might require high inspiratory oxygen therapy, typically in the range of 30 to 120 l/min.^{1,2} However, traditional oxygen delivery devices, such as the low-flow nasal cannula, non-reservoir and reservoir-bag masks, and large volume aerosol systems (used at fraction of inspired oxygen [FiO_2] > 0.4), can only deliver an oxygen flow rate of 6 to 15 l/min, which is

insufficient for many patients. The high-flow nasal cannula (HFNC) is a novel oxygen supply device capable of delivering up to 100% humidified and heated oxygen

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at a maximum flow rate of 60 l/min.^{3,4} It has been shown to confer many potential advantages compared with traditional oxygen delivery devices, and leads to improved physiological outcomes.^{2,5} In recent years, HFNC is being used increasingly with adult critical illness patients, where it has been successfully applied to a variety of patients with a range of different disease conditions.⁶ However, other research noted that treatment with HFNC made no difference to outcome as compared with standard oxygen therapy or noninvasive ventilation.⁷ This review aims to summarize and discuss the current understanding with regard to the physiological effects of HFNC, its mechanisms of action, and its application in a range of clinical settings. This information will help clinicians in determining the potential benefits and limitations in clinical use affecting the outcomes of HFNC oxygen therapy, and will inform clinical strategy decisions relating to adult patients requiring supplemental oxygen.

Potential mechanisms of clinical benefit

High-flow nasal cannula therapy has been shown to produce a range of beneficial physiological effects (Table 1), which will be discussed in detail in the following sections of this review. Studies have demonstrated that its use improves oxygenation, generates positive airway pressure, improves

Table 1. The main physiological effects of high-flow nasal cannula therapy.

Pharyngeal dead space washout
Reduction of nasopharyngeal resistance
Generation of positive expiratory pressure
Alveolar recruitment
Humidification and improved tolerance
Regulation of the fraction of inspired oxygen and improved mucociliary clearance

the end-inspiratory lung volume, weakens inspiratory resistance, reduces metabolic work associated with gas conditioning, washes out nasopharyngeal dead space, and increases functional residual capacity.^{8–13} These physiological effects suggest that HFNC therapy could be effective in the treatment of respiratory depression resulting from many different causes. Moreover, evidence suggests that HFNC is better tolerated by patients and is reportedly more comfortable than other traditional oxygen therapy applications.³

Mechanisms of action of HFNC therapy

Pharyngeal dead space washout

One mechanism of action of HFNC therapy might be through its effect in washing the pharyngeal cavity dead space, thus reducing overall dead space and leading to an improvement in alveolar ventilation in the lungs. However, due to the complexities of dissecting the pharyngeal airway and the inability to measure gas flow *in vivo*, it is difficult to study the precise mechanisms of dead space washout. Although higher flows may reduce dead space, the relationship has still not been determined. So we suggest that HFNC therapy should not be used to care for patients with elevated CO₂ levels.

In 2004, a prospective study was performed that aimed to compare the effects of HFNC with those of traditional low-flow oxygen inhalation devices for patients with chronic obstructive pulmonary disease (COPD).¹⁴ The authors found that patients using HFNC devices could exercise for a longer time period than those using low-flow oxygen delivery devices (10.0 ± 2.4 min versus 8.2 ± 4.3 min, respectively).¹⁴ These patients also experienced less dyspnoea, better respiratory functioning, and lower arterial tension.¹⁴ The authors concluded that the use of HFNC therapy improved

exercise performance in COPD patients, partially by enhancing oxygenation.¹⁴

More recently, a study was undertaken to confirm the dead space washout effect of HFNC and its influence on CO₂ elimination and oxygenation.¹⁵ Thirteen neonatal piglets with acute lung injuries were supported with HFNC with an oxygen flow rate ranging from 2 to 8l/min.¹⁵ Single and double pronged cannulas were used to achieve high and low level leaks around the nasal prongs.¹⁵ Haemodynamics, breathing and blood gas analyses were undertaken in each experimental setting 10 minutes after physiological equilibrium had been reached.¹⁵ The authors concluded that HFNC promoted gas exchange by regulating oxygen flow, that delivery via the double pronged cannula achieved a greater effect on oxygenation, and that delivery via the single pronged cannula had a greater impact on CO₂ elimination.¹⁵

Reduction of nasopharyngeal resistance

Another important observed effect of HFNC therapy is the reduction in nasopharyngeal air flow resistance. After analysing flow volume loops in the nasopharynx, research showed that the nasopharynx has an expandability that results in an alterable resistance.¹⁶ A study that compared the effect of flow rate on resistance in continuous positive airway pressure (CPAP), nasal cannula, and HFNC, found that the order of resistance of these different oxygen delivery methods was as follows: HFNC 783 cmH₂O/l/s > CPAP 280 cmH₂O/l/s.¹⁷ However, the most probable mechanism by which HFNC reduces inspiratory nasopharynx resistance is likely to be by increasing inspiratory flow.¹⁷⁻¹⁹

Positive expiratory pressure

High-flow nasal cannula generates positive pharyngeal pressure, which produces a

certain amount of pulmonary expanding pressure and promotes alveolar recruitment.^{10,20,21} In a recent study in which pharyngeal pressure was recorded with an HFNC oxygen flow rate of 0 to 60l/min, it was found that the expiratory pressure with the mouth closed was significantly higher than with the mouth open ($P < 0.001$).⁹ This study demonstrated that there is a certain degree of CPAP produced by HFNC therapy, which is both flow dependent and mouth position (open versus closed) dependent.⁹ This effect was confirmed by studying the correlation between flow rate and pressure within the context of the OptiflowTM nasal high-flow oxygen therapy system.²² Measurements were performed with nasal high-flow oxygen at flows of 30, 40, and 50l/min, with the patient's mouth both open and closed.²² Pressures were recorded over 1 minute of breathing, and average flows were calculated via simple averaging.²² The authors found that, during nasal high flow oxygen therapy, the mean nasopharyngeal pressure increased as oxygen flow rate increased.²²

Alveolar recruitment

The HFNC device may reduce hypoxaemia via a number of mechanisms, thus alleviating respiratory depression syndromes. By generating positive airway pressure, HFNC generates pulmonary expanding pressure, thus promoting alveolar recruitment. This effect has been demonstrated in healthy volunteers⁹ and in patients recovering from cardiac surgery,¹⁰ but the effects of HFNC on lung volume are still unknown.^{23,24} A study evaluated twenty patients recovering from cardiac surgery and being administered with HFNC oxygen therapy.²⁵ The authors used electrical impedance tomography to assess the impact of HFNC on airway pressure, end-expiratory lung volume (EELV) and the relationship between the two.²⁵ The authors concluded

that HFNC oxygen therapy reduced the respiratory rate and improved oxygenation through increasing both EELV and tidal volume, and suggested that it would be most beneficial in patients with higher body mass indexes.²⁵

Humidification and tolerance

The need to heat and humidify the HFNC device during use has been a point of controversy within the published literature.^{2,8,23,26,27} Compared with other oxygen therapy devices, several studies have reported that use of HFNC therapy results in a lower respiratory rate, and that the device is better tolerated by patients as well as being more comfortable.^{3,17,23,28–32} By employing a heated humidifier alongside HFNC therapy, a reduction of dryness symptoms was observed, which was regulated by increasing the humidity level.³¹ Another study found that patients' comfort was higher during HFNC sessions compared with noninvasive ventilation sessions in acute hypoxaemic respiratory failure.³³ Because cold and dry oxygen generated by the HFNC device increases air flow resistance, it is necessary to warm and humidify the air.^{18,34} This heat and humidification system may also indirectly influence oxygenation.^{3,23}

Fraction of inspired oxygen and mucociliary clearance

Other mechanisms by which HFNC therapy may bring about positive effects include the ability to precisely regulate a patient's FiO_2 and achieve better mucociliary clearance.^{22,28,30,35,36} Primary airway defence systems include sneezing, gagging, coughing and natural filtration. The secondary defence system, the mucociliary transport system, traps and neutralizes inbreathed contaminants and then transports them out of the respiratory tract. However, the

mucociliary transport system is extremely sensitive to humidity. By delivering a humidified flow of oxygen, HFNC may help patients to maintain the functioning of their secondary airway defence system in clearing excretions efficiently, thus reducing the risk of respiratory infection.³⁷

Application of HFNC in various clinical settings

As discussed previously, HFNC therapy can have many positive physiological effects on the airway system. Its advantages over more traditional oxygen therapy devices have led researchers to study HFNC therapy in a range of clinical applications.

Acute hypoxaemic respiratory failure

Amongst patients with acute hypoxaemic respiratory failure (AHRF), HFNC therapy correlates with a lower respiratory rate, and is better tolerated and more comfortable than more traditional alternatives.^{3,22} A study was performed to compare how comfortable oxygen therapy delivered via HFNC was perceived to be compared with oxygen therapy via a traditional face mask in 20 patients with acute respiratory failure.³ HFNC was reportedly associated with less dyspnoea and mouth dryness, and was more comfortable.³ HFNC was also associated with a higher partial pressure of arterial oxygen (PaO_2) and lower respiratory rate.³ More recently, a prospective observational study investigated the impact of HFNC in comparison with traditional oxygen therapy on patients with acute respiratory failure, and has confirmed the aforementioned positive benefits of HFNC.²³ HFNC therapy was again associated with a lower respiratory rate, higher oxygen saturation level, and higher PaO_2 than the other tested modes of delivery.²³ A separate retrospective study assessed several clinical parameters during HFNC therapy and reported success for

patients with acute respiratory failure.³⁸ The authors measured patients' baseline characteristics and continuing changes in respiratory parameters during HFNC therapy at 1 and 24 hours.³⁸ Of the 75 eligible patients, 62.7% avoided intubation.³⁸ During the first 24 hours, HFNC therapy significantly improved a number of respiratory parameters including PaO₂, saturation of arterial oxygen, respiratory rate, and heart rate.³⁸ A further prospective study assessed the short-term physiological effects of HFNC.³⁹ Several parameters were measured, such as inspiratory muscle effort, gas exchange, dyspnoea score, and perceived level of comfort.³⁹ The authors reported that HFNC therapy significantly improved inspiratory effort and oxygenation in comparison with conventional oxygen therapy.³⁹

However, there is still some debate about the positive effects of HFNC therapy in patients with respiratory failure.⁴⁰ A prospective study that aimed to compare HFNC therapy with non-invasive ventilation (NIV) in patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy was undertaken.⁴¹ After randomizing 40 patients to receive either NIV or HFNC therapy, oxygen levels in the NIV group were found to be significantly higher than in the HFNC group.⁴¹ The application of NIV resulted in better outcomes than HFNC concerning oxygenation before, during and after bronchoscopy in patients with moderate-to-severe hypoxaemia.⁴¹ In another retrospective observational study,⁴² the authors found that failure of HFNC to improve patient symptoms might lead to delayed intubation and potentially worsen clinical outcomes in patients with respiratory failure.

Collectively, these findings indicate that patients with AHRF can be safely managed with HFNC therapy during the initial stages.^{3,24} Though it is clear that HFNC therapy can benefit a relatively small number of the total number of AHRF patients, it is

also apparent that its inappropriate use can be potentially detrimental to patient health.^{38,39} Furthermore, the extended use of HFNC therapy before intubation may be harmful.⁴² As careful selection criteria by clinicians is quite important, PaO₂/FiO₂ ratios are helpful as well as respiratory rate as important clinical criteria.⁴¹ Clinicians need established protocols to quickly identify patients who require NIV or intubation and mechanical ventilation when they recognize signs of HFNC therapy failure. As most of the studies mentioned above were based on small patient numbers, larger prospective randomized controlled trials of HFNC therapy in patients with respiratory failure are warranted.

Post-extubation period

It is known that re-intubation of patients is associated with an increased intensive care unit (ICU) and in-hospital length of stay and with increased mortality. Recently, with the increased use of HFNC devices and their proven beneficial effects and better tolerance by patients, research has been extended to investigate their use either to prevent or to treat post-extubation respiratory failure.^{3,8,18,22,23,43} In a randomized cross-over physiological study, 17 patients post-extubation were randomized to either group A who used HFNC therapy for 30 minutes followed by a non-rebreathing mask for another 30 minutes ($n=9$), or group B who used a non-rebreathing mask for 30 minutes followed by HFNC therapy for another 30 min ($n=8$).⁴⁴ Respiratory rate, heart rate, blood pressure, level of dyspnoea, oxygen saturation, and patient comfort were then recorded.⁴⁴ The results showed that HFNC therapy was associated with significantly less dyspnoea ($P=0.04$), a lower respiratory rate ($P=0.009$) and a lower heart rate ($P=0.006$) in comparison with the non-rebreathing mask.⁴⁴ This study clearly demonstrated the potential benefits

of HFNC therapy in enhancing oxygenation in the post-extubation period.⁴⁴ In another study, the authors retrospectively studied 67 oxygen therapy patients in the ICU.⁴⁵ Patients were divided into two treatment groups: HFNC (Group 1, 34 patients); and non-rebreathing oxygen face mask (NRB) (Group 2, 33 patients).⁴⁵ Respiratory parameters were recorded before extubation and 6 hours post-extubation and the primary clinical outcomes included ventilation-free days, oxygen improvement, re-intubation, ICU length of stay, and mortality.⁴⁵ The results showed that there were more ventilator-free days ($P < 0.05$) and fewer patients requiring re-intubation (one versus six) in Group 1 in comparison with Group 2.⁴⁵ The HFNC group also exhibited a significant improvement in $\text{PaO}_2/\text{FiO}_2$ post-extubation ($P < 0.05$).⁴⁵ Overall, the study demonstrated greater beneficial effects on oxygenation in post-extubation patients treated with HFNC in comparison with NRB, and concluded that HFNC therapy may be more effective than other traditional devices for oxygenation in the post-extubation period.⁴⁵

Pre-intubation period

Intubation is often performed for hypoxaemic and unstable patients in the ICU, and is associated with severe life-threatening complications. NIV can be applied to enhance oxygenation before tracheal intubation takes place. Due to the beneficial effects and better tolerance of HFNC therapy, it has been suggested that it could be used to deliver oxygen during the apnoeic period of tracheal intubation instead of other traditional (mask) oxygen devices.^{6,18,46–48} In an experimental research study involving eight anaesthetized piglets with lung injury induced by lung lavage, it was found that direct use of HFNC therapy at a flow rate of 10 l/min through the pharynx during intubation markedly alleviated hypoxaemia

during apnoea.⁴⁹ This indicated that HFNC therapy could be utilized for ICU patients during tracheal intubation.⁴⁹ In a prospective clinical study of 101 patients, researchers compared pre- and per-procedure oxygenation with either HFNC therapy or a non-rebreathing bag reservoir face mask during tracheal intubation of ICU patients.⁵⁰ The results showed that the median lowest pulse oxygen saturation during intubation was 100% with HFNC versus 94% with the non-rebreathing bag reservoir facemask ($P < 0.0001$).⁵⁰ The authors concluded that HFNC significantly improved pre-oxygenation and decreased the morbidity rate of severe hypoxaemia, and that its use could improve patient safety during intubation in the ICU.⁵⁰

Emergency department

The most common presenting problems in patients who come to the emergency department (ED) are acute dyspnoea and hypoxaemia, and oxygen therapy is an essential supportive treatment to address these symptoms. Heated and humidified HFNC therapy represents a new alternative to traditional oxygen therapy in the ED setting. A prospective observational study demonstrated the possible application and effectiveness of HFNC therapy in patients with respiratory failure in the ED.⁵¹ The study included 17 patients with acute respiratory failure requiring oxygen therapy above 9 l/min or with persistent clinical signs of dyspnoea despite oxygen therapy.⁵¹ The results indicated that use of HFNC therapy is feasible in the ED, and that it effectively relieved respiratory distress and ameliorated respiratory symptoms in patients with acute hypoxaemic respiratory failure.⁵¹ In a recently published single-centre study, the effect of HFNC therapy in patients with acute respiratory distress syndrome (ARDS) was evaluated.⁵² HFNC oxygen therapy was applied to more than 25% of patients with

ARDS who required non-invasive ventilator support and generated a significant improvement in respiratory parameters.⁵² The authors concluded that HFNC should be used as a first-line therapy in acute respiratory failure, including in patients with ARDS.⁵² A further prospective randomized study investigated the physiological effects of HFNC therapy compared with traditional oxygen therapy in 40 patients with acute dyspnoea and hypoxaemia in the ED.⁵³ HFNC therapy significantly improved dyspnoea ($P=0.01$) and patient comfort ($P=0.01$) compared with traditional oxygen therapy.⁵³ HFNC was also better tolerated and no serious adverse events occurred.⁵³ The hospitalization rate in the HFNC group was also lower than in the traditional oxygen therapy group.⁵³ The authors concluded that HFNC improved dyspnoea and comfort in patients with acute dyspnoea and hypoxaemia in the ED.⁵³

Respiratory infection

There has been limited research on the use of HFNC oxygen therapy in the treatment of severe acute respiratory infection (SARI). In a single-centre *post-hoc* analysis, researchers assessed the effectiveness of HFNC oxygen therapy in ICU patients who were admitted with SARI due to the 2009 influenza A/H1N1 outbreak.⁵⁴ Of the 25 non-intubated adult SARI patients in this study, 20 could not sustain oxygen saturation over 92% with traditional oxygen therapy and needed HFNC therapy, which was successful in nine cases (45%).⁵⁴ With HFNC oxygen therapy, non-responders presented lower PaO₂/FiO₂ 6 hours later, and required higher oxygen flow rates.⁵⁴ There were no secondary infections reported in the health care workers.⁵⁴ There were also no nosocomial (hospital-acquired) pneumonias occurring during HFNC oxygen therapy.⁵⁴

Bronchiolitis is the most common cause of lower respiratory tract infection.⁵⁵ Whilst

evidence relating to the effectiveness of HFNC therapy in patients with bronchiolitis is available for infants, it is limited in adults. Studies of HFNC therapy use in infants with bronchiolitis suggest that it is a safe mode of respiratory support that may provide an alternative to nasal CPAP.^{56–62}

In a retrospective single-centre study, researchers reviewed the medical records of 45 acute respiratory failure adult patients in order to recognize possible predictive parameters for successful treatment.⁶³ The nosetiological classification of these patients was as follows: pneumocystis jirovecii pneumonia (17.8%), bacterial pneumonia (57.8%), bronchiolitis obliterans organizing pneumonia (8.9%), and pulmonary oedema (8.9%).⁶³ The authors found that the probability of success of HFNC oxygen therapy was significantly higher in the survivors compared with the non-survivors, and the percentage of bacterial pneumonia was significantly higher in the HFNC treatment failure group compared with the HFNC treatment success group ($P=0.004$).⁶³ In another study, authors randomized 108 patients diagnosed with COPD or bronchiectasis to HFNC therapy or usual care for 12 months, with exacerbations recorded.⁶⁴ Authors found that patients on HFNC therapy had markedly fewer exacerbation days ($P=0.045$), increased time-to-first exacerbation ($P=0.0495$) and reduced exacerbation frequency ($P=0.067$) compared with the usual care group of patients.⁶⁴ HFNC oxygen therapy also significantly improved the quality of life scores and lung function of the patients.⁶⁴ These results indicate that HFNC offers an alternative to invasive ventilation in patients with respiratory infection.^{54–64}

Obstructive airways disease

Persistent airway inflammation with phlegm retention in patients with obstructive airway disease, such as COPD, might cause

frequent exacerbations, lung function reduction and poor quality life. To date, several studies have highlighted that airway surface dehydration is important in pulmonary damage associated with chronic airway disorders. The previously mentioned prospective study,¹⁴ found that patients could exercise for longer on HFNC with better breathing pattern, less dyspnoea, and lower arterial pressure compared with patients on low-flow oxygen delivery, in part as a result of enhanced oxygenation. A recent study has also found that HFNC therapy significantly improved quality of life scores and lung function in patients with COPD compared with more traditional therapies.⁶⁴ Obstructive sleep apnoea (OSA) is also common, and is attributed to upper airway destruction that is correlated with discontinuous hypoxaemia, cardiovascular morbidity, and neurocognitive dysfunction. HFNC therapy, with the ability to deliver high-flow, humidified, pressurized oxygen, may have potential as a treatment for OSA,⁶⁵⁻⁶⁷ but to date there has not been a clinical trial to investigate the efficacy of HFNC therapy in treating OSA patients.

Other clinical applications

In patients with respiratory failure, coordinated movement of the rib cage and abdominal wall is often impaired. Patients displaying asynchronous thoraco-abdominal movement have increased risk of ventilator failure, necessitating mechanical ventilation and consequently leading to poorer prognoses. In a recent study where researchers assessed the effects of HFNC therapy on thoraco-abdominal synchrony, it was found that breathing frequency significantly decreased from 25 breaths/min to 21 breaths/min ($P < 0.01$) with the use of HFNC therapy.⁶⁸

However, HFNC is not a panacea, it also has many limitations as follows:⁶⁹ (i) expense

and complexity (air/O₂ blender, humidifier and requirement for a large oxygen supply); (ii) mobility (limited ambulation); (iii) leak mitigating positive airway pressure effect and inability to compensate for leaks; (iv) nasopharyngeal airway pressure and positive end-expiratory pressure warrant more exploration; (v) potential for delayed intubation; and (vi) potential for (inappropriate) delay of end-of-life decisions.

Conclusions

High-flow nasal cannula oxygen therapy has been proven to be a valuable clinical application alternative to conventional oxygen therapy for critically ill patients. It would seem to be effective for treating patients with respiratory failure, respiratory infection, and obstructive airways disease, either during the post-extubation period or pre-intubation. However, the positive end-expiratory pressure is hard to measure in these settings because of the non-invasive nature of HFNC therapy, and air leaks have been reported. Despite these uncertainties, a growing body of evidence indicates that HFNC oxygen therapy is an effective treatment modality for the early treatment of critically ill adult patients. Further research is required to confirm the long-term effects of HFNC and identify the adult patient population(s) to whom it could be most beneficial.

Declaration of conflicting interest

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