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Review Article

A Review of High Flow Nasal Cannula Oxygen Therapy in Human and Veterinary Medicine

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A B S T R A C T

Respiratory distress is a common ailment in small animal medicine. Oxygen supplementation is a mainstay of initial therapy. High Flow Nasal Cannula Oxygen Therapy (HFNCOT) has become increasingly popular as a treatment modality in human medicine, and more recently in canine patients. These devices deliver high flow rates of heated and humidified oxygen at an adjustable fraction of inspired oxygen . This article reviews current literature in human patients on HFNCOT as well as studies that have evaluated its use in veterinary patients. A discussion of the respiratory physiology that is associated with respiratory distress, in addition to an overview of currently available oxygen supplementation modalities is provided. The physiologic benefits of HFNCOT are explained, as are technical aspects associated with its use. Recommendations on initial settings, maintenance therapy, and weaning are also described.

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Introduction

Respiratory distress is a common clinical presentation in veterinary and human medicine. Depending on the cause and severity of the respiratory distress, patients may present with evidence of hypoxemia. This is defined as decreased arterial oxygen concentration, with a partial pressure of arterial oxygen (PaO_2) concentration of less than 80 mm Hg.[1] Causes of hypoxemia include hypoventilation, physiologic shunt, diffusion impairments, low inspired oxygen, and ventilation-perfusion mismatch.[2]

As a brief review of respiratory physiology, inspired gas travels through the conducting airways (trachea, mainstem bronchi), and eventually reaches the respiratory zone. The conducting airways (which includes the nose, nasal passages, nasopharynx, larynx, trachea, bronchi, and bronchioles) do not participate in gas exchange and are the dead space of the respiratory system. The respiratory zone includes the respiratory bronchioles, alveolar ducts, and alveolar sacs, the termination of which is the alveolus.[3] This is the location of diffusion of oxygen and carbon dioxide (CO_2).

All causes of hypoxemia are at least variably responsive to oxygen supplementation except for anatomic and physiologic shunts, since these involve blood reaching the arterial system without having been exposed to ventilated alveolar units. [4] Supplemental oxygen provided to a subject will increase the fraction of Inspired Oxygen (FiO_2), which is typically recorded as a decimal or a percentage (ambient room air being 0.21 or 21%). Conventional oxygen supplementation requires spontaneous breathing efforts by the patient. This will improve the hypoxemia associated with hypoventilation, but intervention with positive pressure ventilation (mechanical ventilation) is sometimes required depending on the severity of the underlying cause. Hypercapnic respiratory failure in veterinary patients is associated with lower motor neuron disease processes such as tick paralysis, myasethenia gravis, botulism, polyradiculoneuritis, polymyositis, as well as hypokalemia, elapid snake envenomation, and toxicoses (organophosphates, aminoglycosides).[5,6] Humans have similar differentials, though have a higher incidence of chronic obstructive pulmonary disease (COPD) or asthma. These require either non-invasive ventilation (NIV) or mechanical ventilation to improve respiratory acidosis seen with these patients if the patient is in respiratory failure.[7] Thus, conventional oxygen therapy alone will not benefit patients with hypercapnic respiratory failure but should benefit those with most other causes of hypoxemia.

Oxygen supplementation can be achieved through a variety of means, including flow by oxygen, nasal/nasotracheal insufflation (typically using red rubber catheters inserted into the nares at different depths), nasal prongs, tracheal catheters, oxygen cages/tanks, and hood type devices.[8] These less invasive means of providing oxygen are relatively inexpensive and available to many practitioners. However, they have disadvantages, including low and inconsistent FiO_2 delivery (an average range of 24%-77%[1,9]), rebreathing of expired CO_2, nasal/nasopharyngeal trauma, stress,[10] and poor tolerance due to inadequate warming and humidification of inspired gas.[11] It is difficult to determine the patient's FiO_2 without using an oxygen sensor, which can be challenging when supplementation is provided by nasal prongs or cannulae. Oxygen delivery flow rates of these traditional means of supplementation can reach 15 L/min, but this is often uncomfortable. The patient's inspiratory flow rate while in respiratory distress may exceed these flow rates.[12] Depending on the severity of the underlying disease, patients may continue to decompensate while receiving supplemental oxygen. Criteria for defining failure of standard oxygen therapy include increased work of breathing that leads to respiratory fatigue and failure, as well as severe hypoxemia as indicated by a PaO_2 of less than 60mmHg or by a peripheral oxygen saturation (SpO_2) of less than 90%.[13] In these instances, escalation to endotracheal intubation and mechanical ventilation is often necessary. Unfortunately, mechanical ventilation is an invasive and

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Abbreviations: APACHE, Applied Physiologic Assessment and Chronic Health Evaluation; CO_2, Carbon Dioxide; COPD, Chronic Obstructive Pulmonary Disease; CPAP, Continuous Positive Airway Pressure; FiO_2, Fraction of Inspired Oxygen; HFNCOT, High Flow Nasal Cannula Oxygen Therapy; NIV, Non-Invasive Ventilation; PaO_2, Partial Pressure of Arterial Oxygen; $PaCO_2$, Partial Pressure of Arterial Carbon Dioxide; PEEP, Positive End Expiratory Pressure; SpO_2, Peripheral Capillary Oxygen Saturation; SOFA, Sequential Organ Failure Assessment

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expensive therapeutic modality with a high mortality rate in people[14] and companion animals.[15] In addition to factors that affect patient outcome in mechanically ventilated patients, such as iatrogenic complications and underlying disease processes, veterinary studies have high levels of euthanasia bias. This makes retrospective studies difficult to truly evaluate for survival. Regardless, survival to discharge has been reported to be between 10.3% (ARDS patients) to 91.7% (elapid snake envenomation) for patients receiving mechanical ventilation in veterinary medicine.[5,6,15–17] Furthermore, mechanical ventilation may not be readily available as a therapeutic option in many veterinary facilities.

Non-invasive positive pressure ventilation, often shortened to non-invasive ventilation (NIV), is a popular modality in human respiratory therapy as a bridge between conventional oxygen supplementation and mechanical ventilation. The NIV devices provide higher levels of FiO_2 than conventional oxygen supplementation along with some level of positive pressure ventilatory support to the patient without intubation; these pressures can range to upwards of 12.5 cmH_20.[18]

Different types of NIV have been investigated in veterinary medicine as researchers seek a means of respiratory support that is superior to conventional oxygen therapy but does not require intubation. Inherent anatomical differences between small animals and humans have made many of the NIV devices that often cover the nose and mouth technically impractical in the veterinary setting. A nasal mask designed for human neonates was compared to traditional mechanical ventilation in 8 healthy cats. The authors concluded that this interface of NIV in cats is plausible but "cannot yet be considered feasible."[19]

NIV and invasive mechanical ventilation devices have the ability to provide continuous positive airway pressure (CPAP). This is a mode of ventilatory support where positive pressures are delivered to the airways at all phases of respiration to prevent atelectasis and upper airway collapse during spontaneous ventilation. Respiratory mechanics, lung compliance, and oxygenation are improved.[20] Provision of CPAP at 2.5 or 5.0 cmH_20 supplied by a commercially available veterinary face mask to 16 healthy dogs that were undergoing anesthesia for elective surgeries or diagnostic procedures showed increased PaO_2 in both groups, and good tolerance.[21] Another study evaluating the use of a pediatric CPAP helmet device in 15 healthy postoperative ovariohysterectomy dogs showed decreased respiratory rates, decreased arterial partial pressure of carbon dioxide ($PaCO_2$), and increased PaO_2 when CPAP of 5 cmH_2O was applied.[22] A custom-made mask, a standard conical mask, and a CPAP helmet device connected to a unit providing positive pressure in 10 healthy anesthetized dogs were compared in another study. Each of the three interfaces were able to provide adequate CPAP.[23] The use of the helmet device in 17 dogs with acute hypoxemic respiratory failure has been investigated, and these patients exhibited improvement in various respiratory parameters and an acceptable tolerance rate.[24] Similar tolerance and improved oxygenation was noted when this device was applied to 15 healthy cats recovering from anesthesia.[25] These devices show promise, however the units are not widely available in veterinary medicine.

Recently, high flow nasal cannula oxygen therapy (HFNCOT) has become widely used in human respiratory therapy. HFNCOT has also been referred to as high flow nasal oxygen, high flow nasal cannula, high flow nasal insufflation, high flow nasal prongs, heated humidified high flow nasal cannula, and high flow therapy. Although it is also non-invasive, this modality is technically a separate entity from traditional NIV since it is not designed to provide true ventilatory support. Some of the first HFNCOT devices were patented in 1988 for use in horses,[26] but were later adapted for use in human respiratory therapy. These devices deliver warmed, humidified (44 mg H_2O/L) oxygen through nasal canulae. HFNCOT can deliver flow rates up to 60L/min, with a flow velocity of up to 360% greater than that of other types of oxygen cannulas.[27] The FiO_2 can be independently adjusted on some HFNCOT devices from 21% to 100%, whereas other HFNCOT units act similar to conventional oxygen supplementation with nasal cannulae, as the FiO_2 can only be adjusted by increasing the flow rate. HFNCOT has proven to be an attractive option in human patients with respiratory failure and is now being used in canine and feline[28] patients.

This article seeks to explain the methodology behind HFNCOT oxygen therapy, evaluate its uses in human medicine, and review the literature on its use in veterinary patients.

Delivery of High Flow Nasal Oxygen: Technical Aspects and Physiology

Several commercially available HFNCOT oxygen delivery units are available. High-pressure oxygen and medical air are combined in an air-oxygen blender with a sterile water source, which adds humidity to the gaseous mixture via either a cartridge, heat plate, or a water chamber.[29] The oxygen flow rate can be adjusted, and on some devices, the level of oxygen provided (FiO_2) can be adjusted independently. The gas is heated and delivered at 95%-100% relative humidity. This humidified and blended gas is warmed and delivered to the patient via a heated inspiratory circuit to maintain heat and humidity in transit. The inspiratory circuit is then connected to a nasal cannula.[30] These nasal cannulae vary in design; some have moldable, soft, wide-bore prongs with an adjustable head strap. Other systems include standard caliber nasal cannulae that are similar to those used in conventional oxygen therapy. For people, adapters exist for use with tracheostomy tubes. There should be less than 50% nostril occlusion by the cannulae, in both human[31] and veterinary[32] patients, in order to allow for CO_2 exhalation. In a porcine lung injury model, $PaCO_2$ was higher in patients that had prongs in both nares as compared to a prong inserted in one naris, which decreased rebreathing of exhaled CO_2.[33] This concept was further validated by a computational three dimensional modeling study which demonstrated that smaller nasal prong sizes had a better ability to eliminate CO_2 out of extrathoracic dead spaces at lower flow rates than did larger size prongs.[34]

There are numerous physiologic benefits provided by HFNCOT. The inspired gas is warmed and humidified to a relative humidity of 95%-100%. Canine models have shown that breathing heated and humidified gas improved mucociliary function as measured by tracheal mucous velocity.[35] Normal formation and expectoration of respiratory secretions is dependent on proper function of the respiratory epithelium, which in turn relies on appropriate moisture. Dry, cold gas that is provided through conventional oxygen therapy is desiccating to the airways and can lead to mucociliary dysfunction; further, the secretions themselves become altered with a decreased moisture content.[36,37] Healthy canine patients breathing cold, dry gas show histologic evidence of inflammatory cells invading into the lamina propria of the trachea.[35] Additionally, humidified air also allows for better patient comfort,[38] especially since cold, dry gas is associated with decreased respiratory compliance and conductance,[39] as well as bronchoconstriction,[40] The energy requirement expended to moisten inspired gas is alleviated by the provision of appropriately humidified gas.[11] In 47 human patients receiving HFNCOT treatment, there is minimal interruption of eating and drinking when compared to conventional oxygen therapy.[41] A set gas temperature of 31°C was found to improve patient comfort in people as compared to 37°C.[42]

Another benefit of HFNCOT is thought to be secondary to the nasopharyngeal "purging" of CO_2. Net pressures that are translated to the pharyngeal airways is positive.[11] A major benefit of this pressure is that the CO_2 that is typically retained in the anatomic dead space (upper airways that are not involved with gas exchange) has less of a chance to be rebreathed by the patient. Other gases can be diluted by entrainment of ambient air, including oxygen, though the high flow rate and high concentration of oxygen delivered to the patient will increase overall oxygen delivery. The reduction in dead space leads

to better respiratory dynamics through reduction of the minute ventilation that is required to provide appropriate alveolar ventilation. By decreasing the resistance in the upper airways, work of breathing and patient comfort is also improved.[38]

The provision of positive end expiratory pressure (PEEP) is another beneficial feature of HFNCOT therapy. Devices that provide PEEP add positive pressure to the airways only at the end of the expiratory cycle, typically during positive pressure ventilation. PEEP is a similar concept to CPAP, however CPAP provides positive pressure during all phases of respiration. Both have the same goals of preventing alveolar collapse and to recruit atelectic areas of the lungs, which will help to mitigate hypoxemic complications. HFNCOT has been described as providing PEEP,[43] as well as providing CPAP[44]; clinically, the differences are largely semantic.

Peak expiratory pressures (correlating to PEEP) generated by HFNCOT have been found to range from 3.01 to 4.86 cmH_20 at flow rates ranging from 30 L/min to 50 L/min in humans, respectively. It has been recommended in human patients that HFNCOT be considered in patients requiring an escalation in respiratory support prior to instituting NIV, as this is typically more invasive and has more side effects.[45] Increasing HFNCOT flow rates has been shown to increase the pressure provided to the patient; these high flow rates act as an impediment to full expiration, thus increasing mean airway pressures and providing PEEP.[46] An increase in peak expiratory pressures, as well as increased end-expiratory volumes and increased tidal volumes also aid in respiratory dynamics.[47] Table 1 summarizes the benefits of HFNCOT as well as their proposed mechanisms.

Recommendations for transitioning from HFNCOT to standard oxygen supplementation in adult human patients include when flow rates are less than 25 L/min and FiO_2 is less than 40%.[30] It is important to recognize that the FiO_2 delivered to the alveoli is lower than what is set on the HFNCOT device. It was demonstrated in an experimental, manikin model, that a set 100% FiO_2 only achieved a true FiO_2 delivery of 78.67% and 76.67% at 300 L and 500 L tidal volumes, respectively. Increasing the flow rate from 15 to 30 L/min mildly improved the true delivery of oxygen by 7%.[48]

Indications of HFNCOT in Human Medicine

Hypoxemic Respiratory Failure

HFNCOT is being increasingly used in patients with hypoxemic, nonhypercapnic respiratory failure, as HFNCOT provides flow rates that exceed the inspiratory flow rates of patients in acute respiratory failure.[12] Experimental models simulating decreased chest wall compliance in people showed that HFNCOT provided higher FiO_2 (when measured at the oropharynx) compared to conventional oxygen therapy.[49] An expert panel strongly recommends with moderate certainty that HFNCOT should be used in hypoxemic respiratory failure over conventional oxygen therapy in people.[50] When compared to NIV and conventional oxygen therapy, HFNCOT was shown to decrease mortality at 90 days and an increase ventilator free days in an open-label, multicenter trial of 310 adults with acute hypoxemic, non-hypercapnic respiratory failure.[51] A majority (64%) of these patients had community acquired pneumonia, and 77% had PaO_2:FiO_2 ratios of less than 200, which indicates severe hypoxemia. HFNCOT was shown to be non-inferior to other forms of NIV in a randomized prospective study of 204 adults presenting to an emergency room, with both HFNCOT and NIV groups showing similar changes in CO_2 parameters.[27] In a randomized trial of 14 adults with acute hypoxemic respiratory failure, dyspnea scores and comfort scores were better for patients with HFNCOT versus NIV, though PaO_2 was slightly higher in the NIV group (129 mm Hg vs. 101 mm Hg). Regardless, the authors deemed that HFNCOT provided a "good balance between oxygenation and comfort" in this group.[52]

Demonstrable early improvements in several respiratory variables (rate, thoracoabdominal asynchrony and oxygenation) were improved with HFNCOT in a pilot study of 38 adult ICU patients with hypoxemic respiratory failure.[53] Fewer desaturation events were noted in a randomized comparative trial of adults with mild to moderate hypoxemia.[45] A retrospective study exhibited improvements in both 28 and 90-day mortality rates, as well as ventilator free days in 178 adult cancer patients with hypoxemic respiratory failure, 65% of which had pneumonia as an underlying cause.[54] A randomized comparative study employing HFNCOT demonstrated improvements in level of dyspnea, as well as comfort, respiratory rates, and heart rates in 38 adult patients with hypoxemia presenting to an emergency department. The improvement in dyspnea was noted within about 5 minutes of treatment in this cohort.[55] HFNCOT has also proved to be useful in people experiencing hypoxemia secondary to the SARS-CoV-2 (COVID-19) virus, decreasing ventilator free days and ICU length of stay versus early intubation in a prospective cohort study of 122 patients.[56]

Table 1
Beneficial Effects of HFNCOT and Their Proposed Mechanisms

Mechanism	Benefit
Small, pliable nasal prongs	-Increased comfort
Heated and humidified gas delivery	-Facilitation of airway debris removal -Avoidance of airway desiccation and epithelial injury -Decreased work of breathing -Increased comfort
Nasopharyngeal dead space washout	-Improvement in ventilation and oxygen delivery
Positive End-Expiration Pressure	-Improved oxygenation -Decreased work of breathing
High nasal flow rate	-Reliable delivery of FiO_2 -Reduced inspiratory resistance -Improvement in breathing pattern

Adapted from: Hyzy, RC. Heated and humidified high-flow nasal oxygen in adults: practical considerations and potential applications. UpToDate. 2020. Waltham (MA).

Cardiac Failure

The provision of positive airway pressures throughout the respiratory cycle has proven beneficial in human patients with cardiogenic pulmonary edema. As previously mentioned, positive airway pressures improve arterial oxygenation, as well as left ventricular afterload.[57] Prospective evaluation of patients in an emergency department demonstrated improvements in intrapulmonary shunting, arterial oxygen content, and alveolar-arterial oxygen gradients.[58] The successes of positive airway pressure in these settings have prompted evaluation of HFNCOT in cardiac failure patients. A case series of 5 heart failure patients that continued to deteriorate after treatment with a Venturi mask (a type of NIV device used in humans) showed improvements in respiratory rate, respiratory effort, and blood gas parameters while maintaining good comfort after HFNCOT was instituted.[59] Similar results were obtained in a prospective study of 10 adult patients with heart failure (marked limitation of physical activity, discomfort at rest; light physical activity causing fatigue, palpitations, dyspnea, or anginal pain). The respiratory rate in these patients decreased after HFNCOT was initiated at all flow rates. After starting HFNCOT, the right atrial and ventricular preloads were decreased using a surrogate marker for these values.[60]

Perioperative/Periprocedural Use

HFNCOT has been evaluated in the setting of varying levels of invasive procedures and their recovery. One group[61] sought to investigate ways to prolong the apneic period safely in patients with known difficult airways undergoing laryngeal procedures. Traditional

pre-oxygenation aims to decrease the amount of nitrogen in the airways and replace it with oxygen, in an attempt to create an "oxygen reservoir." This takes advantage of the concept of "aventilatory mass flow" (also known as "apneic respiration"), wherein gas exchange at the level of the alveoli creates a negative pressure. This negative pressure will help to drive oxygen into the lung in the absence of chest excursions. This "oxygen reservoir" within the alveoli can sustain the PaO_2 while a patient is apneic.[62] Patients were pre-oxygenated with HFNCOT, and some kept on this throughout the interventional procedure. Interestingly, 2 of 15 patients were able to be maintained on HFNCOT for the entirety of their procedure without the need for intubation (durations of 32 and 65 minutes). All patients who were pre-oxygenated showed no desaturation below 90%, with the average apneic time being 17 minutes. An experimental, before-after study echoed these findings with significant improvement in oxygenation during intubation when 101 patients with mild to moderate hypoxemia were preoxygenated with HFNCOT versus conventional oxygen therapy.[63] Similar results were noted in a prospective trial, prolonging apneic time around the time of intubation in 25 adult patients with difficult airways.[64]

These findings were in contrast with a randomized, open-labelled trial that evaluated preoxygenation with HFNCOT prior to rapid sequence intubation.[65] This was performed in 119 patients with hypoxemic respiratory failure requiring endotracheal intubation for mechanical ventilation. HFNCOT and a high flow mask device did not prevent desaturation in and around the time of intubation, nor did it decrease ventilation free days. However, the patients in this study had respiratory compromise at the time of HFNCOT use, compared to the patients in the other studies.[61,64]

HFNCOT has been evaluated in post-operative human patients. A phenomenon of postoperative hypoxemia has been described in human medicine. These respiratory changes have various etiologies, including respiratory depression (drugs, central nervous system disease), increases in dead space, airway obstruction (secretions, oropharyngeal soft tissues), thoracic wall disease, and venous admixture, among others.[66] HFNCOT was non-inferior to BiPAP (a type of NIV) in a randomized noninferiority trial of 830 patients recovering from cardiac surgery.[67] HFNCOT was shown to be non-inferior to conventional oxygen therapy post-operatively in a matched-controlled study of 58 liver surgery patients,[68] as well as in a randomized controlled trial post cardiac surgery of 155 obese patients.[69]

Decreased Rates of Intubation

In human patients, HFNCOT provides enticing option for oxygen supplementation that may obviate the need for mechanical ventilation. Mechanical ventilation and associated adverse effects such as ventilator associated pneumonia or ventilator induced lung injury, can be associated with in hospital mortality[14,70] and prolonged hospitalization.[70,71] When patients fail traditional oxygen supplementation, escalation to an oxygen delivery device such as HFNCOT that provides positive pressure can augment oxygenation levels and decrease work of breathing.[11,27]

A meta-analysis of 6 human studies investigating hypoxemic respiratory failure in 1,892 adults showed that intubation rates were lower when using NIV and HFNCOT as compared to conventional oxygen supplementation (nasal prongs, etc.). However, NIV strategies showed better PaO_2:FiO_2 ratios, as well as better oxygenation when compared to HFNCOT.[72] When comparing intubation rates and escalation to mechanical ventilation, HFNCOT outperforms conventional oxygen therapy, and has been shown to be non-inferior to NIV in different meta-analyses.[73–75] However, HFNCOT did not provide a survival benefit when compared to standard oxygen therapy, and length of hospitalization did not change in a meta-analysis of 18 trials containing 3,881 adults with acute respiratory failure.[73] HFNCOT was associated with more treatment failures in both newborn children (n = 754)[76] and preterm infants (n = 564)[77] when compared to CPAP provided by a nasal mask or nasal prongs. However, the rate of intubation and mechanical ventilation were not different in the HFNCOT versus CPAP groups in 310 hypoxemic adults.[51] Interestingly, subgroup analysis of this latter trial showed a significantly lower intubation rate of HFNCOT patients that had PaO_2:FiO_2 ratios of less than 200 as compared to patents with PaO_2:FiO_2 ratios greater than 200.

These findings are in contrast to other studies that have shown that HFNCOT can prevent progression to mechanical ventilation in a number of different populations. A meta-analysis of 18 separate trials including 3,881 subjects showed decreased intubation when HFNCOT was employed as compared to conventional oxygen therapy. The patient populations in this meta-analysis were heterogenous, and included patients with pneumonia, cardiac failure, thoracic surgery, trauma, and COPD, among others.[73] A predefined subgroup analysis of a larger randomized trial comparing HFNCOT to NIV in patients with hypercapnia showed a lower, though not statistically significant, rate of intubation for the HFNCOT cohort.[78] A pilot study investigating HFNCOT showed avoidance of intubation in 75% of the patients enrolled with hypoxemic respiratory failure.[53] Another pilot study of 75 adults showed nearly 63% of patients avoided intubation when HFNCOT was used in acute hypoxemic respiratory failure.[79] Similar results were seen in human patients when compared to conventional oxygen therapy post lung transplantation.[80] Several predictors of HFNCOT failure (requiring intubation and mechanical ventilation) have now been identified[53] (Table 2). The ROX index (Fig 1) has been proposed when evaluating the potential for HFNCOT failure in human patients.[81] This was validated in a cohort of 191 adults receiving HFNCOT because of pneumonia.[82] Values less than 4.88 were predictive of failure in the initial study,[81] however this has been challenged and found to be have a poor ability to predict intubation when applied to a cohort of 302 immunocompromised people. After 6 hours of HFNCOT, the ROX index had a 52.1% sensitivity and 68.9% specificity for prediction of intubation.[83] Another predictor of failure of HFNCOT proposed here included a higher sequential organ failure assessment (SOFA) score on day 1 of treatment. A retrospective study evaluating 124 adults with hypoxemic respiratory failure identified increased acute physiology and chronic health evaluation (APACHE IV) scores, lower platelet counts, lower serum sodium levels, higher pH, higher heart rates before and one hour after starting HFNCOT, and lower Glasgow Coma Scores in those that failed HFNCOT. This

Table 2
Characteristics of Human Patients Who Failed HFNCOT Therapy (Time After Instituting Treatment)

Higher respiratory rate at 30 and 45 min
Lower PaO_2 at 60 min
Lower PaO_2:FiO_2 at 60 min
Lower SpO_2 at 15, 30, and 60 min
Thoraco-abdominal asynchrony at 15, 30, 60, and 120 min
Increased pH on admission
Increased APACHE IV scores at admission
Increased SOFA scores at admission
Increased heart rate one hour before and after beginning HFNCOT
Lower platelet counts at admission
Lower serum sodium at admission
Lower Glasgow Coma Scale score at admission

Adapted from:
Lemiale V, Dumas G, Demoule A, Pène F, Kouatchet A, Bisbal M, et al. Performance of the ROX index to predict intubation in immunocompromised patients receiving high-flow nasal cannula for acute respiratory failure. *Ann Intensive Care* 2021;11:17. 10.1186/s13613-021-00801-z.
Lun C-T, Leung C-K, Shum H-P, So S-O. Predictive factors for high flow nasal cannula failure in acute hypoxemic respiratory failure in an intensive care unit. *Austin J Pulm Respir Med* 2020; 7(1): 1064.
Sztrymf B, Messika J, Bertrand F, Hurel D, Leon R, Dreyfuss D, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. *Intensive Care Med* 2011; (37): 1780.

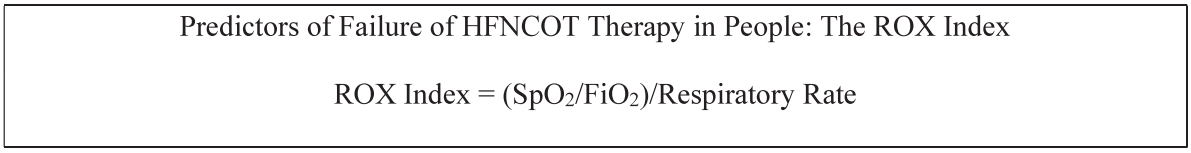


Fig 1. A value of greater than or equal 5.626 indicated a higher likelihood of success (defined as not requiring mechanical ventilation) in patients with various causes of acute hypoxemic respiratory failure when measured 12 hours after initiating HFNCOT therapy.

Adapted from: Lun C-T, Leung C-K, Shum H-P, So S-O. Predictive factors for high flow nasal cannula failure in acute hypoxemic respiratory failure in an intensive care unit. *Austin J Pulm Respir Med* 2020; 7(1): 1064.

group identified a cutoff ROX value of 5.626 at 12 hours to be predictive of failure.[84] While helpful in determining HFNCOT success, it is important to note that the illness scoring systems (APACHE IV, SOFA, Glasgow coma scores) take into account several other variables and encompass more than cardiopulmonary disease.

The use of HFNCOT in avoidance of intubation has also been demonstrated in neonates, in contrast to the previously mentioned studies.[76,77] Neonates in a pediatric intensive care unit with bronchiolitis had a decrease in intubation rates from 37% to 7% after institution of HFNCOT use in their facility in a retrospective study of 298 infants.[85] All patients had improvement in respiratory rate and heart rate while undergoing HFNCOT. However, it was noted that patients that were categorized as having cardiac disease had a higher intubation rate (roughly 50%), potentially indicating that HFNCOT was not as effective for these patients.

The timing of intubation may also play a role in patients receiving HFNCOT. Kang et al cautioned that patients who had HFNCOT therapy and subsequently underwent early intubation (within 48 hours of presentation) had better outcomes than patients who had HFNCOT for >48 hours and were subsequently intubated. The early intubation group in this meta-analysis of 8 studies (2,167 patients) had decreased ICU mortality, better weaning rates, and more ventilator-free days. It was postulated that cardiac dysfunction and respiratory fatigue developed in the >48 hour cohort while spontaneously ventilating with HFNCOT, leading to worse outcomes.[86]

Do Not Intubate Orders

Do-not-intubate orders are frequently encountered in human medicine when patients are being treated palliatively or in a hospice type setting for terminal illness. Fifty subjects who had evidence of hypoxemia were treated with HFNCOT. The average age of these patients was 73 years; the only exclusion criteria included compensated hypercapnia and lack of any intention to progress to NIV or intubation. Retrospective analysis of this cohort showed that 82% were able to achieve and maintain an appropriate SpO_2 until clinical improvement (weaning back onto breathing room air) was achieved or until support was withdrawn.[87]

Weaning From Intubation

Patients who are endotracheally intubated and are being weaned from more intensive forms of respiratory support, such as mechanical ventilation, typically require continued oxygen supplementation until they are ready to breathe ambient room air. The use of HFNCOT has potential benefits in this setting, especially when reintubation is a threat. Patients with low PaO_2:FiO_2 ratios (≤300) being weaned from mechanical ventilation showed improved oxygenation, less need for ventilatory support, better comfort, decreased respiratory rates, and fewer desaturation events when treated with HFNCOT versus NIV in a randomized, controlled trial of 105 adults with hypoxemic respiratory failure.[88] HFNCOT was noninferior and had similar intubation rates in a randomized study of 204 patients with all-cause respiratory failure.[27] Decreased re-intubation rates were reported in a randomized controlled trial of adults who had passed a spontaneous breathing trial, though conclusions about the overall benefit of HFNCOT in this scenario could not be made.[89] HFNCOT also decreased the time it took to pass a spontaneous breathing trial after mechanical ventilation, and decreased the reintubation rate in a randomized, prospective study of 155 adults.[90] Similar effects were seen when applying HFNCOT to 20 patients with tracheostomies who were being weaned from prolonged mechanical ventilation.[91] In a trial of 16 patients with COPD and hypercapnic respiratory failure who had been weaned from mechanical ventilation, the neuroventilatory drive and work of breathing, as measured by electrical activity of the diaphragm and trans-diaphragmatic pressure-time product, respectively were improved.[92]

It is important to note that these findings have not been entirely consistent. In one study, no differences in rates of intubation were appreciated when patients were treated with NIV or HFNCOT[89]; furthermore, no differences in hemodynamics, respiratory rate, or gas exchange when treatment with a high flow mask versus HFNCOT were compared in a randomized crossover trial of 25 extubated patients.[93] Further trials are underway to determine if HFNCOT is truly advantageous to other forms of oxygen supplementation in ICU patients who have been extubated from mechanical ventilation.[94]

Costs and Adverse Effects

The cost of mechanical ventilation in human medicine is high. When compared to oxygen provided via mask or nasal prongs, HFNCOT showed some cost benefit in non-intubated ICU patients.[95] HFNCOT also offers a cost advantage compared to NIV, and proved to be less costly when compared to conventional oxygen therapy in both high risk patients and low risk patients that are post-extubation.[96]

Adverse effects are reported infrequently for HFNCOT therapy. A case report describing the development of mediastinal and subcutaneous emphysema, as well as pneumothorax was documented in a woman who was being weaned from mechanical ventilation with HFNCOT. After cessation of HFNCOT, the complications resolved.[97] Pneumomediastinum, pneumothorax, and subcutaneous emphysema have been reported in children from neonates to adolescents.[98] It is suspected that these complications were caused by increased airway pressures leading to alveolar or bullae rupture, which in turn led to air leak. Case reports and series involving barotrauma in an infant,[99] epistaxis and pneumothoraces in pediatric patients,[100] and tension pneumocephalus in a preterm infant.[101] Other minor adverse effects reported in people include oral and nasal drying, feelings of excessive warmth, and general discomfort.[102]

High Flow Nasal Oxygen: The Veterinary Experience

Due to its novelty, there is a paucity of literature available on the use of HFNCOT in small animals. Three separate commercially available devices have been evaluated in canine subjects. The first published study on safety and efficacy of HFNCOT use in dogs was performed by Daly and colleagues.[103] Healthy nonbrachycephalic dogs received conventional oxygen therapy at 100 mL/kg/min via nasal cannula, followed by HFNCOT at 20, then 30 L/min. Indirect measurement of transpulmonary pressures (obtained via esophageal

balloon catheter measurements) were not different among each of the treatment groups, suggesting safety at high flow rates. The P_aO_2 significantly increased in all treatment groups, however this value was over two times higher in the HFNCOT group than the conventional oxygen therapy group.[103]

A randomized, prospective crossover study compared patient tolerance, respiratory patterns, and measured pressures of CPAP in 8 healthy dogs receiving HFNCOT as compared to traditional oxygen therapy.[104] At a HFNCOT flow rate of >2 L/kg/min, patients exhibited decreased tolerance of the device, as evidenced by agitation, pawing at the face, and as respiratory difficulty. Even in awake patients who were panting, airway pressure at expiration still reached 5.4 cmH_20, indicating that increased airway pressures were achieved even during open mouth breathing. This is important since the level of CPAP has been shown to decrease roughly 50% in humans when breathing with an open mouth.[43] The differences in airway pressure in this study were minimal between 2 L/kg/min and 2.5 L/kg/min. At these flow rates, the measured FiO_2 in the oropharyngeal region reached up to 95%. $PaCO_2$ was significantly lower than baseline readings for HFNCOT dogs that were sedated. This group set forth recommendations that dogs requiring some level of pressure support be titrated up to a flow rate of 2 L/kg/min as clinically indicated.[104]

Keir and colleagues were the first to evaluate HFNCOT in a clinical setting.[105] This retrospective study involved six dogs who had both HFNCOT and conventional oxygen supplementation for hypoxemia. Four of these had aspiration pneumonia, and one each with eosinophilic pulmonary infiltrates and pulmonary contusions. PaO_2 values were significantly greater after instituting HFNCOT therapy. Interestingly, only one of the six patients required sedation during HFNCOT. Four of the six had resolution of hypoxemia, and three were able to be discharged.[105] A case report has been published that showed successful use of HFNCOT after extubation in a dog with severe bronchoconstriction due to a suspected anaphylactic reaction. This group used maxillary nerve blocks to help promote patient tolerance of the nasal prongs.[106]

In a prospective study, eleven dogs with respiratory distress were enrolled and conventional oxygen support was provided on admission.[107] Reasons for hypoxemia included aspiration pneumonia (5/11) and one each of pericardial effusion, pulmonary hemorrhage, cardiogenic pulmonary edema, non-cardiogenic pulmonary edema, and leptospirosis. If there was no improvement within 30 minutes, the patients were transitioned to HFNCOT. PaO_2 more than doubled after 60 minutes of HFNC therapy and SpO_2 significantly increased. No significant differences were seen in heart rate or $PaCO_2$. Five of eleven still had increased respiratory rates (>40 breaths per minute) after 60 minutes of HFNCOT, however all patients showed good tolerance of the device. A total of 5 of the 11 dogs deteriorated and required intubation.[107]

Another prospective trial evaluated the use of HFNCOT in 22 dogs presenting to an emergency service with acute hypoxemic respiratory failure.[108] Causes of hypoxemia included aspiration pneumonia (7), inflammatory disease (3), pulmonary hypertension (3), congestive heart failure (1), trauma (1), and other (6). The dogs enrolled in the study did not show improvement after thirty minutes of traditional oxygen therapy. Twenty-two dogs (including six brachycephalic breeds) were enrolled; oxygenation, respiratory rates, and dyspnea scores improved with HFNCOT. Three of the dogs died and nine were euthanized. Importantly, based upon the criteria evaluated (improvement in respiratory rate, dyspnea scores, and SpO_2), 8 of 22 dogs avoided intubation and mechanical ventilation.[108] The results of this study are comparable to an unpublished study where patients who failed conventional oxygen therapy and were treated with HFNCOT. This group showed improvements in PaO_2, SpO_2, and respiratory rate, with 9 of 20 dogs surviving to discharge.[109]

A prospective investigation on HFNCOT use in animals centered on postoperative recovery in brachycephalic dogs.[110] Patients who exhibited increased work of breathing (including stridor) or hypoxemia were provided HFNCOT. Dyspnea scores improved, and the physical setup of the nasal prongs was well tolerated. The respiratory rates increased in the first 30 and 90 minutes in half of the dogs prior to normalizing. Five of six dogs showed clinical improvement, and one remained unchanged.[110] This is of particular clinical use because the conformational changes noted in brachycephalic breeds create upper airway resistance; the use of HFNCOT can help to overcome the upper airway resistance and improve respiratory mechanics.[111]

Device Setup and Recommendations

HFNCOT devices that were initially developed for human use have been adapted for use in veterinary medicine with a nearly identical setup. Each machine allows for gas flow rate and temperature to be adjusted independently; some models permit direct adjustment of the FiO_2. In human patients, the manufacturers recommend following an algorithm that was set forth by Ischaki et al.[112] This entails an initial FiO_2 of 100% (1.0), temperature of 37°C, and flow rate of 60 L/min. The settings are then titrated after 1-2 hours based upon SpO_2, respiratory rate, accessory muscle excursions, and evidence of respiratory acidosis. If these have improved, the FiO_2 is titrated down first, as prolonged breathing of 100% oxygen can lead to oxygen toxicity. If the patient continues to tolerate progressive decreases in FiO_2, eventually the flow rate can be decreased (recommendation to begin the decrease in flow when FiO_2 is 0.4). At that time, the flow rate can be decreased by 5 L/min. Once the flow rate is less than 15 L/min, conventional oxygen therapy can be instituted. As previously mentioned, prospective work has shown that tolerance is improved in people when the temperature of the inspired gas is 31°C versus 37°C though no specific guidelines are available to suggest routine use of a lower temperature in clinical patients.[42] Recent work in a cohort of 14 dogs that were recovering from general anesthesia and were not dyspneic showed no difference in tolerance scores for HFNCOT when temperature was changed from 31°C to 37°C at different flow rates.[113] Further studies are needed to see if this is applicable to veterinary patients in respiratory distress. It is imperative to note that if the patient deteriorates with HFNCOT at any point, then intubation and ventilation are recommended.

There are no definitive guidelines for canine and feline patients. At the author's institution, the same general guideline of instituting an initial FiO_2 of 100% and temperature of 37°C is reasonable. Based on a recent study, a maximum gas flow rate of 2L/kg/min could be recommended.[104] Alternatively, the flow rate can be set to match the minute ventilation, calculated by multiplying respiratory rate and tidal volume.[107] The size of the nasal cannulae should not be larger than 50% of the opening of the nares. In patients who have small nasal openings that would be occluded by even the smallest sized cannula, consideration can be made to inserting a prong in one naris and leaving the other open to the environment. Further validation of this is needed before extrapolating to clinical patients, however this may be a prudent approach in very small patients who would benefit from HFNCOT. Anecdotally, it is recommended that the distinct flow of oxygen should be audible during treatment with HFNCOT, as this indicates a "leak" and ascertains the nasal prongs are not completely occluding the nares.

Based on clinical experience and the human guidelines set forth, a similar algorithmic approach to weaning of HFNCOT and eventual de-escalation to conventional oxygen therapy are reasonable to consider in veterinary patients. A consensus statement for human neonates recommended titration of FiO_2 to less than 30% before decreasing flow rates. The flow can be reduced when respiratory rates and work of breathing are stable for more than 12-24 hours, and discontinuation can be considered when the flow rate is 1-6 L/min.[114] Though extrapolation to veterinary patients need to be scientifically evaluated, the authors consider these guidelines as clinically

reasonable. Nasal prongs or catheters can then be used to deliver conventional oxygen therapy after weaning off HFNCOT, with typical rates of supplementation between 100 and 150 mL/kg/min.[115] Sedation may be provided for patients that do not tolerate the HFNCOT cannulas. The authors typically utilize butorphanol (0.1-0.4 mg/kg IV every 4-6 hours, or a constant rate infusion at 0.1-0.4 mg/kg/hr) and/or dexmedetomidine (0.5-2 mcg/kg PRN or 0.5-2 mcg/kg/hr).

Complications of HFNCOT appear to be minimal in cats and dogs. Most of the reported complications are minor, such as intolerance of the nasal prongs. Pneumothorax was reported in one abstract,[109] and persistence of a pre-existing pneumothorax was noted in one patient which resolved after discontinuing HFNCOT.[105] Aerophagia was documented in all dogs in one study,[104] and another had one patient whose aerophagia was severe enough that treatment with orogastric intubation was needed to evacuate excessive gas.[110] HFNCOT has not been investigated in cats due to the size limitations of the nares as well as their delicate facial conformations, though has been used with success anecdotally.[28]

The price charged for HFNCOT differs on an institutional basis. The costs of doctors' and technicians' time, costs associated the HFNCOT unit as well as the level of care required for a specific patient should be accounted for. The cost of mechanical ventilation at the authors' institution, which does not account for other supportive care measures (IV fluids, drugs, nursing care, etc.) is roughly $900 per day. This is almost five times as much as one day of HFNCOT.

Conclusions

HFNCOT has shown great promise for people with hypoxemia. Potential benefits of HFNCOT include its ease of use and physiologic benefits as compared to mechanical ventilation. Decreased need for mechanical ventilation is beneficial, however results in people have been mixed. In human patients, it appears that there is a benefit to using HFNCOT in situations of cardiac failure and under do-not-intubate orders. There are also benefits in situations of periprocedural use, preoxygenation prior to intubation, post-anesthesia, and de novo hypoxemic respiratory failure, although some studies show contradictory results. Clear recommendations for the use of HFNCOT cannot be made across these subgroups of patients.

Prevention of mechanical ventilation is of utmost concern in companion animal veterinary medicine, as this is labor intensive and frequently financially prohibitive for pet owners. HFNCOT is an attractive option in patients that fail conventional oxygen therapy, however it cannot act as a substitute for mechanical ventilation in some patient populations. The current body of literature surrounding HFNCOT is encouraging, as there appear to be improvements in respiratory parameters, and its use is generally well tolerated. The setup is user friendly and more cost efficient than other forms of ventilation. More studies are required for more information about patient selection, indications, and success rates.

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