High Flow Nasal Cannula Oxygen Therapy in Dogs

by

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ABSTRACT

HIGH FLOW NASAL CANNULA OXYGEN THERAPY IN DOGS

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High flow nasal cannula (HFNC) oxygen therapy is a non-invasive respiratory support modality that warms and humidifies inspired gases to physiologic conditions and delivers flow rates up to 10 times that of traditional oxygen supplementation, while allowing for FiO_2 titration. This system has demonstrated success in improving work of breathing (WOB) and averting intubation in people with respiratory failure. The purpose of this thesis was to determine whether Optiflow^{TM} HFNC oxygen therapy could be applied to dogs safely with acceptable tolerance, and whether this modality could improve oxygenation and WOB in dogs with acute hypoxemic respiratory failure (AHRF) and in those with post-anesthetic upper airway obstruction (UAO).

A comparison of HFNC to traditional nasal cannula (TNC) oxygen therapy in 8 healthy dogs was conducted in a randomized, incomplete block design. High flow oxygen rates of 0.4, 1, 2, 2.5 L/kg/min and standard TNC oxygen flow rates of 0.1, 0.2, 0.4 mL/kg/min were evaluated. Data collection included physiological variables, respiratory/tolerance/sedation scores, arterial blood gas analysis, as well as inspiratory/expiratory gases and airway pressures. HFNC therapy provided a less variable FiO_2 than TNC, reliable FiO_2 titration, acceptable tolerance and low-level continuous positive airway pressure (CPAP) at flow rates of 1-2 L/kg/min. There was a small increase in $PaCO_2$ associated with HFNC use in addition to subclinical aerophagia in 8/8 dogs. There was no evidence of air-leak syndrome in any dog.

High flow oxygen support was then applied to dogs with AHRF and UAO to determine whether HFNC could improve respiratory status. The investigations in AHRF and UAO were prospective, sequential clinical trials, with 22 and 6 dogs enrolled, respectively. There was an improved WOB and good tolerance in both clinical trials. In dogs with pulmonary pathology, there was improved oxygenation without an increase in PCO_2; however, periodic hypercapnia was noted in dogs with UAO. Monitoring of PCO_2 is recommended given the correlation with increasing flow rates. Overall, this research has revealed the potential for HFNC as a valuable respiratory support modality in veterinary medicine.

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TABLE OF CONTENTS

CHAPTER 1: Literature Review

CHAPTER 2:

Comparison of high flow nasal cannula oxygen administration to traditional nasal cannula oxygen therapy in healthy dogs

CHAPTER 3:

High flow nasal cannula oxygen therapy in acute hypoxemic respiratory failure in 22 dogs requiring oxygen support escalation

CHAPTER 4:

Preliminary evaluation of the use of high flow nasal cannula oxygen therapy during recovery from general anesthesia in dogs with obstructive upper airway breathing

CHAPTER 5: Summary & Conclusions

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AHRF	Acute hypoxemic respiratory failure
BRPM	Breaths per minute
BOAS	Brachycephalic obstructive airway syndrome
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
COPD	Chronic obstructive pulmonary disease
$ETCO_2$	End-tidal carbon dioxide
ETO_2	End-tidal oxygen
FiO_2	Fraction of inspired oxygen
Ft	Feet
HFNC	High flow nasal cannula
MV	Mechanical ventilation
NIV	Non-invasive ventilation
PAP	Positive airway pressure
PEEP	Positive end-expiratory pressure
P/F	PaO_2:FiO_2
S/F	SpO_2:FiO_2
SpO_2	Oxygen saturation measured by pulse oximetry
TNC	Traditional nasal cannula
UAO	Upper airway obstruction
V/Q	Ventilation / perfusion
WOB	Work of breathing

LIST OF APPENDICES

CHAPTER 1

Literature Review

1.0 Introduction

Dyspnea is a predictor of mortality in human medicine and considered an aversive sensory experience much like pain.[1] The reduction of this sensation in patients with emergent or critical illness is imperative to improving patient comfort and survival. The sensations of dyspnea have been described to include: air hunger (altered pulmonary chemical loads), increased work of breathing (altered pulmonary mechanical load) and tightness (bronchospasm).[1] Oxygen supplementation is a life-saving intervention that can alleviate the first two sensations experienced by dyspneic patients. A secondary goal in providing oxygen should be to do so with minimal additional stress, resulting in improvement of discomfort and notable changes in the oxygen content of the blood, and thus oxygen saturation. New oxygen support modalities such as delivery through a high flow nasal cannula (HFNC), may offer improved patient comfort with increased efficacy relative to standard means of providing oxygen, in the spontaneously breathing patient. The following review will examine current respiratory support techniques in veterinary medicine and review the available evidence evaluating the use of HFNC in people. There are limited animal-based investigations using this oxygen delivery modality.

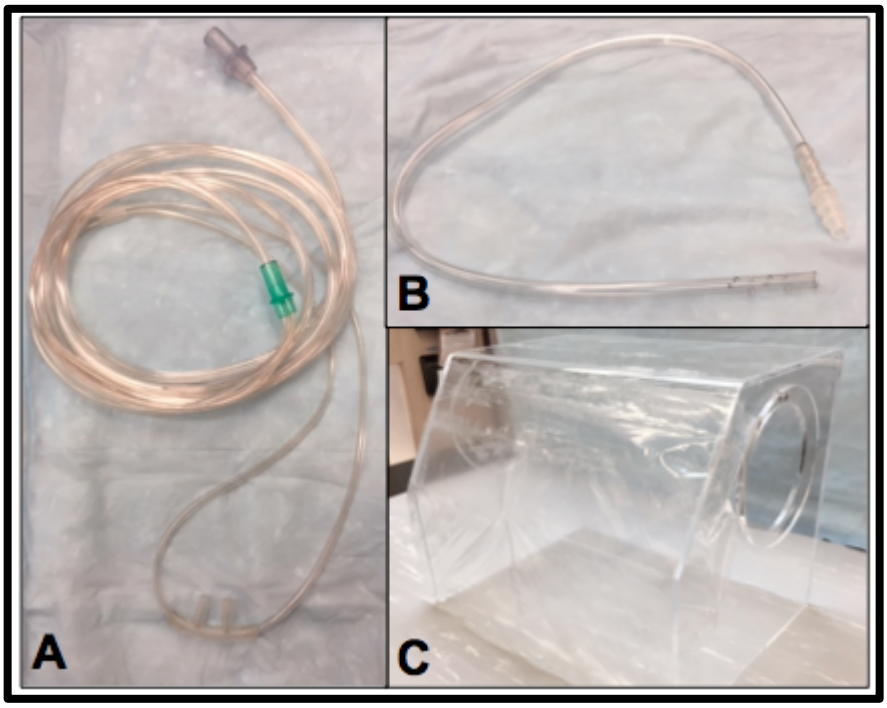
1.1 Traditional Oxygen Therapy

1.1.1 Methods & Efficacy of Oxygen Supplementation

Oxygen can be provided by in-hospital tanks or generators and is delivered to patients via a calibrated flow meter. Oxygen should be prescribed when there is clinical evidence of hypoxia, such as in patients that display dyspnea, with a primary goal of reducing life-threatening outcomes. Dyspnea is a sensation and as such is difficult to ascertain in animals. However, dogs showing

signs of distressed breathing such as the use of accessory muscles of respiration (extended head and neck, abducted elbows), that are restless and unable to eat or drink due to their respiratory difficulty are considered to be dyspneic in this review. Traditionally, oxygen is delivered to animals in many ways including flow-by or facemask, nasal prongs or catheters, and hoods or cages (Figure 1).[2,3,4] Step up oxygen therapy can include: non-invasive ventilation via facemask/nasal interface (i.e. using a mechanical ventilator without an endotracheal tube) or invasively via endotracheal/tracheal intubation and positive pressure ventilation.[2,3,4] It should be noted that the latter is more commonly employed in animals at this time, but requires financial commitment by the pet owner. Non-invasive ventilation will be discussed in section 1.2.

Figure 1. Traditional oxygen supplementation delivery systems



A: nasal prongs;[a] B: multifenestrated nasal oxygen catheter;[b] C: oxygen hood[c]

Administration of oxygen via facemask to small animals, can provide a moderate increase in the mean fraction of inspired oxygen (FiO_2) of 0.46 with a variable range of 0.3-0.7, compared to room air FiO_2 of 0.21.[2] However, facemasks are associated with lack of tolerance in many dyspneic patients. Resentment of the facemask can lead to patient distress and negate improvements in oxygen status.[3] Moreover, concerns for CO_2 and heat retention exist with occlusive facemasks.[4]

Flow-by oxygen supplementation (i.e. placement of oxygen tubing within 2 cm of the nose/mouth, with passive inhalation of oxygen flow) is a first-line method for oxygen delivery and offers the advantage of improved tolerance and lack of intrusiveness relative to facemask oxygen supplementation.[2,3,4] It provides less effective oxygen support with a reported FiO_2 range of 0.3-0.5 in immobile dogs,[2] and thus should only be considered in minimally hypoxemic patients or as an interim while preparing more effective means of supplementation.[2]

Oxygen hoods are enclosed areas where oxygen is piped into the enclosure, to increase the FiO_2 within that space. The hoods can easily be made by loosely covering the front opening of an Elizabethan collar or plexiglass box, with plastic wrap and placing oxygen tubing within the hood. These devices result in larger areas for the head to rest comfortably wherein oxygen concentration can be increased substantially; FiO_2 of up to 0.95 has been reported with oxygen flow rates of 300 mL/kg/min.[2] It should be noted that this delivery method must not be an air-tight environment, as carbon dioxide (CO_2) must be allowed to escape in order to avoid CO_2 rebreathing. Oxygen hoods are a cost-effective option for providing oxygen to small patients that are minimally mobile. They allow handling of the patient while oxygen support is provided, and monitoring of the FiO_2 within the hood can be measured using a separate FiO_2 meter. Disadvantages with this oxygen delivery system include leakage resulting in lower oxygen levels within the hood, with possible CO_2 and heat retention leading to patient hypercarbia and hyperthermia. Reduced patient cooperation relating to an unwillingness to stay within the hood or tolerate a canopy (Elizabethan collar), must also be

considered.[2] One study performed in 1996 recommended initiating canopy (Elizabethan collar) oxygen at 1 L/min, though this may be more often considered a maintenance flow rate for canopy oxygen after the canopy has been pre-oxygenated with higher flows. This Elizabethan collar oxygen delivery system was shown not to have more complications relative to intranasal supplementation.[2,5]

Commercial oxygen cages also offer a controlled environment that allows for monitoring of FiO_2 and with the potential for humidification and temperature control. Disadvantages of this means of support include cost of the cage, CO_2 and temperature-control (cage-dependent), ambient noise within the chamber, and decrease in oxygen levels at any time the seal is broken (i.e. opening of the cage door), resulting in reduced support to the patient.[4] Both oxygen hoods/collars and cages offer the advantage of allowing for natural humidification of the supplemental oxygen via the patient's nasal airways.

Intranasal oxygen supplementation is administered by nasal cannulas that are further characterized as prongs or catheters.[2] Intranasal oxygen administration generally provides a more consistent flow of oxygen if the prongs/catheters are not dislodged, however the FiO_2 provided can still be variable.[4] It also has the advantage of being less wasteful of hospital oxygen supply than flow-by or cage methods since lower oxygen rates are administered directly to the nares.[2]

Nasal cannula prongs, designed for people, can be easily and quickly placed in very stressed animals that require more concentrated oxygen support than may be provided by flow-by.[2] These prongs are very short (~1 cm) and soft. Their design is better adapted to the facial features of brachycephalic dogs; for non-brachycephalic dogs, an additional method of securing the device to the face is often necessary. Nasal prongs can be easily removed by the patient with minimal manipulation.

A nasal catheter, relative to nasal prongs, is more deeply seated within the nasal cavity. Catheter selection includes those specifically designed for oxygen

supplementation such as multi-fenestrated oxygen catheters, or alternatives such as feeding tubes/red rubber catheters. Multi-fenestrated catheters are preferred since oxygen flow is more diffusely dispersed rather than delivered through one single fenestration causing a pressurized jet of oxygen, which may result in nasal mucosal lesions, discomfort and intolerance as oxygen flow rates are increased.[4] To place these cannulas, the tip of the catheter is pre-measured to the medial canthus of the eye and subsequently inserted into the ventral meatus of the nasal cavity, in a ventromedial direction to the premeasured mark, under topical anesthesia and mild sedation.[3] In severely dyspneic patients, this procedure may have to wait until some stabilization has occurred, as the stress of the procedure can worsen or even decompensate the dyspneic patient.[2] Oxygen flow rates of 50-150 mL/kg/min can achieve FiO_2 of 0.3-0.7 with this system.[4,6] An experimental study by Dunphy et al. investigated the effect of dividing oxygen flow rates between bilateral nasal catheters using red rubber (non-fenestrated) catheters.[6] They found that both FiO_2 and arterial partial pressure of oxygen (PaO_2) increased in a flow-rate dependent manner, but was independent of the number of catheters.[6] Initial oxygen flow rates of 50-100 mL/kg/min have been previously regarded as a reasonable starting point,[4] but may be insufficient in moderate to severe hypoxemia, as Dunphy's study demonstrated that these flow rates provide a mean tracheal FiO_2 of only 0.29-0.37.[6] At 200 mL/kg/min, an FiO_2 of 0.6-0.8 can be achieved.[6] However, aversion to oxygen supplementation was seen at flow rates greater than 100 mL/kg/min/catheter; dogs began shaking their heads and pawing at the catheter.[6] While a higher FiO_2 can be achieved, patient discomfort and agitation may utilize limited metabolic reserves and result in patient decompensation, limiting the utility of administering oxygen via a single intranasal catheter when the flow is above 100-200 mL/kg/min. However, improved tolerance may be achieved by distributing the flow across two nasal catheters, one placed in each nostril, or by using a designated oxygen catheter that has multiple fenestrations to reduce mucosal irritation/discomfort.

1.1.2 Controversies and Complications of Oxygen Supplementation

While hypoxia poses imminent concern for respiratory arrest, hyperoxia can likewise lead to complications including death.[7] Oxygen toxicity can occur when oxygen supplementation increases alveolar PO_2 above normal conditions.[7] Pulmonary toxicity is likely to occur if there is exposure to a FiO_2 of 0.60 for ≥24 hours, though exposure duration, FiO_2 and atmospheric pressure play a role in determining the cumulative oxygen dose.[4,7] Experimental and laboratory studies have demonstrated that supra-normal oxygen exposure results in reactive oxygen species that target the pulmonary capillary endothelium and alveolar epithelium resulting in lung injury.[7] With provision of standard oxygen supplementation via facemask, flow by, or nasal prongs/catheters, the exact FiO_2 that a patient is receiving is unknown regardless of flow rate, and the FiO_2 ranges from that which is considered safe to potentially dangerous.[8] Methods of oxygen delivery that allow controlled FiO_2, such as oxygen cages or mechanical ventilators, are therefore preferable for avoiding hyperoxia.

Another complication associated with the provision of oxygen is intolerance and the behavioural response of the patient to the type of system used for oxygen supplementation. The veterinary literature has limited studies that explore tolerance (or lack thereof) and the exact cause for this sequela. In neonatal human patients with oxygen supplementation via nasal prongs that fully occlude the nostrils for nasal positive pressure ventilation, nasal deformities and mucosal injury have been demonstrated.[9] Currently, there are no veterinary studies that have investigated damage to the nasal mucosa, and tolerance evaluations are anecdotal beyond those reported by Dunphy et al.[6] Moreover, patient intolerance may not be due to the animal's behavioural nature, but could represent physical discomfort and possible injury that is not externally visible and is not routinely evaluated.

1.2 Alternative Oxygen Support Strategies

In human medicine, there are alternative means of supplementing oxygen that offer additional respiratory support beyond that of passive oxygen delivery systems (i.e. standard oxygen) as previously described. These alternative oxygen delivery systems are implemented in hopes of stabilizing the hypoxemic patient and avoiding invasive mechanical ventilation (MV). The British Thoracic Society defines noninvasive ventilation (NIV) as a means of providing ventilatory support via the patient's upper airway by use of a mask or similar device such as nasal prongs.[10] These advanced oxygen support modalities often offer continuous positive airway pressure (CPAP) support in order to increase mean airway pressure while the patient continues to breathe spontaneously.[10] Increasing airway pressure reduces the collapse of compromised lung units, allowing improved gas exchange in affected lung regions.[10] Randomized clinical trials in people comparing NIV to standard passive oxygen support have demonstrated that while there is a physiologic improvement in oxygenation ratios, the results regarding a reduction in need for invasive intubation are controversial.[11,12] For patients in severe respiratory distress that fail other respiratory support strategies, the only option is MV; this can be provided by endotracheal (initially) or tracheal intubation through a tracheostomy (prolonged ventilation). Endotracheal intubation carries increased risk of morbidity such as local injury to the airways, loss of respiratory defenses, and potential for nosocomial infections such as ventilator-associated pneumonia.[11,12,13] The artificial airway present in endotracheal intubation and tracheostomy, also poses a risk for life-threatening occlusion due to decreased secretion clearance and as a result of impaired ciliary defenses. Moreover, these invasive techniques require increased personnel and financial dedication while carrying a higher morbidity and mortality rate.[10,14] Given the desire to avoid intubation, NIV has gained favour as a respiratory support technique whenever feasible.

The veterinary literature that evaluates NIV is limited to three publications of which two are in dogs.[13-15] Delivery of NIV in animals has proven feasible but,

is technically challenging and may not offer advantages relative to invasive mechanical ventilation. In the most recent study by Staffieri et al, a human 7L pediatric helmet designed to allow provision of CPAP, was placed on 15 healthy dogs, post-ovariohysterectomy, in a randomized, crossover design.[13] Every dog received pre-CPAP (0 cmH_2O), CPAP (5 cmH_2O), and post-CPAP (0 cmH_2O), each for 20 minutes.[13] The study findings demonstrated that the helmet was a well-tolerated interface for applying CPAP during recovery from a short general anesthesia.[13] During application of CPAP, there was a significant decrease in respiratory rate and $PaCO_2$, with an increase in PaO_2 despite an FiO_2 of 0.21 (room air).[13] Another study trialed CPAP by use of a facemask in 16 heavily sedated dogs.[14] The study noted that the mask was well-tolerated with sedation, and noted that the provision of CPAP with a facemask improved PaO_2 relative to facemask oxygen supplementation without CPAP.[2] Unfortunately, this study did not determine the FiO_2 delivered to the dogs, but it did successfully demonstrate that non-invasive application of CPAP in dogs was feasible.[14] Lastly, nasal mask NIV was applied to eight healthy cats.[15] While NIV was feasible in cats, the level of sedation/anesthesia required, in the absence of having a protected airway, may preclude any advantage over traditional invasive ventilation.[15] To date, a functional and simple non-invasive system has not been identified for veterinary patients.

The motivation in veterinary medicine to find an alternative, potentially intermediate, means of oxygen support between standard oxygen supplementation and MV remains high and was the motivation for the research presented in this thesis. For the moderately hypoxemic patient, traditional low-flow oxygen support systems may not provide a sufficient increase in FiO_2 as a result of the method of delivery (such as opening an oxygen cage) or intolerance to higher flow rates (drying/discomfort of nasal mucosa). The potential insufficiency of current systems necessitates exploration of other means of support, such as the HFNC oxygen delivery system. High flow nasal cannula oxygen therapy has been used in neonatal, pediatric and adult human patients

for over a decade, and given the success documented in people, was an important advancement worthy of evaluation in veterinary medicine.[16]

1.3 Low and High Flow Oxygen Nasal Cannula Oxygen Therapy Methodology

According to the American Association for Respiratory Care, high-flow oxygen systems are those that deliver a prescribed gas mixture at a rate that exceeds the patient's demand for oxygen delivery, and should have a means of humidification.[17] With the advent of HFNC therapy, preconditioning of the high gas flows has allowed for administration of oxygen up to 8 L/min in neonates and 60 L/min in adults.[18] These systems have been shown to improve patient comfort relative to traditional oxygen supplementation despite the very high flow rates, likely due to the ability to successfully heat and humidify the oxygen flow being delivered.[19,20] The following section will detail the differences in humidification between traditional systems i.e. low-flow oxygen systems and HFNC, as well as the specific logistics of set-up for each modality.

Humidification of inspired gases is of utmost importance to the airways as it prevents damage to the airway epithelium, inspissation of secretions that can cause obstruction, atelectasis and bronchospasm.[21] The latter two sequelae can be greatly ameliorated by providing gas that is successfully preconditioned, more specifically - heated and humidified. The result and goal of HFNC humidification systems are to provide flow of gas at 37°C and 100% relative humidity, similar to physiologic conditioning provided by the nasal passages in periods of health.[19] Humidification in HFNC modalities, involves either a cartridge or heated chamber that results in warming of sterile water to produce water vapour.

Traditional low-flow oxygen systems involve a simple set-up wherein an oxygen source is connected to a calibrated oxygen flow meter (litres per minute), which then affixes to the patient interface.[16] There is often an unheated bubble-type humidifier inserted at the level of the oxygen flow meter. Depending on the level of distress, the interface may include a facemask, nasal prongs or

cannulae, or an oxygen canopy,[2] which are all traditional means of providing low-flow oxygen therapy and are quickly set-up by urgent care personnel.

When traditional oxygen supplementation is administered via nasal cannulae in adults and neonates, at flow rates above 6 L/min, sinus pain, discomfort, and drying/damage to the nasal mucosa is often seen.[16] Thus, gas delivery above these rates is cautioned in the absence of a proven humidification modality, as is present on mechanical ventilators and HFNC systems.[16] Low-flow oxygen systems, considered to be flow rates <4 L/min in adult patients, do not require humidification.[17] Regardless, unheated bubble-type humidifiers are often employed despite lack of evidence for their efficacy.[16,22] The most recent study, performed in 1982, investigated four unheated bubble humidifiers and demonstrated that none of the brands were able to provide adequate relative humidity.[22] As well, a hospital survey-based study demonstrated that patients receiving oxygen with and without bubble-type humidifiers had a similar quantity of complaints and their nasal symptoms were not alleviated with use of bubble humidifiers.[23] Unfortunately, low-flow oxygen systems that utilize standard bubble-type humidifiers do not meet guidelines for achieving levels of humidification found in the upper airway since they are unheated, and saturated water vapour pressure is dependent on air temperature.[16,24] The lack of humidity may in part explain the lack of tolerance when using higher flow rates in traditional oxygen supplementation systems.[19, 24]

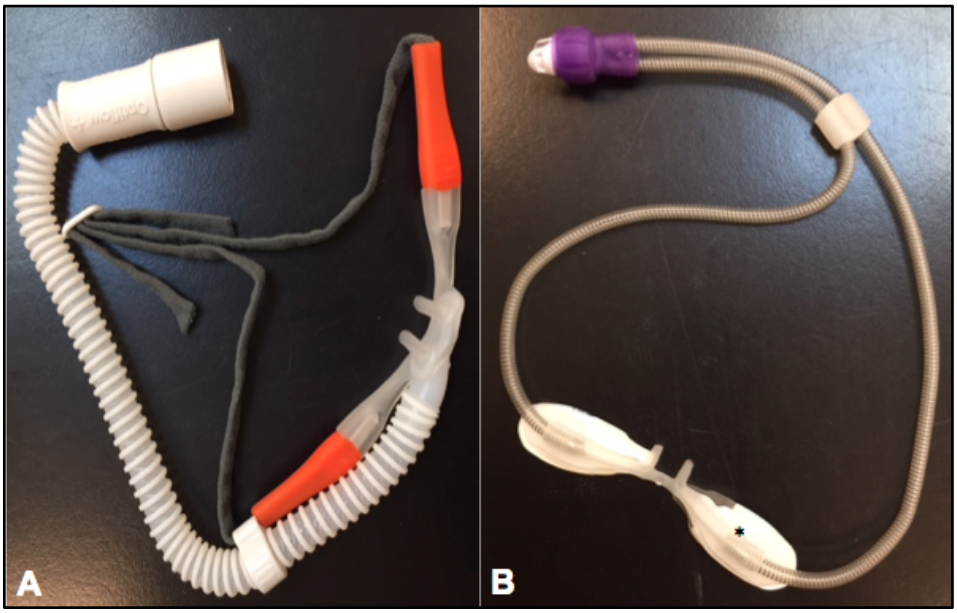
The HFNC system set-up involves the admixture of oxygen and air within the system. Depending on the type of HFNC unit, this air is either entrained from the room or provided by compressed medical air. Air is then mixed with medical oxygen by a blender. This ability to combine gases allows HFNC to provide high-flow rates at a specific and controlled FiO_2, which is set by the prescribing clinician between 0.21-1.0. This is a major benefit of the HFNC system as it allows the clinician to titrate oxygen levels to the patient's immediate needs, and may allow for reduction in the risk of oxygen toxicity with appropriate FiO_2 tracking.[19] Once the gases are blended to the prescribed FiO_2, they are

administered at the selected flow rates based on patient size. Flow meters are available to deliver both pediatric (dials up to 25 L/min) and adult (dials up to 70 L/min) flow rates, which may vary slightly depending on the manufacturer. Before delivery to the patient, the gases are heated and humidified as described above. From the humidifier, the gas flow continues toward the patient within wire-heated tubing, (similar to circuits used for mechanical ventilators), and then connects to the nasal cannula interface. There is a broad variety of nasal interface sizes to optimize fit to a wide range of patient sizes. In the pediatric HFNC set-up, a pressure-release valve must be activated at the level of the flow meter to prevent pressures within the circuit from exceeding 45 cmH_2O and inappropriate exposure of infants to excessively high pressures.[25] The importance of a pop off valve was demonstrated by a study evaluating the efficacy of this feature.[25] At a flow rate of 5-6 L/min, inactivation of the pressure-release valve resulted in pressure build up within the system leading to breakage of the tubing at the insertion to the humidifier and an acute drop in pressures within the system, as a result of the leak.[25]

High flow nasal cannulae are wide-bore binasal prongs made of silicon (Figure 2), that have a simpler interface than nasal CPAP modalities.[d,18,27] Nasal prong selection should aim to occlude no more than 50% of nare diameter.[26] It is recommended that the nasal prongs be fitted such that they are non-obstructive, having a low nasal prong-to-nare ratio, due to potential for over-pressurization of the system.[26] Fisher-Paykel prongs are unique in their configuration relative to other forms of HFNC and are made of soft silicon material, versus standard nasal prongs that are made of latex free tubing. In the Optiflow™ system, there are differences among neonatal/pediatric and adult interfaces. The neonatal and pediatric interfaces have soft adhesive pads lateral to each prong, and are known as Wigglepads™, which follow the natural curvature of the infant's face in order to reduce dislodgement.[d] The tubing of the interface runs laterally on each side of the patient's face and has a clasp that cinches the tubing in place at the back of the head. The tubing is designed to reduce condensate and kinking.[d] Depending

on the generation of prongs selected, there are four or five sizes for neonatal/pediatric human patients, each have a specified allowable flow range.[d] The adult nasal prong interface varies from the pediatric versions in that the oxygen tubing from the nasal prongs is unilateral, and remains on one side of the face prior to connecting to the adult wire-heated tubing. The prongs are supported by an elastic band around the head that secures the interface in place. The adult interface has oval-shaped nasal prong orifices that are likewise soft and comfortable.[16] They are available in three sizes that can accommodate up to 60 L/min flow rates and both interface groups have comparable efficacy and mechanisms of action.[16]

Figure 2. Fisher & Paykel Optiflow™ HFNC adult (A) and pediatric (B) wide-bore silicon binasal prongs with Wigglepads™ (*)



1.4 High Flow Oxygen Therapy - Mechanisms of Action and Clinical Effects

There are five main mechanisms that result in improved oxygenation observed with HFNC usage, however the degree to which each contributes varies from patient to patient and may depend on the cause of dyspnea.[20]

1.4.1 Washout of Nasopharyngeal Dead Space

HFNC systems provide very high flows of oxygen directly to the upper airways, flushing out the remaining gas similar to tracheal gas insufflation maneuvers. Continuously providing the nasal cavity, pharynx/larynx, and upper airways with high fresh gas flows allows the upper airways to be flooded with a controlled FiO_2 and ensures that the next inspiratory breath takes in less residual end-expiratory gas.[28,29] A study on HFNC in a lung-injured porcine model demonstrated that nasopharyngeal dead space washout occurred at 50% and 100% nare occlusion.[28] Oxygenation and ventilation were improved in a flow rate-dependent manner in this study, in both leak categories.[18, 28] Furthermore, oxygenation was more rapidly improved in the high leak scenario, likely due to the enhanced ability to flush out dead space and replace residual air with higher fresh gas flows.[18,28] Improvements in patient oxygenation and ventilation were attributed to the increased FiO_2.[28] Interestingly, nasopharyngeal washout may improve CO_2 elimination via reduction in rebreathing, and is sufficient to account for the lack of elevation in $PaCO_2$ in studies with pulmonary pathology.[18,28,30] High oxygen flow rates reduce CO_2 retention by dead space elimination, and result in increased alveolar ventilation.[18] This has been demonstrated in a human chronic obstructive pulmonary disease (COPD) model where patients received either HFNC or low-flow oxygen supplementation during exercise.[30] In this study, oxygenation was improved in the HFNC group who demonstrated a lower respiratory rate and unchanged tidal volume. The results supported enhanced oxygenation with high flows. In addition, these patients were able to exercise longer and did not have changes in arterial CO_2 despite less frequent respiration.[30]

1.4.2 Reduced Inspiratory Resistance

The nasopharynx has an intrinsic distensibility that varies with the phase of spontaneous respiration. The boundaries of the upper airway are pulled inward during inspiration offering some resistance to breathing.[29] With the application of high gas flows, this resistance may be reduced especially where the HFNC flow rate is set to exceed the patient's peak inspiratory flow rate (PIFR). In a study of healthy adults exercising with a HFNC, patient FiO_2 approached the prescribed HFNC-delivered FiO_2 when gas flow rates were higher than PIFR, that is, higher flow rates resulted in a higher FiO_2 as well as positive airway pressure.[27] The effects of nasal CPAP in neonates have been shown to reduce total airway resistance by 60% due to mechanically splinting the supraglottic region open as a result of the continuous positive pressure.[31] The application of CPAP is the current standard recommendation for delivery of NIV in human patients with mild to moderate respiratory distress.[29] High flow nasal cannula therapy provides CPAP to human patients by providing high flows that stent upper airways open, rather than applying pressure.[29] Differences between HFNC use and nasal CPAP on inspiratory resistance have been explored in neonatal and adult human medicine. Saslow et al. investigated nasal CPAP versus HFNC use in preterm neonates, and found both systems reduced work of breathing (WOB) equally, based on pulmonary mechanics, without a change in respiratory rate or tidal volume.[32] In this study, although HFNC therapy at 5 L/min reduced WOB similar to treatment with nasal CPAP at 6 cmH_2O, the effects were more likely caused by a mechanism other than distending pressure since HFNC patients demonstrated lower esophageal pressures despite the noted equivalency in reduction of WOB.[32] Evidence of an alternate mechanism has been demonstrated in a sleep study of healthy adults and in vitro with a nasal cavity model to evaluate pressure and flow characteristics, wherein HFNC use increased expiratory resistance while decreasing inspiratory resistance but CPAP did not alter respiratory resistances relative to normal breathing.[33] These findings support that flow dynamics between HFNC systems and other NIV support systems differ. In the

case of HFNC therapy, lowering of inspiratory resistance seems to play a larger role in converting the normal negative inspiratory pressure to above atmospheric pressure, thus reducing inspiratory resistance.[33]

1.4.3 Enhanced Mechanics Due to Warming and Humidification

High flow nasal cannula oxygen modalities utilize the normal anatomy of the patient, but provide preconditioned gas to improve tolerance of the high flows at the level of the upper airway. The normal function of the nasal passages is to warm and humidify air to 37°C with 100% humidity as well as to prevent foreign material/pathogens from entering the body playing an important role in defense mechanisms.[2,18] Direct application of oxygen into the nasal cavity can lead to discomfort due to dryness and potentially erosions, with subsequent infection and epistaxis as possible sequelae.[35] A study in 30 neonatal human patients weaned from MV to either high flows of unheated, unhumidified oxygen or a HFNC, demonstrated that there were significantly decreased nasal mucosal scores after 24 hours using a HFNC when compared to mean scores for unheated, unhumidified high-flow oxygen (scores 2.7 vs. 7.8 respectively; p=<0.0005, maximum pathology score = 10).[34] Additionally, no patients receiving HFNC therapy 'failed' extubation in the first 24h, while seven patients failed when receiving unheated, unhumidified high gas flows.[34] Five of these seven high-flow failures were rescued successfully with a HFNC and two required reintubation.[34] Overall, the HFNC outperformed high-flow oxygen that was not preconditioned with respect to nasal mucosal health and averting reintubation.[34]

Beyond supporting the upper airways, preconditioning of inspired gas has been suggested to potentially improve pulmonary compliance. In the study by Saslow et al. where work of breathing was evaluated in preterm infants with nasal CPAP (6 cmH_2O) versus HFNC (5 L/min = ~3 L/kg/min), HFNC use resulted in significantly improved pulmonary compliance and equivalent improvements in WOB.[32] This study established that both inspiratory resistance and compliance were improved with the use of a HFNC at higher flow rates, and

that HFNC therapy could provide a comparable level of support to infants compared to the standard of care nasal prong CPAP system.[32]

The nasopulmonary bronchomotor reflex is a physiologic response to cold irritants wherein activation of cold receptors or osmoreceptors induces bronchoconstriction, and has been reported in both people and animals.[36,37] Using a heated, humidified respiratory support system can decrease this response and limit not only discomfort but, increased resistance to breathing. In a study of healthy adults breathing cold dry, only dry, and only moist air, airway resistance was significantly increased when breathing cold dry, and only dry air.[36] The magnitude of increase in airway resistance was proportional to the degree of air cooling and was a result of the nasopulmonary bronchoconstrictor reflex.[36] Though the prevention of cold-induced bronchospasm and elevated airway resistance from dry gas supplementation have not been conclusively proven as the reason for improvements in work of breathing with HFNC systems, they are likely major contributors to the success of this new oxygen supplementation modality.

1.4.4 Reduced Metabolic Cost of Preconditioned Gas

In critically ill patients, energy requirements are often higher than normal, especially in patients with high work of breathing. High flow nasal cannula oxygen therapy has been shown to improve the energy demands via preconditioning of the respiratory gases.[29] Ambient air is generally considered to be 21°C and have 50% relative humidity.[29] The nasal passages warm and humidify this air to physiologic conditions expending 150 calories per minute to condition the gas when breathing with a normal tidal volume and respiratory rate of 12 breaths per minute, in adult humans.[29] Although the airways may be efficient in capturing heat and moisture on expiration, there remains a cost to conditioning gas for comfortable spontaneous breathing.[29] When gas is provided to the patient under colder/drier conditions (as with supplemental oxygen), the patient's nasal mucosa has to produce the heat energy to condition this gas to a

physiologic state, resulting in a metabolic cost to the patient.[29] In a neonatal study comparing weaning from respiratory support, HFNC therapy applied as part of an early extubation protocol versus a nasal CPAP system, improved growth was documented in the HFNC group.[38] In this study, discharge weights were significantly higher in the HFNC group despite similar gestational ages and similar feeding practices.[38] Poor growth is often observed in infants with acute severe lung disease requiring ventilation.[38] Moreover, the degree of respiratory dysfunction is correlated with oxygen consumption, likely due to both the increased need for oxygen and higher work of breathing.[38] The authors of this study speculated that since the children appeared to have a lessened work of breathing, that their energy demands were lower, allowing for improved weight gain and growth.[38] Although improving energy demands of the body may not be the paramount benefit of HFNC systems (distending pressure is thought to be to be its largest benefit), any advantage to the critically ill small patient should not be overlooked.

1.4.5 Provision of Positive Airway Pressure

The major benefit of using HFNC therapy has been the provision of positive airway pressure (PAP) with a more comfortable interface.[19,39] Continuous positive airway pressure is the mainstay of NIV but, its provision by a facemask interface limits speaking, eating/drinking, etc. and its administration by NIV nasal prongs has been associated with discomfort and damage to the mucosa.[9,10,19] High flow nasal cannula therapy can offer similar benefits to use of nasal CPAP systems and many studies have demonstrated that both treatment modalities have similar outcomes but, with improved comfort when HFNC support is utilized.[32,38]

High flow nasal oxygen supplementation results in PAP as a direct result of the constant administration of high gas flow into the airway, producing resistance to exhalation.[27,33] This was demonstrated in a study by Ritchie et al.

where oropharyngeal airway pressures were measured in healthy human adults by a sampling catheter. In this study, there was a flow-dependent increase in airway pressure, and at 50 L/min (~0.7 L/kg/min) mean attainable airway pressures were 7 cmH_2O.[27] The significance of PAP associated with HFNC use relates to the fact that various forms of positive pressure application are central to treating many hypoxemic conditions. Positive end-expiratory pressure (PEEP) is fundamental to success in mechanically ventilating patients, and is a ventilator setting that is frequently adjusted in order to improve oxygenation and prevent alveolar inflammatory injury.[40] Moreover, many hypoxic conditions lead to alveolar collapse and the provision of constant pressure to the lungs maintains alveolar integrity, subsequently allowing for more effective ventilation.[29] Positive end-expiratory pressure not only prevents alveolar collapse, but facilitates recruitment of diseased alveoli further improving gas exchange.[40] If PAP provided by HFNC use is effective down to the level of the alveoli, it may approximate provision of PEEP via constant high-flows, and could be administered in a non-invasive manner.[20,29]

Esophageal pressure has been widely used as a surrogate for pleural pressure, which is one method used to accurately titrate PEEP settings in mechanically ventilated people.[40] Tailoring provision of PEEP helps to prevent both over-distension (excessive PEEP) or collapse of alveoli (insufficient PEEP), thus improving oxygenation and possibly ventilation while minimizing potential complications of MV.[40] Given the use of pleural and transpulmonary pressure approximations in MV, Rubin et al. measured esophageal pressures, defined as the pleural pressure at end-expiration, while delivering HFNC flows at 2, 5, 8 L/min in infants.[41] This study demonstrated higher baseline esophageal pressures at 8 L/min relative to lower flow rates, indicating generation of positive pressure by higher HFNC flow rates.[41] Additional studies have used measurement of oropharyngeal or tracheal pressures to assess PAP (and approximate PEEP) given the invasive monitoring required to measure pleural pressures in dyspneic patients. Consistent amongst these studies, is the finding

that the level of PAP is dependent on flow rate.[27,28,39,42] In a human study with healthy volunteers, for every 10 L/min increase in flow rate, pharyngeal pressures increased by 0.5-1.0 cmH_2O in a linear fashion,[42] and by 0.7 cmH_2O in another.[43] In a porcine lung injury model, HFNC use at flow rates of 2-8 L/min provided a linear increase in PAP of approximately 2-5 cmH_2O and these pressures were comparable to CPAP pressures at the same flow range.[28]

While studies in people have demonstrated that provision of PAP occurs with HFNC systems, concerns exist regarding how different patterns of breathing such as open-mouth versus closed-mouth respiration, and leak conditions may affect this main reason for improvement in the patient's work of breathing. In a pilot study of healthy volunteers, clinically relevant mean PAP values were achieved with closed mouth respiration and a linear increase in PAP was seen as the flow rate increased.[27] For example, at 30 L/min the PAP was 3 cmH_2O, at 40 L/min PAP was 4 cmH_2O and at 50 L/min PAP was 5 cmH_2O.[27] In another study of adult volunteers using pharyngeal pressure measurements, significant positive expiratory pressures were likewise noted in a flow rate-dependent manner, and expiratory pressures were significantly higher with mouth-closed versus mouth-open respiration (5.5 cmH_2O vs. 2.2 cmH_2O) at 40 L/min.[42] This latter study also noted that expiratory pressures were higher in female subjects likely due to smaller facial features.[42]

The hypothesis that smaller nasal anatomy increases the upper airway pressure generated by HFNC has also been found to be true based on a study of preterm infants. In this study specifically, for every 1 kg increase in infant body weight, pharyngeal pressure decreased by 1.4 cmH_2O.[44] Further, the feasibility of providing CPAP with median flow rates of ~2.5 L/kg/min was demonstrated, although positive airway pressure was noted as low as 1 L/kg/min.[44] Interestingly, this study found no difference in PAP with passive mouth position and mouth closure.[42] Neonates are obligate nasal breathers and it is postulated that relative to nasal leak, escape of air at the level of the mouth has a minimal role.[42] With respect to leak, a porcine study compared low versus high leak scenarios at the

level of the nasal prongs and, as expected, found that tracheal pressures were lower in the high leak condition.[28] It must be noted that in studies where upper airway pressures are lower when leak conditions are higher, high leak conditions still demonstrate PAP.[28,42] More importantly, the high leak condition is a main requirement in fitting of the nasal prongs for HFNC since it is required for passive removal of CO_2.[28]

Only one small animal veterinary study currently exists assessing HFNC use and the potential for positive airway pressure. In this study of six dogs undergoing prophylactic dentistry, a HFNC was applied at 20 and 30 L/min in dogs weighing 17-36 kg (using the Vapotherm® system) and transpulmonary pressure was measured with use of an esophageal balloon catheter.[45] There was no significant change in transpulmonary pressure with use of the HFNC system at the flow rates selected.[45] Given the small sample size and limited flow rates used, it is difficult to say whether PAP provision occurs in canine patients without further investigation.

It is clear that HFNC systems have been demonstrated to provide PAP in people. Use of nasal CPAP and HFNC both provide PAP, though by different mechanisms.[33] The latter provides PAP mainly by increasing expiratory resistance via a jet-flow effect that results in a pressure gradient from the high flow rates, and thus, higher expiratory pressures at the upper airway.[33] Ultimately, despite the variation in how a HFNC may achieve PAP relative to other NIV therapies, it is a well accepted mechanism that HFNC use offers positive distending pressure.[29] Whether this PAP can be translated down to the level of the alveoli has been more difficult to determine. The possibility for the non-invasive provision of PEEP has been suggested. Indeed one study has demonstrated that airway pressure correlates with end-expiratory lung volume (EELV) measured by electrical impedance tomography.[46] When compared to low-flow oxygen therapy, HFNC oxygen delivery increased EELV by 25% and airway pressure by 3 cmH_2O, while reducing respiratory rates, improving oxygenation, and reducing dyspnea scores.[46] For this reason, HFNC systems

have been used extensively for provision of PAP in acute hypoxemic respiratory failure.

1.5 Acute Hypoxemic Respiratory Failure & HFNC Therapy

Acute hypoxemic respiratory failure (AHRF) is defined as a new or acute worsening of a respiratory condition within less than one week, elevated respiratory rate, normal $PaCO_2$, and the presence of hypoxemia despite provision of traditional oxygen therapy.[47,48] In people experiencing AHRF, the rate of NIV treatment failure can be up to 50% necessitating endotracheal intubation and mechanical ventilation. This failure rate has lead to research into alternatives with improved outcomes/less requirement for MV, such as HFNC systems.[48] Several etiologies of AHRF have prompted investigation into the utility of HFNC use and will be discussed independently below. Studies commonly compare HFNC use to other NIV or oxygen supplementation modalities while reporting primary outcomes such as need for intubation, mortality rates, and improvements in respiratory parameters. Secondary outcomes of comfort and dyspnea scoring are often also reported.

1.5.1 Use of HFNC Oxygen Therapy in Dogs with AHRF

To date, the veterinary literature that reports on use of HFNC devices is limited to one pilot study in healthy dogs, one retrospective AHRF case series, and one AHRF prospective clinical trial which is currently only available as an abstract.[45,49,e]

A pilot study in six healthy dogs demonstrated that the Vapotherm® HFNC device appeared to be a safe and effective method for increasing PaO_2 in dogs.[45] The same group published a retrospective study assessing the use of HFNC in six hypoxemic canine patients that failed traditional oxygen supplementation.[49] High flow nasal cannula therapy significantly improved arterial oxygen tension with a median PaO_2 of 134 mmHg versus 62 mmHg with traditional oxygen supplementation by nasal cannula or oxygen cage.[49] Median HFNC flow rates

used in this study were 0.7 L/kg/min and were compared to traditional oxygen flow rates of 0.1 L/kg/min.[49]

More recently, this same group presented and published an abstract at the 22nd International Veterinary Emergency and Critical Care Symposium regarding the impact of HFNC oxygen administration in 20 hypoxemic dogs failing traditional oxygen supplementation.[e] They noted that all 20 dogs initially demonstrated an improved PaO_2, SpO_2 and respiratory rate, when HFNC was initiated, however 6/20 dogs required escalation to invasive MV, and 9/20 dogs receiving HFNC therapy survived to discharge.[e]

1.5.2 Use of HFNC Oxygen Therapy in People with AHRF

Due to the very minimal amount of research on HFNC systems in dyspneic dogs, evidence of the utility of HFNC support in AHRF will be reviewed based on evidence in the human literature.

Congestive Heart Failure

High flow nasal cannula oxygen supplementation has been explored as a means to improve comfort and stabilization in patients with dyspnea due to acute congestive heart failure. In a randomized controlled trial comparing conventional oxygen supplementation and HFNC support in patients presenting to an emergency department (ED) with cardiogenic pulmonary edema, respiratory rates were significantly lower in the HFNC group, at 15 and 30 minutes post-intervention.[50] Delivered flow rates in this study were 0.5-1 L/kg/min.[50] Hyun Cho et al. used similar flow rates in a retrospective study assessing AHRF of various causes. This study found that the use of a HFNC to avoid intubation in cases of cardiogenic pulmonary edema was 81%, which was significantly greater than patients with other conditions.[51] In this study, the overall success of HFNC oxygen supplementation in avoiding intubation was 63% and the improvement in PaO_2 at one and 24 hours post-HFNC use was associated with its success.[51] It was postulated that a modest level of PAP provision by HFNC systems was responsible for success in cases of congestive heart failure.[51] This low level of

pressure is not unlike application of CPAP in these cases, which has been used to effectively treat cardiogenic pulmonary edema.[51]

Improvement in cardiac function with the use of HFNC systems has also been demonstrated.[51,52] A 2013 prospective study by Roca et al. demonstrated that HFNC delivery at 20 and 40 L/min in ten patients with New York Heart Association class III heart failure (marked physical limitations but, comfortable at rest; 8 diagnosed with dilated cardiomyopathy), reduced respiratory rates, and decreased median inspiratory collapse of the inferior vena cava relative to baseline on assessment by transthoracic echocardiography.[52] This demonstrated that HFNC therapy provided an improved measure of preload, and removal of HFNC support reversed this positive effect.[52] While HFNC oxygen supplementation may have a clear benefit in comfort and pulmonary parameters, it may also have a role in improving cardiac function as part of the stabilization protocol for heart failure patients.

Pneumonia

High flow nasal cannula therapy has been used for treatment of patients with respiratory infections, resulting in avoidance of intubation in 60% of these acutely hypoxemic patients.[51] In a cohort of people with AHRF from influenza, HFNC oxygen supplementation was successful in 45% of patients that failed to maintain an SpO_2 above 92% with traditional oxygen administration.[53] Similar to the early improvement of PaO_2 in acute congestive heart failure, lack of acceptable improvement in oxygenation, i.e. PaO_2:FiO_2 (in particular ratios <100) was an indicator of potential failure with HFNC therapy.[53] The need for vasopressors was associated with need for intubation within 24 hours[53] and inversely associated with ICU survival.[51] A study by Sztrymf et al. determined that patients with community-acquired pneumonia were good candidates for HFNC support after lack of success with traditional oxygen therapy.[54] Seventy percent (14/20) of these patients avoided intubation with use of HFNC oxygen supplementation.[54] According to the authors of this study, it is their opinion that HFNC therapy may fall between low-flow oxygen and NIV, wherein future larger

scale trials should focus on comparing these three respiratory support modalities and their effect on subsequent need for intubation.[54]

Frat et al. completed a study in AHRF patients investigating the use of standard oxygen via facemask, NIV positive pressure ventilation delivered by facemask connected to a ventilator, and HFNC oxygen therapy.[48] This study was a prospective, multicenter, randomized trial with community-acquired pneumonia as the most common etiology of AHRF.[48] The primary outcomes were intubation and mortality rates, as well as the number of ventilator-free days.[48] Intubation rates were 50% in the NIV group, 47% in the standard oxygen group, and 38% in the HFNC group, but were not significantly different.[48] The number of ventilator free days was improved with use of HFNC and NIV.[48] Lastly, 90-day mortality rates and the severity of dyspnea were reduced with HFNC therapy.[48] Overall, HFNC therapy was as effective as NIV, but, offered improved comfort and lower mortality rates in AHRF patients presenting with community-acquired pneumonia.[48] It is uncertain whether the cause of AHRF or severity of comorbid illness may play a role in selecting the appropriate patients for use of HFNC oxygen supplementation.

Neoplasia

Respiratory failure in cancer patients is often associated with mucositis, tracheal or alveolar bleeding and the pulmonary sequelae of sepsis due to the immunosuppressed nature of these patients.[55] A study using HFNC oxygen support in between sessions of NIV found that this combination was associated with an increase in ventilator free days, less occurrence of septic shock, and improved survival relative to a combination of NIV-standard oxygen therapy or standard oxygen alone.[55] HFNC therapy was proposed to have a beneficial effect on maintenance of mucosal secretions and possible prevention of atelectasis in these cancer patients with respiratory failure.[55] Additional studies have investigated the use of HFNC oxygen therapy in patients with neoplasia, in an attempt to avoid the complications associated with invasive MV such ventilator-associated pneumonia. A retrospective study of HFNC use in patients with

hematological malignancies was conducted to determine the feasibility and efficacy of HFNC use in this immunocompromised patient population.[56] The majority of patients in this study were afflicted with acute myeloid leukemia, lymphoma or myelodysplastic syndrome and had pulmonary parenchymal disease.[56] Flow rates of approximately 30 L/min were used and the rate of HFNC failure (requiring MV) was 67%.[56] Some have speculated that selection of a lower HFNC flow rate (HFNC is commonly titrated up to a maximum of 60 L/min in adults) potentially contributed to a higher HFNC failure rate. In this study, immunosuppressant use, neutropenia, and cause of malignancy was not associated with failure.[56] Interestingly, longer length of ICU stay and bacterial pneumonia as the etiology of AHRF were significantly associated with HFNC failure.[56] Given the reported high failure rate of HFNC therapy in these cases, controversy remains regarding when to apply HFNC oxygen support and whether doing so actually delays MV, ultimately affecting mortality.

Neonatal and Pediatric Patients

Another major area of research is centered on the use of HFNC oxygen therapy in neonatal and pediatric patients with AHRF.[32,44,57,58] Bronchiolitis due to respiratory syncytial virus is a common cause of AHRF in children under two years of age; mucus plugging and subsequent airway obstruction are noted in this disease.[57] Nasal CPAP systems were previously routinely used in bronchiolitis, however infant intolerability of the obtrusive mask can be problematic.[57] Introduction of HFNC therapy to this patient population while controlling for other factors, has resulted in a 68% decrease in need for intubation.[57] With HFNC oxygen support, children experienced a significant reduction in respiratory rate at one hour post-initiation, that did not occur with other forms of therapy.[57] This early reduction in breathing rate was associated with a decreased need for intubation.[57] Given the rapidity with which infants experienced relief, researchers suspect it is due to a degree of positive airway pressure support from HFNC systems rather than thinning of secretions, which is likely to take hours to reach peak effect.[57] Given positive outcomes and

immediate improvements, HFNC oxygen supplementation improved WOB in these infants while offering a more comfortable and tolerable interface.[57]

In another large randomized, controlled trial of neonates requiring respiratory support, patients were randomized to either nasal CPAP or HFNC therapy within the first 24 hours of life or at any age at the time of extubation from MV. The overall infant mortality rate was 1% (5/432 neonates; 4/5 in CPAP group; 1/5 HFNC group); wherein the one death within the HFNC group was due to pulmonary artery hypertension.[58] Given the overall success in this study, HFNC oxygen therapy was deemed as effective and safe as NIV as a primary means of respiratory support in neonates.[58] Although concerns in the neonatal literature exist regarding the potentially high amount of distending pressure HFNC devices can provide, this study found no difference in the rate of air leak (pneumothorax) between the two groups.[58]

The utility and improved tolerability of HFNC oxygen systems in pediatric medicine has led to avid investigative interest into reforming the use of this oxygen modality in babies. Constant attention should be paid to recently published data in these patients as their size and characteristics may best approximate those of our small to medium canine patients.

1.5.3 Complications Associated with High Flow Oxygen Therapy in AHRF

Though HFNC oxygen therapy shows promise for use in a variety of causes of AHRF in many patient populations, it is not without risks. The major concern regarding high flow oxygen therapy, particularly in smaller patients, is provision of unknown levels of positive airway pressure leading to air-leak syndromes. Air-leak syndrome is a known complication of positive pressure ventilation and can manifest as pneumothorax (alveolar overdistension) or pneumomediastinum.[59] Although this is considered a rare complication of HFNC use, there is one case series of air leak syndrome in three children treated with HFNC oxygen therapy.[59] Though body weights were not provided, flow rates of

up to 20 L/min were used and thought to contribute enough PAP to cause alveolar overdistension and subsequent pneumothorax in 2 of the children with the third case developing pneumomediastinum.[59] Given the highly compliant chest wall of infants, PAP provided by the HFNC device could feasibly lead to volutrauma and barotrauma and subsequent air leak, not unlike other forms of ventilation.[59] Two large-scale randomized trials found no difference in the rate of pneumothorax using HFNC therapy (0.5% and 0.7%) versus NIV CPAP (2.0% and 2.6%).[58,60] Although the consequences of serious air leak can be catastrophic, the rate of pneumothoraces seen with HFNC oxygen supplementation and CPAP are greatly reduced relative to the incidence of 4-15% reported in mechanically ventilated people.[61]

In the limited veterinary literature, persistence of a pre-existing pneumothorax was the only complication associated with HFNC use in a case series of 6 dogs with AHRF.[49] This pneumothorax resolved when HFNC therapy was no longer needed for oxygen support.[49] In the veterinary abstract reporting on the use of HFNC oxygen supplementation in 20 hypoxemic dogs, the only noted complication was development of a pneumothorax in 1/20 dogs.[e] With HFNC therapy, there must be a balance between titration of flow rate (and thus, linear provision of positive pressure) with the potential for an air-leak syndrome to occur. Although this is a rare complication, risk:benefit rationale must be effectively communicated with owners prior to initiation of HFNC oxygen therapy.

Concerns are present in the literature regarding potential for an elevation in $PaCO_2$ with HFNC use, particularly if employing HFNC therapy in severe hypercapnia.[11,48] Due to the high inspiratory flows provided by the HFNC system, there is resistance to exhalation, which can lead to an elevation in arterial carbon dioxide, particularly in the absence of an appropriate leak. In AHRF, the risk of causing hypercapnia seems to be ameliorated by improvement in WOB or a decrease in ventilation need in hypoxemic patients due to the high inspiratory flows and nasopharyngeal washout of CO_2.[28,46] In a prospective randomized controlled trial conducted by Mauri et al., HFNC oxygen supplementation was

compared to standard non-occlusive facial mask oxygen therapy in 15 AHRF patients; there was no significant difference in $PaCO_2$ when HFNC oxygen therapy was applied.[47] The authors postulated that AHRF patients with a higher dead space fraction may particularly benefit from HFNC therapy due to washout of CO_2 from the upper airways.[47] Similarly, the study by Frat et al. comparing HFNC therapy, NIV, and traditional oxygen via facemask in AHRF, found no difference in the incidence of adverse events including change in $PaCO_2$.[48]

In the only veterinary AHRF case series, $PaCO_2$ was noted to be significantly higher when HFNC oxygen supplementation was applied compared to traditional oxygen therapy, by approximately 3 mmHg in conscious dogs.[49] However, the increase in $PaCO_2$ did not significantly affect pH, and clinically relevant changes in $PaCO_2$ were not identified.[49]

Overall, since HFNC therapy is not a primary means of ventilation, close attention must be paid to blood gas values after its initiation. While monitoring for an elevation in $PaCO_2$ is appropriate in respiratory failure patients, current evidence suggests the development of hypercapnea in AHRF patients is an unlikely complication of HFNC use.

1.6 Other Indications

Beyond the utility of HFNC oxygen therapy in AHRF, human medicine has integrated this support modality into peri-procedural protocols, weaning from mechanical ventilators, and palliative patient scenarios.

Post-extubation

The prophylactic use of HFNC oxygen therapy has been investigated in extubated post-cardiac surgical patients as a means to reduce morbidity in risky anesthetic recoveries.[46] Postoperative atelectasis and alveolar collapse are frequent sequelae in both human and veterinary anesthesia, and PAP may assist with lung recruitment after lengthy procedures. This post-extubation atelectasis can reduce functional residual capacity by 20%.[46] In a study by Corley et al., investigating use of HFNC oxygen supplementation in 20 human patients post-

cardiac surgery, HFNC support was found to increase the end-expiratory lung volume by 25%.[46] Patients in the HFNC group had a significant reduction in both respiratory and dyspnea scores as compared to patients receiving standard low-flow oxygen supplementation.[46]

In infants born very preterm (i.e. <32 weeks gestation), intubation immediately following birth is commonly employed to allow for continued pulmonary development. The standard of care for weaning from MV for these infants is transition to nasal CPAP.[60] Manley et al., demonstrated that in extubated very preterm infants, HFNC oxygen therapy is as effective as nasal CPAP for improving oxygenation, and is associated with less nasal trauma.[60] Beyond the physiologic benefits of providing PAP to post-extubation patients, HFNC oxygen therapy has been shown to have significantly better tolerance when compared to supplementation via facemask.[62] If this were translatable to animals requiring oxygen post-anesthesia, reduction in anxiety by not being made to keep their head in an oxygen mask or hood, may offer a significant advantage to patient comfort and anxiety on recovery. As well, administration of PAP via high-flow oxygen support may have a place in improving post-extubation atelectasis and desaturation, especially in dogs with pre-existing pulmonary compromise. Further, although there is no veterinary literature for this type of use of HFNC therapy, extension of its utility in post-operative airway management and oxygenation support for post-procedure brachycephalic dogs may be warranted given their propensity for upper airway obstruction on recovery. Providing PAP in the post-procedure brachycephalic dog may allow stenting of the upper airways, improving oxygenation and quicker saturation stabilization without the need for ongoing sedation or prolonged intubation.

Bronchoscopy

Bronchoscopy and bronchoalveolar lavage in people is performed for similar reasons as in veterinary medicine. It is associated with a drop in PaO_2 of 20 mmHg in an already compromised pulmonary patient, due to altered ventilation-perfusion matching from the lavage fluid and increased resistance to inspiration from the physical presence of the bronchoscope.[63] In a study of HFNC use in adult bronchoscopy, HFNC therapy at higher flow rate (60 L/min) was superior to its use at a lower flow rate (40 L/min), or oxygen via facemask.[63] Reduction in inspiratory resistance was postulated to be the source of improved respiratory function. Furthermore, prevention of bronchoconstriction and pre-warmed, humidified air providing decreased metabolic oxygen demand may offer benefit in this patient population, improving recovery.[63] Although there is no veterinary data on HFNC use in the peri-bronchoscopy period, short-term airway stabilization or use during recovery could have substantial positive impact on veterinary patient management.

Obstructive and restrictive lung disease

Chronic obstructive lung disease (COPD) is a chronic respiratory condition that presents additional physiological challenges to patients in maintenance of normal gas exchange. In obstructive lung diseases, air-trapping can increase the ventilatory demand of patients given the resistance to exhalation. In a study of COPD patients, HFNC oxygen therapy improved exercise performance and breathing patterns not only by increasing oxygenation, but likely due to reduced end-expiratory volumes.[30] While this concept is counterintuitive to previous concepts evident in AHRF, COPD offers the challenge of causing patients to have an intrinsic level of PEEP present in the alveoli, resulting in pulmonary hyperinflation.[30] The low-level of PAP provided by HFNC systems may provide dyspnea relief to patients with obstructive lung disease by matching their level of required PEEP in a more uniform fashion. Unfortunately, at this time there are no studies that have investigated the use of HFNC oxygen therapy in obstructive breathing disorders (such as asthma) in animals.

Restrictive lung disease, such as idiopathic pulmonary fibrosis (IPF), is a disease common to both people and West Highland white terriers.[64] In a study by Braunlich et al. investigating HFNC support in obstructive and restrictive lung disease, human patients with IPF had a reduction in minute volume likely attributable to the significant decrease in respiratory rate with HFNC use.[30] Interestingly, $PaCO_2$ was significantly reduced after 8 hours of conservative high-flow administration at 20 L/min in both COPD and IPF patients.[30] While improvement in breathing efficiency and reduction in metabolic energy demands likely play a role in dyspnea relief with HFNC oxygen therapy in these patients, nasopharyngeal washout of CO_2 is suspected to be the main cause of this finding.[28,30] While no studies exist investigating the use of HFNC oxygen therapy in West Highland white terriers with IPF, this study sets a precedent for exploration of its safety and utility in acute exacerbations of this disease in dogs.

Do-not-intubate status

In terminal patients, especially those with COPD and cardiac failure, NIV is standard of care for those with end-of-life directives not to be intubated.[65] The tight-fitting mask associated with NIV has been discussed as a point of contention in all dyspneic patients, but is of particular concern in distressed patients potentially facing death.[65] For this reason, Peters et al. investigated the efficacy of HFNC oxygen therapy in do-not-intubate (DNI) patients comprised mostly of patients with COPD, IPF, heart failure, pneumonia and neoplasia.[65] High flow nasal cannula oxygen therapy was well-tolerated and provided sufficient support (avoiding transition to NIV) in 82% of patients.[65] In veterinary medicine, HFNC support may likewise have a place in palliative medicine or assisting patients through their crisis when owners decline mechanical ventilation. Moreover, the improved comfort and tolerability with HFNC systems are directly in line with the fundamentals of palliative care and improved quality of life in the final stages of disease for terminal respiratory patients.

1.7 Conclusion

High flow nasal cannula oxygen therapy may have a place in veterinary medicine in diverse patient care scenarios such as crisis management of the AHRF patient, post-anesthesia/post-extubation or even as part of end-of-life care. The use of HFNC oxygen therapy in human medicine has been shown to reduce the need for endotracheal intubation and mechanical ventilation in several different clinical scenarios. However, there is minimal investigation of HFNC use in veterinary patients. Currently, the veterinary literature contains a single report of the safety of the Vapotherm® HFNC device in dogs, and no literature exists surrounding Optiflow™ HFNC oxygen therapy in dogs.[45] Likewise, though HFNC oxygen therapy using the Vapotherm® system did not demonstrate positive airway distending pressures, whether this finding differs with different flow rates or extends to other HFNC systems (eg. Optiflow™) is unknown. There is little evidence to suggest serious adverse events or complications associated with the use of HFNC oxygen therapy (eg. hypercarbia and air leak syndromes), that would preclude its implementation by veterinarians or discourage clients from this modality in the face of declining respiratory function.

Additionally, major differences exist in the timing and consequential utility of initiating HFNC therapy with respect to various disease conditions in humans. That is, should HFNC oxygen support be used only in moderate to severe hypoxemic respiratory failure and thus, act as a stepping stone to MV, or should it replace traditional oxygen therapy altogether? Though there are many unanswered questions surrounding timing and the appropriate place for HFNC use in human respiratory care, veterinary medicine first requires determination of the tolerability, feasibility and safety of HFNC systems. Secondly, evidence regarding whether this device will have an effect on improving outcome in canine pulmonary pathologies is lacking. This forms the basis of our investigation into this oxygen support system in dogs.

In our study, we have chosen to investigate the Optiflow™ HFNC system in dogs. In the first of two studies, we seek to validate the safety, tolerability and

efficacy of HFNC oxygen therapy in healthy dogs of varied sizes. Size variation is imperative, so as to determine whether CPAP can be provided by this device in dogs, and if so, at what levels and with what consequences. Subjective tolerability and respiratory score evaluation will be conducted, the latter based on a human pediatric score to determine whether the HFNC device can be integrated into clinically relevant use.[66]

The second study will be conducted as a randomized clinical trial. The first arm of this study will evaluate HFNC oxygen therapy in dogs and its effects on blood gas analysis, tolerability/dyspnea scores, and outcome in any pulmonary or systemic pathology leading to AHRF demonstrating lack of improvement with traditional oxygen therapy. The second arm will evaluate use of HFNC support systems in brachycephalic dogs or dogs with upper airway obstruction, recovering from anesthesia. Briefly, post-anesthesia brachycephalic patients pose a challenge to the small animal clinician at the time of recovery, due to their facial anatomy, which is worsened by possible inflammation to the airway as a result of intubation +/- surgery. If HFNC oxygen therapy does provide CPAP, much akin to HFNC use in human sleep apnea studies, we seek to investigate whether this device can improve blood gas parameters and recovery outcomes in these patients.

In conclusion, HFNC oxygen therapy has demonstrated improved outcomes relative to traditional oxygen supplementation in people, and may even support patients through a crisis that wish not to be intubated.[48,65] Primary mechanisms of action include preconditioning of gas, high gas flows leading to low inspiratory resistance and high dead space washout, as well as provision of positive airway pressure.[28,29] High flow nasal cannula oxygen therapy has further been shown to improve comfort scores and is simple to set-up in the emergent situation.[19] If HFNC systems can be safely and effectively used in veterinary medicine, they may have the potential for reduced financial burden for clients and thus reduce mortality rates due to euthanasia, especially in resource-limited scenarios. Ultimately, improvement in patient comfort and morbidity is paramount

to small animal critical care and our study seeks to determine whether this oxygen supplementation modality is worthy of further investigation.

1.8 Objectives and Hypotheses

In the first study, a healthy canine pilot investigation of Optiflow^{TM} HFNC oxygen supplementation, our objectives are to determine the feasibility, tolerability and effect of HFNC use compared to traditional oxygen administration on canine vital and respiratory parameters under light sedation. A second objective of this study is to identify differences in pharyngeal gas/pressures between traditional and HFNC oxygen administration in healthy dogs.

The second of two studies will be aimed at evaluating HFNC oxygen supplementation in clinical patients. Dogs experiencing primary hypoxemic respiratory failure, as well as hypoxic dogs requiring support post-extubation will have HFNC support or traditional oxygen therapy initiated. Response to therapy, including the primary outcome of oxygenation, along with change in respiratory rate, heart rate, and comfort score will be assessed. The requirement for intubation and secondary outcomes including positive response with HFNC use and survival to discharge will also be recorded. Finally, utility of HFNC use in brachycephalic dogs will be investigated with the effects on oxygenation, comfort, degree of stridor/work of breathing, and rate of respiratory complication (eg. aspiration pneumonia) in recovery from general anesthesia.

We hypothesize, in healthy research dogs, that the application of HFNC oxygen supplementation will be tolerable and safe, and provide positive nasopharyngeal pressures beyond that achieved by traditional low flow oxygen administration. In hypoxic veterinary patients, we predict that a higher PaO_2 and/or SpO_2 and a decrease in respiratory rate will be achieved using HFNC oxygen therapy when compared to traditional oxygen supplementation. In brachycephalic dogs, we hypothesize that HFNC therapy will improve oxygenation and respiratory effort in patients with upper airway obstruction on recovery from general anesthesia. Moreover, we hypothesize that there will be

no difference in the level of tolerability and safety of HFNC devices when compared to standard low-flow nasal oxygen cannula therapy, but that blood gas, vital parameters, and work of breathing will be improved with their use.

1.9 Footnotes

a. Adult nasal cannula with crush resistant oxygen tubing, Intersurgical Inc., Liverpool, NY.

b. Airlife oxygen catheter 16” 10Fr, Carefusion, Yorba Linda, CA.

c. Custom made oxygen hood, locally manufactured, Kitchener, ON.

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CHAPTER 2

Comparison of high flow nasal cannula oxygen administration to traditional nasal cannula oxygen therapy in healthy dogs

Abstract

Objective – To determine the feasibility, degree of respiratory support and safety of high flow nasal cannula (HFNC) oxygen therapy in sedated and awake healthy dogs, when compared to traditional nasal cannula (TNC) oxygen administration.

Design – Randomized experimental crossover study.

Setting – University research facility.

Animals – Eight healthy dogs.

Interventions –Variable flow rates (L/kg/min) were assessed, TNC: 0.1, 0.2, and 0.4 and HFNC: 0.4, 1.0, 2.0 and 2.5. HFNC was assessed in sedated and awake dogs.

Measurements - Variables measured included: inspiratory/expiratory airway pressures, FiO_2, ETO_2, $ETCO_2$, PaO_2, $PaCO_2$, temperature, heart/respiratory rate, arterial blood pressure, and pulse oximetry. Sedation status, complications, and predefined tolerance and respiratory scores were recorded.

Main Results - Using HFNC, continuous positive airway pressure (CPAP) was achieved at 1 and 2L/kg/min. CPAP was not higher at 2.5 than 2L/kg/min, with worse tolerance scores. Expiratory airway pressures were increased when sedated (P=0.006). FiO_2 at 0.4L/kg/min for both methods was 72%. FiO_2 with TNC 0.1L/kg/min was 27% and not different from room air. The FiO_2 at all HFNC flow rates ≥1L/kg/min was 95%. PaO_2 for HFNC 0.4L/kg/min was lower than at other flow rates (P=0.005). The only noted complication was aerophagia. $PaCO_2$ was increased with sedation and use of HFNC when compared to baseline (P=0.006; P<0.01).

Conclusions – Use of HFNC in dogs is feasible and safe, provides predictable oxygen support and provides CPAP, but may cause a mild increase in $PaCO_2$. Flow rates of 1-2L/kg/min are recommended. If using TNC, flow rates above 0.1 L/kg/min may attain higher FiO_2.

Key Words – Oxygen supplementation; high flow nasal oxygen; HFNC; non-invasive ventilation, Optiflow™

Abbreviations

Brpm	Breaths per minute
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
$ETCO_2$	End-tidal carbon dioxide
ETO_2	End-tidal oxygen
FiO_2	Fraction of inspired oxygen
Ft	Feet
HFNC	High flow nasal cannula
IBP	Invasive blood pressure
MV	Mechanical ventilation
NIV	Non-invasive ventilation
PEEP	Positive end-expiratory pressure
TNC	Traditional nasal cannula
V/Q	Ventilation / perfusion

Introduction

Oxygen supplementation is a life-saving component of the therapeutic plan for a wide range of conditions including upper airway obstruction, hypoventilation, and hypoxemic respiratory failure. The oxygen typically available in veterinary clinics, though often attached to an unheated bubble-type 'humidifier', provides cold dry oxygen gas delivered to the patient via a mask or nasal prongs. This system, if used for a prolonged period of time results in irritation to the nasal mucosa.[1,2] The traditional nasal cannula (TNC) or catheter, offers a variable fraction of inspired oxygen (FiO_2) nearing a mean of 60% at 0.2 L/kg/min.[1] Higher flow rates may not be tolerated despite clinical need for oxygen support.[1] In veterinary medicine, if oxygenation cannot be achieved with standard low-flow oxygen supplementation, mechanical ventilation (MV) is indicated to maintain normal oxygenation and ventilation parameters.

Non-invasive ventilation (NIV) systems offer an additional means of respiratory support by providing continuous positive airway pressure (CPAP) without intubation, which may mitigate the need for MV. Traditionally, non-invasive administration of CPAP involves the application of constant airflows through an interface with applied airway pressures of 1-10 cm H_2O dictated by control of an ICU ventilator or CPAP machine.[3] It is used extensively in neonatal and adult human respiratory patients.[4] Preliminary veterinary studies show that the fitting of CPAP prongs/masks to the varied facial structures of dogs and cats poses extensive difficulties with regard to tolerance.[5,6] Similar levels of anesthesia are necessitated when compared to MV, which carries a high level of risk since the airway is unprotected.[5,6]

Use of a high-flow nasal cannula (HFNC) is one method of NIV that offers superior oxygen support, and has been available in human medicine for over a decade.[2,7,8] The system involves a medical air and oxygen blender that connects to a humidifier and circuit, similar to that of mechanical ventilators. Once the air/oxygen mixture is heated and humidified, it is delivered to the patient via wire-

heated tubing and then via a soft silicone binasal prong interface that is sized to occlude approximately 50% of the nares.[2,9] The FiO_2 can be adjusted between 21-100% and flow rates can be administered at up to 25 L/min on a junior circuit, or 60 L/min on an adult circuit depending on the patient size and associated interface.[2,9] The warm, moist air, although administered at nearly 10 times the flow rate of traditional low flow systems, remains well tolerated in human patients[10] and reduces the incidence of nasal mucosal lesions in neonates.[11]

The advantage of the HFNC system over traditional systems is attributed to its ability to provide CPAP.[12, 13] This can improve oxygenation by recruiting alveoli, allowing for more efficient gas exchange and lessened work of breathing.[10,12,14,15] Improved oxygenation is also achieved as the high flow rates cause washout of nasopharyngeal dead space.[12, 13] The adjustable FiO_2 is of similar benefit to that seen on mechanical ventilators; the lowest tolerable FiO_2 can be selected, washing out less nitrogen and allowing for the alveoli to remain open, leading to improved ventilation/perfusion (V/Q) matching and respiratory parameters.[13] While the heated and humidified air increases tolerability and facilitates higher flow rates, it also improves secretion clearance and lessens bronchial hyper-responsiveness in people.[10]

Reported disadvantages of HFNC systems in people are cervico-thoracic discomfort and air-leak syndrome.[10,16] Though HFNC offers an excellent means of improving oxygenation, it has not been shown to assist with ventilation and thus, is not recommended in the hypercapneic patient population, wherein MV may be more appropriate.[2]

Non-invasive systems have been minimally explored in veterinary medicine. High-flow nasal oxygen has been assessed in a small retrospective study of 6 dogs failing traditional oxygen therapy, wherein oxygen tension was significantly improved and hypoxemia resolved in 4/6 dogs.[17] The noted complications were the requirement for mild sedation in 1/6 dogs, and persistence of a pneumothorax that resolved when HFNC was discontinued in another dog.[17] A clinical veterinary study investigating HFNC in dogs requiring

oxygen has been published in abstract form, with positive clinical results in hypoxemic patients.[a]

The objective of this pilot study was to determine whether use of HFNC in healthy dogs of varied size was feasible, tolerable and safe when compared to traditional oxygen administration via a nasal catheter. Secondary objectives included measurement of airway pressures in sedated and awake dogs, as well as determining the effect of HFNC on oxygenation, ventilation and vital parameters. The hypothesis was that the HFNC interface could be placed on and tolerated by dogs of varied canine facial structures/sizes. We also hypothesized that HFNC will produce CPAP at higher flow rates, with a more consistent FiO_2 than traditional oxygen therapy via nasal catheter.

Methods

Animals

Eight dogs were enrolled in the study, six were colony-bred research beagles and two were client-owned. Prior to study enrolment, determination of health was established using a general physical examination and quick assessment tests including: hematocrit, total solids, blood urea nitrogen stick, blood glucose, urine specific gravity, and urine dipstick, along with 2-view thoracic radiography assessed by a board-certified Diplomate of the American College of Veterinary Radiology. The study protocol was approved by the University of Guelph Institutional Animal Care and Use Committee.

Experimental Design

This was a prospective randomized crossover study performed in May 2016. High flow nasal cannula and TNC oxygen supplementation were assessed at pre-selected oxygen flow rates. Flow rates selected for TNC were 0.1, 0.2, and 0.4 L/kg/min given previous veterinary studies and clinical experience.[2] Flow rates of 0.4, 1, 2, and 2.5 L/kg/min were selected for the HFNC system, based on previous human pediatric studies[18,19] that select flow rates based on minute

ventilation using a 6-8 mL/kg tidal volume with age-specific respiratory rates.[4] Oxygen provided by the HFNC system was delivered with the FiO_2 set at 100%, to maintain equipoise and to assess the accuracy of this set point at each flow rate. Each dog received oxygen delivery via TNC, HFNC (awake), and HFNC (sedate). The order of TNC versus HFNC was randomized, as was the order of the flow rates, and the sequence of awake versus sedate. Blinding was not possible given the appearance of each system.

Instrumentation and Monitoring

Dogs were fasted for 12 hours prior to study commencement. Subjects were sedated using hydromorphone[b] (0.1mg/kg) and dexmedetomidine[c] (10-15 ug/kg intramuscularly, based on individual temperament). Ten to fifteen minutes later, a 22-Ga 1" intravenous cephalic catheter was placed for subsequent administration of dexmedetomidine[c], and a 22-Ga 1" arterial catheter was placed in the dorsopedal artery for direct blood pressure monitoring and sampling of arterial blood for analysis.

For oropharyngeal airway pressure and gas monitoring, a 10 Fr multifenestrated nasopharyngeal catheter[d] was placed using topical nasal proparacaine[e] drops. This nasopharyngeal cannula was advanced into the caudal oropharynx and confirmed to be just rostral to the larynx by oral examination using a laryngoscope. The catheter was connected to a gas analysis port of a multiparameter anesthesia monitor[f] for inspired/expired gas analysis, and the pressure transducer of a multiparameter intensive care monitor[g] for airway pressure measurements.

Calibration. Daily calibration was performed for the HFNC FiO_2 measurement (at 21%, 60%, and 100% to within +/- 3% per manufacturer's instructions using an oxygen analyzer[h]). The airway pressure transducer was also calibrated daily using a test lung and a mechanical ventilator[i] with pressures set at 2, 5, and 10 cmH_2O. If the measured PEEP was within 0.9 cmH_2O of the set PEEP, the system was considered acceptably calibrated. Calibration of the

arterial blood pressure monitor and airway gases was completed at the commencement of the study.

Traditional nasal cannula. During TNC oxygen administration, a second 10 Fr multifenestrated nasal oxygen cannula[d] was placed in the opposite naris using topical proparacaine[e] drops and secured with the tip of the catheter placed to the level of the medial canthus of the eye. The nasal cannula was connected to a 25ft oxygen line attached to a standard flow meter (maximum 15 L/min) with an in-line, prefilled, sterile water bubble humidifier.[j]

High-flow nasal oxygen therapy. The HFNC oxygen was provided using the Optiflow™ system.[k] The interface consists of soft silicone bilateral nasal prongs with tubing that connects to the circuit either around the head for junior interfaces (Figure 1) or to the side of the face for adult interfaces (Figure 2). During HFNC oxygen administration, the nasal prongs were fitted over the single nasopharyngeal multifenestrated catheter.[d] Nasal prongs are available in seven sizes (3 adult, 4 junior) with the Optiflow™ system.[k] The largest size that occluded 50% of the nares was selected for each subject. Circuit tubing (adult vs. junior) was mandated based on the nasal prong size selection. If the nasal prongs were not seated appropriately, modeling clay was adhered to the interface, using Krazy Glue,[h] to better seat the prongs (Figure 2). A simple interrupted suture secured the tubing of the nasal prongs to the lateral aspect of the dog's face, just rostral to the zygomatic arch.

Data Collection

Immediately after instrumentation, baseline vital parameters, airway pressure and gas values, as well as tolerance and respiratory scores were recorded. Equilibration at each flow rate occurred for 8 minutes prior to each subsequent recording. Flow rates were reduced to 0 for a minimum of 30 seconds between flow rates based on previous findings.[1] Each flow rate is referred to as a trial.

Airway pressure waveforms were visually monitored throughout pressure analysis. Measurements were recorded in duplicate when airway pressure waveforms were clearly visualized. When aberrant airway pressure waveforms were present (due to condensation and/or oropharyngeal secretions), a 20-mL air-filled syringe was rapidly evacuated three times into the nasopharyngeal cannula until the waveform normalized.

At the time of airway gas recording, a rectal temperature was taken and an arterial blood gas sample was collected into a heparinized syringe and immediately analyzed by a blood gas analyzer.[m]

Throughout the sedated phase of the HFNC study, an intravenous bolus of 2 ug/kg of dexmedetomidine was used for top-up sedation as needed. Animals were considered to have an awake status if they were able to hold their head up, sit sternal or stand. Atipamezole[n] and naloxone[o] were administered only if subjects were not able to stand or sit sternal when the awake phase of the study was commenced.

Scoring Systems. A predefined qualitative interface tolerance score was established for tolerance of the system (Table 1). A respiratory score was also adapted from a previously established human pediatric score,[20] to characterize noticeable changes in respiration (Table 2). Both scores were completed at the end of each data collection trial. If a study subject was unable to complete a trial at one flow rate, the highest score was assigned for both scores i.e. a tolerance and respiratory score of 3/3.

After completion of HFNC trials (all flow rates, both awake and sedate) each dog underwent 2-view thoracic radiography (with the field extended to include the stomach). A Diplomate of the American College of Veterinary Radiology evaluated post-HFNC thoracic radiography.

Statistical Analysis

For all parameters of interest, three models were applied and run using standard statistical software.[p] For the first model, HFNC at all flow rates was evaluated with ANOVA, with fixed effects of sedation and flow rate, as well as their interaction. In model two, ANOVA was applied with fixed effects of device rate (TNC 0.4, HFNC 0.4, HFNC 1, HFNC 2) and sedation as well as their interaction, and used to determine any significance in effect of the parameters. The third model was a one-way ANOVA comparing flow rates within TNC and the effect on the parameters of interest. Tukey adjustments were performed if the overall F-test was significant for main effects with more than two levels. Data was checked for normality with Shapiro-Wilk test as well as examination of the residuals. To improve normality, data was log-transformed when necessary.

Sample size determination. Oropharyngeal pressures and partial pressure of oxygen (PaO_2) between HFNC and TNC groups were expected to be markedly different based on human studies.[14,21,22] Power analysis was run on the parameter with the smallest difference (pharyngeal pressures) between TNC and HFNC.[27] A power of 98% was achieved with 5 animals. Eight dogs were selected in case the data was not normally distributed. Other outcome measures (PaO_2 and nasopharyngeal FiO_2) were anticipated to have larger differences and minimal variation such that power would only be increased. All calculations were performed with an alpha = 0.05.

Results

Eight dogs were used in the study: 4 intact males, one castrated male, and 3 spayed females. Breeds included six beagles, one Rhodesian ridgeback, and one Springer spaniel. Dogs were between the ages of 1 and 12 years of age, and weighed between 9.3 and 33.6 kg. Preliminary thoracic radiography was normal in 7 dogs, with one 12-year-old intact male beagle having a mild cranioventral interstitial pattern consistent with chronic bronchial disease,

deemed to be within normal limits for his age group, and thus was included in the study.

Data was collected from eight dogs at all TNC flow rates for a total of 24 trials. Seven dogs were trialed at all 4 HFNC flow rates while both awake and sedate. The first study subject received all four flow rates only while sedate due to laboratory timing at the initiation of the study. A total of 60 HFNC trials were completed with 15 trials per flow rate. For statistical analysis, when comparing TNC and HFNC at 0.4 L/kg/min, 15 HFNC trials (7 awake, 8 sedate) were compared to 8 TNC trials (1 sedate, 7 awake), forming an incomplete block design and leading to analysis being completed in 3 models.

Interface Fitting, Feasibility, and Scoring Systems

Three subjects were fitted to the junior interface and a junior circuit. Five subjects required an adult circuit (4 adult small, 1 adult medium). Modeling clay was placed under the nasal prong interface in all dogs wearing an adult interface. No adjustments were needed for the junior interface, which consistently remained in place.

TNC was well tolerated at all flow rates (Table 3). HFNC flow rates of 0.4 and 1 L/kg/min were well tolerated, 2 L/kg/min was acceptably tolerated, and a flow rate of 2.5 L/kg/min was not well tolerated (Table 3). The HFNC junior interface was well tolerated with only 2 dogs pawing at the interface at all flow rates assessed throughout the study. Tolerance was not significantly different in dogs receiving HFNC awake versus sedate.

Respiratory scores were higher for flow rates at or above 2 L/kg/min (Table 3). At flow rates of 2.5 L/kg/min dogs had a change in respiratory pattern, and 2 dogs developed deep breathing at 2 and 2.5 L/kg/min, and only 1 dog at 1 L/kg/min.

Sedation Status

The heart rate and systolic, diastolic, and mean arterial pressures were lower when the dogs receiving HFNC were sedated ($P<0.001$, $P= 0.002$, $P=0.003$, $P<0.001$ respectively). Sedated dogs receiving HFNC also had a

significantly lower respiratory rate with a mean of 18 brpm while sedated and 35 brpm in awake dogs (P=0.045). In 7 of 35 awake trials, dogs were panting. $PaCO_2$ was found to be significantly higher when dogs were sedated (39.0-72.7mmHg) than when dogs were awake (39.2-63.8mmHg) (P=0.0063). Expiratory airway pressure was significantly lower when dogs were awake (0-9.5 cmH_2O) versus sedate (0-12.9 cmH_2O) (P = 0.006).

Vital Parameters

Other than sedation effects, there was no significant difference in respiratory rate, heart rate, blood pressure, pulse oximetry, and temperature due to using HFNC or TNC.

Airway Pressures

Mean inspiratory and expiratory airway pressures for dogs receiving TNC at 0.1, 0.2 and 0.4 L/kg/min are provided in Tables 4 and 5 respectively. Airway pressures returned to 0 cmH_2O during the respiratory cycle in 7 out of 8 dogs during each TNC flow rate trial. One dog (the largest dog) had a continuous positive airway pressure of 1.4 cmH_2O during administration of TNC flow rates of 0.2 and 0.4 L/kg/min.

Mean inspiratory and expiratory airway pressures for dogs receiving HFNC at flow rates of 0.4, 1, 2, and 2.5 L/kg/min are provided in Tables 4 and 5, respectively. Of the dogs receiving HFNC flow rates of 1 and 2 L/kg/min, 7/13 and 13/15 dogs respectively, maintained airway pressures above 0cmH_2O and achieved CPAP on graphic assessment, whether awake or sedate (Table 6).

When TNC and HFNC were delivered at equal flow rates (0.4 L/kg/min), airway pressures were not significantly different between devices (inspiratory P= 0.31; expiratory P=0.51).

When HFNC flow rates were compared to each other, inspiratory and expiratory airway pressures were significantly increased as the flow rate was increased from 0.4 up to 2 L/kg/min (Tables 4 and 5).

Oxygenation

For dogs receiving TNC, the FiO_2 was significantly higher than baseline when flow rates of 0.2 and 0.4 L/kg/min were delivered ($P<0.001$ and $P<0.001$ respectively), however no significant difference was noted between room air and TNC delivered at 0.1 L/kg/min. The FiO_2 was significantly increased as the flow rate was increased (Table 7). At all flow rates, PaO_2 and ETO_2 were higher than baseline ($P <0.010$). ETO_2 increased with higher flow rates ($P<0.05$). No further increase in PaO_2 was noted at flow rates of 0.2 and 0.4 L/kg/min ($P=0.14$).

For dogs receiving HFNC, all flow rates produced significantly higher FiO_2, PaO_2, and ETO_2, when compared to baseline ($P<0.001$). FiO_2 values for dogs receiving HFNC at all flow rates are provided in Table 7. The FiO_2 was significantly increased as the flow rate was increased (Table 7). The PaO_2 ranged between 360-429mmHg at 0.4 L/kg/min, and was between 474-564mmHg at all other HFNC flow rates. The ETO_2 ranged between 68-77% at 0.4 L/kg/min, and between 85-98% while on all other HFNC flow rates. PaO_2 and ETO_2 were significantly lower at 0.4 L/kg/min when compared to higher HFNC flow rates ($P<0.010$).

No significant differences in PaO_2, ETO_2, and FiO_2 were found between HFNC and TNC at 0.4 L/kg/min.

Ventilation

No significant differences were noted in $PaCO_2$ or $ETCO_2$ during TNC at all flow rates.

During HFNC, $PaCO_2$ was significantly lower at baseline relative to all HFNC flow rates and higher when sedated ($P < 0.010$ and $P <0.006$). $ETCO_2$ was lower at 2.5 L/kg/min than at all other flow rates ($P <0.010$), but there was no difference in $ETCO_2$ when 0.4, 1, and 2 L/kg/min were compared.

When TNC and HFNC were both delivered at 0.4 L/kg/min, no differences were noted in $PaCO_2$ or $ETCO_2$.

Complications

Aerophagia was noted on thoracic radiographs in 8/8 dogs on completing HFNC oxygen administration. Air-leak syndrome (e.g. pneumothorax or pneumomediastinum) was not noted in any dogs. In 2 dogs at initiation of HFNC at 2 and 2.5 L/kg/min, systolic and mean arterial blood pressure were noted to drop, but remained within reference intervals, and were not significantly different from other flow rates.

Discussion

This pilot study demonstrated that the Optiflow™ HFNC system is feasible to use in healthy dogs of varied body sizes and facial conformation. The junior interface required no adjustments and accommodated the facial structure of dogs well, with excellent tolerance in adult healthy dogs. A suture on each side of the muzzle kept the interface well secured. The dogs were able to move and behave normally and the nasal prongs did not move out of place. In the adult interface design, a suture to secure the one-sided tubing at the zygomatic arch and a small quantity of malleable modeling clay at the nasal philtrum were necessary to support the weight of the system and adapt the system to the canine face. With these simple adjustments, the dogs could move their heads, sit and stand, similar to their smaller counterparts with the junior interfaces.

For HFNC delivery, this study found that at flow rates above 2 L/kg/min, dogs became much less tolerant of the system and respiratory scores were higher. In human medicine, HFNC therapy is classified as humidified, heated blended air/oxygen delivered at flow rates of 2-8 L/min (~0.4-3.2 L/kg/min) in neonates and 15-60 L/min (~0.2-1 L/kg/min) in adults.[11,23] In our study, the flow rate of 2.5 L/kg/min was trialed as a maximum rate tested to determine the safety profile of this new device in healthy dogs. Given the level of mild intolerance associated with 2 L/kg/min and severe intolerance when trialed at 2.5 L/kg/min, a flow rate between 0.4-2 L/kg/min is recommended for use in clinical dogs,

starting at lower flow rates and titrating up to the maximal tolerated rate. This finding is in accordance with many current pediatric HFNC studies.[18,24] However, further clinical trials are needed, as it is possible that patients in respiratory distress may tolerate the system better due to lessened work of breathing and improved oxygenation.

Our study demonstrated that CPAP is achieved in a flow rate-dependent manner with HFNC in dogs. These findings are similar to human studies in adult healthy volunteers.[13] At lower flow rates, airway pressures were noted to return to 0 cmH_20 during the inspiratory phase of respiration in our study dogs. Once 1 L/kg/min was administered, approximately half of our dogs maintained airway pressures above 0 throughout the respiratory cycle, and at 2 L/kg/min nearly all dogs had continuous positive airway pressures.

Human studies have assessed HFNC in healthy subjects under various conditions such as at rest and when exercising, to mimic the effects of HFNC for patients with respiratory disease.[21] Mouth open respiration is associated with a decrease in the degree of CPAP achieved. One adult human study looking at 0.6 and 1 L/kg/min oxygen flow rates reported mean positive airway pressures of 2.2 and 2.7 cmH_2O, respectively during mouth-open respiration versus 5.5 and 7.4 cmH_2O with closed-mouth respiration.[13] In our study design, we made an attempt to create experimentation conditions where airway pressure could be assessed while awake (and possibly open-mouth breathing) and sedated (closed-mouth breathing). In our study, slightly lower expiratory airway pressures were noted in awake dogs. Though not all dogs could be made to breathe with their mouths open, respiratory rates were significantly higher when dogs were awake. In the dogs that were noted to pant, an undulating airway pressure waveform was identified; inspiratory pressure would return to zero, however, during expiration the airway pressure would still reach 5.4 cmH_2O at 2.5 L/kg/min. Mean airway pressures, though not measured in this study, are expected to be greater than 0, suggesting that CPAP could be achieved in dogs with open mouth breathing due to respiratory distress. Previously reported benefits of positive pressure

application within an oxygen support system have included reduced airway resistance and work of breathing, as well as improved oxygenation with V/Q matching.[13] The airway pressure results from this study support the application of HFNC to provide positive airway pressure to dogs with respiratory disease, with titration of flow rates in an attempt to provide increasing airway pressures. Although flow rates above 2.5 L/kg/min may provide higher airway pressures, a significant increase in airway pressure was not achieved compared to a flow rate of 2 L/kg/min and the latter was consistently better tolerated. At the lowest HFNC flow rate, HFNC did not provide significantly higher positive airway pressures when compared to traditional oxygen supplementation. Within the flow rates assessed, TNC did not produce significantly higher pressures in a flow rate-dependent manner, although TNC was not tested at rates above 0.4 L/kg/min. Previous literature indicated lack of tolerance above this rate, though this may not be directly comparable given bilateral nasal cannula oxygen administration was not assessed.[1]

Superior oxygen support is one of the major indications for implementing HFNC over conventional oxygen therapy. The FiO_2 values recorded with TNC oxygen supplementation were unpredictable. Despite FiO_2 increasing with increasing TNC flow rates (ie. 0.4 L/kg/min), the FiO_2 remained highly variable at all flow rates (Table 7). Interestingly, when TNC oxygen supplementation was delivered at 0.1 L/kg/min, the FiO_2 was approximately 27% and was not significantly higher than room air. Whether 27% would support a very mildly hypoxic clinical patient is debatable, however starting rates greater than 0.1 L/kg/min should be considered. At 0.4 L/kg/min the mean FiO_2 was 72%, which may be more clinically efficacious. Dunphy et al. investigated unilateral and bilateral nasal catheters for oxygen administration in dogs, and found similar FiO_2 results to our study.[1] They found that bilateral nasal catheters with a total flow rate of 0.4 L/kg/min produced a tracheal FiO_2 of 77%.[1] Unfortunately, dogs were intolerant of that flow rate.[1] In Dunphy's study, bilateral nasal catheters at a total oxygen flow rate of 0.2 L/kg/min produced a mean FiO_2 of 56% with improved

tolerance.[1] The tolerance data in our study does differ from theirs, which may be related to the difference in nasal catheters used. In the aforementioned study, an 8 Fr red rubber catheter was utilized,[1] and in our study a 10 Fr multifenestrated catheter[d] for oxygen delivery was used. The latter provides more fenestrations, and may produce fewer jet mucosal lesions leading to improved patient comfort. Furthermore, airway gas sampling differed between our study and that of Dunphy's, since the latter utilized intratracheal oxygen concentrations and our investigation measured oropharyngeal oxygen concentrations. However, results are similar, and as mentioned above, the FiO_2 delivered via nasal catheter in general may be variable. Our results suggest that oropharyngeal measurements can be considered in lieu of more invasive intratracheal measurements.

With HFNC, FiO_2 was more tightly regulated and mean FiO_2 remained consistently above 90% at flow rates of 1-2.5 L/kg/min. This may be due to a change in the respiratory pattern of dogs to compensate for the very high flow rate. It is unknown whether this change would be appreciated in a canine patient with pathologic pulmonary disease. One major mechanism of HFNC is that the high flow rates of air/oxygen provide nasopharyngeal washout of dead space. The high FiO_2 levels achieved in the dogs in this study receiving HFNC support the finding that HFNC washes out deadspace and prevents entrainment of room air and dilution of the delivered oxygen. Though all measured PaO_2 values in our healthy dogs remained high using a set FiO_2 of 100%, it is possible that a significant difference in PaO_2 would be seen in a flow rate-dependent manner with a hypoxemic patient population.

In this study, an increase in $PaCO_2$ relative to baseline was seen using HFNC, which was not seen with TNC, nor when comparing TNC and HFNC. These results indicate a small rise in $PaCO_2$ using HFNC, which may or may not be clinically significant. In human medicine HFNC is contraindicated in hypercapneic patients given it does not offer primary ventilation assistance, which is consistent with these results.[25,26] The mild increase in $PaCO_2$ associated with sedation was likely attributable to a lower minute ventilation, due to a lower

respiratory rate or as a result of decreased respiratory drive. The study also found that the $ETCO_2$ was lower at the maximum HFNC flow rate; while this may indicate washout of deadspace at very high flow rates, difficulty to exhale given increased resistance at maximal flow rates may have occurred. It is also possible that the sample was diluted due to high oxygen flow rates. However, blood gas analysis did not reflect any clinically significant difference in carbon dioxide levels between HFNC flow rates. Regardless, the effects of high flows on CO_2 elimination may become deleterious in the compromised respiratory patient. Conversely, the decreased resistance to inhalation and superior oxygenation may produce lessened work of breathing and more efficient gas exchange. Further investigations are required in clinical canine patients.

Vital parameters were, as could be anticipated, affected by sedation in this study. The respiratory rate was lower in sedated patients, however no significant difference in respiratory rate was noted between HFNC flow rates or when HFNC was compared to TNC. Vital parameters remained within normal reference intervals for all TNC flow rates assessed and for HFNC flow rates assessed until 2 L/kg/min was exceeded. With HFNC at 2.5 L/kg/min a drop in arterial blood pressure was noted. Subjectively during HFNC, there were increased respiratory rates, higher heart rates and a drop in blood pressure at the initiation of higher flow rates. However, these changes normalized by the end of the stabilization period and time of recording, as the animal became accustomed to the higher flow rates. The effects of HFNC on vital parameters for dogs without clinical respiratory disease may differ significantly in the patient with hypoxia where the support provided by HFNC may demonstrate an improvement in vital parameter derangements due to improved hypoxemia. Based on initial changes in vitals seen in our healthy dogs, HFNC should be titrated up and the patient closely monitored while achieving higher CPAP levels.

No clinically significant complications were encountered during HNFC oxygen supplementation. The complications associated with HFNC reported in human medicine include air-leak syndrome, cervical-thoracic pain and less

commonly nasal trauma.[10,16,27] The only complication noted in the 8 study subjects post-HFNC was aerophagia noted only on radiographs. No abdominal distension was detected in any dog, and dogs did not show any clinical signs such as abdominal discomfort, retching, or regurgitation. Radiographs were not taken post TNC therapy and as such, the degree of aerophagia that can be expected with traditional therapy is also unknown. Thoracic radiographic assessment was not done after each HFNC flow rate and thus, the effects of flow rates on the degree of aerophagia cannot be assessed. The clinical significance of the aerophagia is currently unknown, although aerophagia is commonly diagnosed in patients presenting with respiratory distress. Cervico-thoracic pain was not assessed in this study since subjects received hydromorphone[b] and dexmedetomidine[c] analgesics in their sedation protocol, which may have masked any signs that the investigators may have otherwise noted. Lastly, air leak syndrome is an uncommon occurrence during HFNC, and no dogs in this study had evidence of this on post-HFNC thoracic radiography though patients should still be monitored for this closely. One human case series describes 2 cases of pneumothorax and one case of pneumomediastinum within hours of initiation of HFNC in 3 children.[16] The cause was speculated to be the provision of airway pressure by HFNC at higher than recommended inspiratory flows, calculated by dividing the minute ventilation by the inspiratory time fraction.[16] In these children, flow rates of 6, 8 and 20 L/min were thought to cause alveolar overdistension, especially given their highly compliant chest walls.[16] A study published in the NEJM in 2013, comparing HFNC to nasal CPAP in very preterm infants, found the rate of pneumothorax in the HFNC group to be 0.6%.[27] In a retrospective veterinary study describing the use of HFNC in hypoxemic dogs, one dog was found to have persistence of a pre-existing pneumothorax that sealed once HFNC was no longer required.[17] With the provision of pressure to the lungs, expansion in lung volume and ideally alveolar recruitment, it follows that barotrauma is a risk of CPAP therapies. When compared to the risk of

pneumothorax in mechanically ventilated patients of 4-15%, this risk is greatly reduced with the use of HFNC in people.[28]

There are several limitations to this study. Our study design did not have a complete randomized block design given TNC was not assessed in equal numbers in awake and sedated states. Also, though an attempt was made to rouse the dogs, and each one was able to lift their head and sit sternal on their own, it was challenging to have dogs in the awake phase of the study open-mouth breathe at every flow rate for the entire period. However, given this finding can be applied to dealing with veterinary patients in general, results are likely appropriately representative. Though the complication of aerophagia was noted in each animal, the small sample size may have limited our ability to appreciate air leak syndrome given the extremely low incidence reported in human medicine and healthy lungs may have been more tolerant to high flow rates. Additionally, abundant efforts were made to acquire pulse oximetry readings in the study dogs, however given it was consistently unattainable despite PaO_2 >300mmHg, we speculate that it did not lend much additional information in this healthy dog population sedated with dexmedetomidine. With respect to instrumentation, an oropharyngeal nasal catheter was used for airway gas sampling and oropharyngeal pressure measurements and condensation was encountered during data collection. Condensation and secretions could have affected values recorded. However, condensation and secretions were evacuated when airway pressure waveforms were aberrant. Despite human studies previously utilizing similar hypopharyngeal catheters to monitor airway pressures and gases,[21] it is possible that some interference may have occurred.

In conclusion, this pilot study has demonstrated that Optiflow™ HFNC can be applied to dogs of different sizes. The tolerance of the system was excellent at lower flow rates of 0.4 and 1 L/kg/min, and acceptable at 2 L/kg/min. The system was minimally tolerated at a flow rate of 2.5 L/kg/min in healthy dogs, and was accompanied by changes in respiratory pattern and blood pressure at initiation. CPAP was achieved using HFNC at 1 and 2 L/kg/min, and higher

expiratory airway pressures were noted with increasing flow rates. No additional CPAP was gained by increasing the flow rate to 2.5 L/kg/min. Based on the study findings, we recommend titrating up to a maximum flow rate of 2 L/kg/min, to obtain CPAP support if needed. The oropharyngeal FiO_2 was predictably 95% at flow rates of 1 L/kg/min and higher when the HFNC FiO_2 is set to 100%, and was 72% when at a lower flow rate of 0.4 L/kg/min. The FiO_2 of TNC was highly variable with a large range but on average was 28% at 0.1 L/kg/min, 50% at 0.2 L/kg/min, and 72% when set at 0.4 L/kg/min. The $PaCO_2$ was lower at baseline than when on HFNC, and higher in sedated subjects. The only complication noted other than intolerance of the system at higher than recommended flow rates, was aerophagia. Overall, use of Optiflow™ HFNC in dogs is feasible and safe, provides predictable oxygen support and offers the additional advantage of providing low-grade CPAP.

This study demonstrated that HFNC could provide positive airway pressure and deliver a more predictable FiO_2. These findings suggest that HFNC warrants further investigation in the clinical setting for patients failing conventional oxygen therapy, or may be considered as a step-down therapy for those being weaned from mechanical ventilation.[26]

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Footnotes

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e. Proparacaine, Alcon Canada Incorporated, Mississauga, ON.
f. Datex-Ohmeda Cardiocap5 monitor, Planar Systems Inc., Beaverton, OR.
g. Mindray PM-9000Vet, Shenzhen Mindray Biomedical Electronics CO. Ltd., Nanshan, Shenzhen
h. Teledyne oxygen analyzer, CE, Industry, CA.
i. Evita 4 mechanical ventilator, Drager Medical, Lubeck, Germany.
j. Aquapak sterile water for inhalation, Teleflex Medical, Research Triangle Park, NC.
k. Fisher-Paykel Optiflow™ HFNC System, Fisher-Paykel Healthcare, East Tamaki, Auckland.
l. Krazy Glue, Elmer’s Products Inc., Westerville, OH.
m. ABL800 Flex Radiometer, Radiometer Copenhagen, Bronshoj, Denmark.
n. Atipamezole, Zoetis Canada Incorporated, Kirkland, QC.
o. Naloxone, Omega, Montreal, ON.
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Table 1. Tolerance scoring system

Score	Parameter
0	Did not ever bother at interface
1	Paw/rub interface 1x
2	Paw/rub interface 2x
3	Paw/rub interface >2x

Table 2. Respiratory scoring system

Score	Parameter
0	Minimal change in overall breathing pattern, normal respiratory rate
1	Mild change in respiratory pattern, mild increase in respiratory rate, appeared to notice flow rate
2	Moderate change in respiratory pattern, moderate increase in respiratory rate, appeared to be less tolerant of flow rate
3	Increase in work of breathing, clinical concern for keeping patient at this flow rate or completely intolerant of flow rate

Table 3. Tolerance and respiratory score results for dogs receiving HFNC & TNC

Flow Dose (L/kg/min)	Tolerance Score				Respiratory Score			
	0	**1**	**2**	**3**	**0**	**1**	**2**	**3**
HFNC 0.4	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
HFNC 1	14 (93)	0 (0)	1 (7)	0 (0)	14 (93)	0 (0)	1 (7)	0 (0)
HFNC 2	8 (53)	3 (20)	3 (20)	1 (7)	12 (80)	0 (0)	2 (13)	1 (7)
HFNC 2.5	5 (33)	0 (0)	2 (13)	8 (53)	5 (33)	1(7)	1 (7)	8 (53)
TNC (All flow doses)	22 (92)	1 (4)	1 (4)	0 (0)	24 (100)	0 (0)	0 (0)	0 (0)

Scores presented as number of dogs and percentage in parentheses. There were 15 trials at each HFNC flow rate. TNC flow rates were combined and represented as a total of 24 trials given the overall low scores.

Table 4. Inspiratory airway pressure at each flow rate

	Inspiratory Airway Pressure (cmH_2O)		
Device & Flow Rate (L/kg/min)	**Mean**	**Lower Limit**	**Upper Limit**
$Baseline_x$	-0.45	-2.70	0
TNC 0.1_{xy}	0	0	0
TNC 0.2_y	0.21	-1.4	1.4
TNC 0.4_{ay}	0.41	0	1.40
HFNC 0.4_a	0.92	0	2.70
HFNC 1_b	2.27	0	5.40
HFNC 2_c	4.81	1.4	8.1
HFNC 2.5_d	4.65	1.4	10.2

Note: TNC was compared to TNC flow rates and TNC 0.4 which was compared to HFNC flow rates. HFNC groups represent a combination of sedated and awake dogs. Letters that are different denote significance where P <0.05.

Table 5. Expiratory airway pressure at each flow rate

	Expiratory Airway Pressure (cmH_2O)		
Device & Flow Rate (L/kg/min)	**Mean**	**Lower Limit**	**Upper Limit**
Baseline$_x$	0.91	0	4.1
TNC 0.1$_x$	0.77	0	1.4
TNC 0.2$_x$	1.06	0	2.7
TNC 0.4$_{ax}$	1.26	0	2.7
HFNC 0.4$_a$	2.09	0	4.1
HFNC 1$_b$	4.20	1.4	8.1
HFNC 2$_c$	6.56	2.7	12.2
HFNC 2.5$_d$	6.58	4.1	12.9

Note: TNC was compared to TNC flow rates and TNC 0.4 which was compared to HFNC flow rates. HFNC groups represent a combination of sedated and awake dogs. Letters that are different denote significance where P <0.01.

Table 6. Number of dogs receiving HFNC achieving CPAP

	Sedation Status		
Flow Rate (L/kg/min)	**Awake**	**Sedate**	**Total**
0.4	0/7 (0)	0/8 (0)	0/15 (0)
1	3/7 (43)	4/8 (50)	7/15 (47)
2	6/7 (86)	7/8 (88)	13/15 (87)
2.5	2/3 (67)	4/4 (100)	6/7 (86)

Scores presented as number of dogs over total number of awake/sedated trials at that flow dose with percentage in parentheses.

Table 7. FiO_2 measured with unilateral TNC and HFNC at varied oxygen flow rates

Device	**None**	**TNC**	**TNC**	**TNC**	**HFNC**	**HFNC**	**HFNC**	**HFNC**
Flow Rate (L/kg/min)	**0**	**0.1**	**0.2**	**0.4**	**0.4**	**1**	**2**	**2.5**
Mean	20.2	27.7	49.9	72.4	72.2	94.8	95.0	95.0
Range	20-22	23-79	25-81	53-94	36-96	87-97	90-97	86-96
Variation	2	56	56	41	60	10	7	10
Significance	a	a	b	cd	c	d	d	-

Device and flow rate are listed in the top row with all table values represented as percentages. FiO_2 was set at 100% and measured at the oropharynx. All variables were compared to baseline, and all flow rates for that device. TNC 0.4 was compared to HFNC 0.4, 1 and 2. Letters that are different denote significance where $P < 0.05$.

Figure 1. Junior HFNC interface.

Figure 2. Modeling clay adjustment to allow for better fitting of adult HFNC interface.

CHAPTER 3

High flow nasal cannula oxygen therapy in acute hypoxemic respiratory failure in 22 dogs requiring oxygen support escalation

Abstract

Objective – To determine the effect of high flow nasal cannula (HFNC) oxygen therapy on cardiopulmonary variables and outcome, in canine patients with acute hypoxemic respiratory failure (AHRF).

Design – Prospective, sequential clinical trial.

Setting – University veterinary teaching hospital.

Animals – Twenty-two client-owned dogs that failed traditional oxygen support.

Interventions – Initiation of HFNC therapy after traditional oxygen supplementation failed to: increase SpO_2 >96%, PaO_2 >75mmHg, or improve work of breathing (WOB).

Measurements & Main Results – Physiological variables, blood gas analysis and dyspnea/sedation/tolerance scores were collected prior to HFNC initiation (on traditional oxygen support (time 0 or T0)), and subsequently during HFNC oxygen administration at time 30, 60 minutes and 7±1 hours. Relative to T0, use of HFNC resulted in a decreased respiratory rate at 1 hour ($P = 0.022$) and 7 hours ($P = 0.012$), a decrease in dyspnea score at all times ($P<0.01$), and an increase in SpO_2 at all times ($P<0.01$). There was no difference in arterial/venous PCO_2 relative to T0, though $PaCO_2$ was correlated with flow rate. Based on respiratory assessment, 60% of dogs responded to HFNC use by 30 minutes and 45% ultimately responded to HFNC use and survived. No clinical air-leak syndromes were observed.

Conclusions – HFNC use improved oxygenation and WOB relative to traditional oxygen therapies, without impairing ventilation. HFNC use appears to be a beneficial oxygen support modality to bridge the gap between standard oxygen supplementation and mechanical ventilation.

Key Words – HFNC, high flow nasal cannula, oxygen supplementation, dyspnea, acute hypoxemic respiratory failure, Optiflow™

This study was funded by the Ontario Veterinary College Pet Trust Fund.

Abbreviations

AHRF	Acute hypoxemic respiratory failure
BRPM	Breaths per minute
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
HFNC	High flow nasal cannula
MV	Mechanical ventilation
NIV	Non-invasive ventilation
PAP	Positive airway pressure
PEEP	Positive end-expiratory pressure
P/F	PaO_2:FiO_2
S/F	SpO_2:FiO_2
SpO_2	Oxygen saturation measured by pulse oximetry
WOB	Work of breathing

Introduction

Traditional methods of oxygen supplementation, delivered using flow-by, nasal prongs/cannulas or oxygen hoods/cages, may be insufficient for patients with moderate to severe acute hypoxemic respiratory failure (AHRF). In current veterinary practice, there is no non-invasive step-up method of respiratory assistance beyond traditional oxygen support. In hypoxemic patients failing traditional oxygen support, options for advanced care are limited to invasive mechanical ventilation (MV), which is associated with substantial resource investment. Although other veterinary studies have evaluated various methods of non-invasive ventilation (NIV) such as those that apply continuous positive airway pressure (CPAP),[2,3] the integration of these devices in clinical practice has been limited in the awake, potentially critically ill, dog. High flow nasal cannula (HFNC) oxygen therapy is a well-recognized non-invasive respiratory support modality used in human medicine in neonatal, pediatric and adult patients.[1] In veterinary medicine, HFNC therapy could serve as an intermediate means of oxygen support between traditional oxygen supplementation and mechanical ventilation.

Briefly, HFNC systems are relatively inexpensive devices that blend high flow rates of oxygen and air (room or compressed medical air) to achieve a prescribed and pre-selected fraction of inspired oxygen (FiO_2) ranging from 21-100%. This gas mixture is delivered to the patient via soft silicone binasal prongs.[1] The high flow rates that can be delivered to the patient are dependent on the appropriately sized nasal interface (adult versus pediatric/neonatal sizes), and associated connecting circuits (adult/pediatric). Adult circuits can provide up to 60 L/min (~2 L/kg/min for a 30 kg dog) flow rates, and pediatric sizes allow up to 25 L/min.[1] Such high flow rates, in comparison to traditional oxygen rates of 0.1-0.4 L/kg/min,[4] are tolerated due to active preconditioning of the gas, which is performed by the HFNC unit.[1] Admixed oxygen and air are warmed and humidified to 37°C and 100% relative humidity via a hot-plate heated humidification chamber or cartridge system, before delivery to the patient via

wire-heated tubing.[1,5] Previous studies using traditional oxygen supplementation via nasal cannula observed that dogs become intolerant of flow rates exceeding 100 mL/kg/min through a single, non-fenestrated nasal catheter.[4] In people, traditional supplemental oxygen delivered at flow rates above 4 L/min have been avoided due to frontal sinus pain and discomfort due to nasal mucosal drying and possible erosion.[1] Many hospitals use bubble-type humidifiers, attached to the oxygen flow meter. There is no evidence of adequate humidification with these systems, and this may account for the decreased tolerance noted in people when unheated oxygen gas is bubbled in traditional cold humidifiers and applied to the nasal mucosa.[6] With HFNC use, the physiologic heating and humidification of the gases (to 37°C and 100% humidity) allows provision of the inspired gas mixture at 10 times the standard oxygen flow rates.[1,5] In dyspneic human patients HFNC use has demonstrated better tolerance and has been described as more comfortable than traditional oxygen via facemask.[5]

Currently, the veterinary literature investigating oxygen delivery via a HFNC is limited.[a,b,7,8] A retrospective case series, using the Vapotherm® HFNC system found that PaO_2 improved in dogs with hypoxemia relative to traditional oxygen supplementation.[7] In a subsequent prospective trial of dogs with respiratory failure, use of a HFNC was noted to initially improve PaO_2, SpO_2 and respiratory rate with 9/20 (45%) dogs receiving HFNC support surviving to discharge.[a] However, 6/20 (30%) dogs did require escalation to mechanical ventilation in that study.[a]

In people, the term AHRF is used to describe individuals presenting with an elevated respiratory rate of greater than 25 breaths/min, SpO_2 <96% or a low arterial oxygen tension relative to FiO_2 despite supplemental oxygen for 15 minutes or more, along with an appropriate clinical history supportive of an acute onset.[9,10] Approximately 50% of people with AHRF trialed on intermediate respiratory support modalities, require invasive assistance.[11] This escalation requirement prompted investigation into alternative modalities, such as HFNC

systems, with the hopes of reduced requirement for MV with improved outcomes.[9,11]

High flow nasal cannula therapy has demonstrated success in improving respiratory function and blood gas variables in human patients.[6,10,12,13] Select studies have documented the success of HFNC use in patients with hypoxemia resulting from many etiologies. In a small-scale randomized controlled trial of emergency patients with cardiogenic pulmonary edema, HFNC delivery at 0.5-1 L/kg/min resulted in significantly lower respiratory rates at 15 and 30 minutes post-intervention, relative to traditional oxygen delivery via facemask.[5] Another retrospective study of HFNC use in human patients with AHRF documented an improvement in PaO_2 at one hour and 24 hours post-HFNC initiation and reported a 63% rate of aversion of intubation.[12] In a prominent prospective, multicenter, randomized controlled trial comparing HFNC use to traditional oxygen therapy (facemask) and non-invasive ventilation (facemask attached to a ventilator applying CPAP) in human patients with AHRF, 90-day mortality rate and severity of dyspnea were both reduced with use of HFNC.[10] Further, in a cohort of people with influenza-induced AHRF, HFNC use was successful in maintaining an SpO_2 above 92% in 45% of patients that had failed a traditional oxygen administration method.[13] The HFNC modality has also been reported to be very successful in the post-extubation period in human patients after cardiac surgery by increasing end-expiratory lung volume and thus, improving oxygenation.[14] In critically ill patients with respiratory failure, HFNC use has found a place for those with do-not-intubate (DNI) orders. In this study, a HFNC was well-tolerated and provided sufficient oxygen support to avoid escalation to other means of non-invasive ventilatory support, in 82% of individuals with end-of-life directives not to be intubated or resuscitated.[15]

Due to the documented utility of HFNC systems in human medicine, the purpose of this study was to determine the feasibility and effect of the Optiflow™ HFNC oxygen delivery system in acutely hypoxemic dogs, to maintain gas exchange as measured by physiological variables, pulse oximetry, and blood gas

analysis when compared to traditional nasal cannula oxygen supplementation. Secondary objectives were to assess the effect of HFNC oxygen delivery on dyspnea and tolerance scores, sedation requirements and respiratory outcome. We hypothesized that in dogs with AHRF, HFNC use would improve oxygenation and respiratory parameters (respiratory rate and effort) beyond that provided by traditional nasal cannula oxygen administration. As well, we hypothesized that there would be similar sedation requirements and tolerance, with no difference in negative outcomes (such as hypercapnia, clinical air-leak syndrome, intubation, and death/euthanasia), when compared to traditional oxygen support.

Methods

Animals

Dogs presenting to the Ontario Veterinary College Health Sciences Centre (OVC HSC) emergency department or hospitalized within the OVC HSC intensive care unit (ICU) that were experiencing signs of AHRF, with no improvement in oxygenation and/or WOB after 30 minutes on traditional oxygen supplementation (via nasal prongs or cannula, oxygen hood/cage/flow-by), were considered for enrolment.

Acute hypoxemic respiratory failure was defined as lack of increase in pulse oximetry >96% or arterial oxygen >75 mmHg and/or significant WOB (use of accessory muscles of respiration, inability to rest or eat, and clinician assessment of distress) with an appropriate clinical history of acute onset. A patient could be included based solely on significant WOB that did not improve with traditional oxygen therapy, despite improvement in oxygenation parameters. Patients with severe respiratory failure wherein immediate mechanical ventilation as determined by the primary clinician was recommended, could be enrolled only if the clients had declined intubation/MV for financial or other reasons and the alternative decision was euthanasia. Exclusion criteria included need for urgent intubation (SpO_2 <90%, PaO_2 <60 mmHg, $PaCO_2$ >65 mmHg, respiratory fatigue,

concern for respiratory arrest) precluding a trial on HFNC. A senior resident or faculty member in emergency and critical care at the OVC HSC assessed each patient for candidacy of enrolment. The study protocol was approved by the University of Guelph Institutional Animal Care and Use Committee. Informed owner consent was obtained prior to enrolment.

Experimental Design

A prospective, sequential clinical trial was performed over an 18-month period (July 2016-January 2018) using the Optiflow^{TM} HFNC unit (Figure 1). Hypoxemic canine patients requiring oxygen support were treated using traditional oxygen delivery modalities. Treatment was not standardized, and management included sedation (butorphanol 0.2-0.4 mg/kg IM/IV), and oxygen supplementation titrated to effect (improved respiratory effort or SpO_2) by nasal cannula (unilateral or bilateral), nasal prongs or oxygen hood, along with appropriate treatment for the underlying respiratory disease. Patients that continued to show signs of respiratory distress beyond 30 minutes of maximized traditional oxygen support and meeting the inclusion criteria for HFNC enrolment, had time 0 (T0) data collected while receiving traditional oxygen support. Subsequently, dogs were fitted with a HFNC interface and oxygen support was initiated using the HFNC system.

Flow rate and FiO_2 were prescribed at the discretion of the primary clinician, however flow rates of >0.4 and <2.5 L/kg/min were recommended based on previous data.[b]

Oxygen support via HFNC was maintained as long as the patient tolerated the system with mild to moderate sedation, or clinical improvement negated the need for augmented respiratory support. Data was collected post-initiation of HFNC therapy at 30 minutes, 60 minutes, and every 6 hours thereafter. FiO_2 was weaned and flow rate adjusted at the discretion of the attending clinician. Flow rates were increased up to 2 L/kg/min based on ongoing signs of dyspnea according to previously established HFNC recommendations,[b] and flow rates

were reduced based on lack of patient tolerance or improving respiratory function/patient comfort. The HFNC trial was discontinued if the patient was not tolerating the system or if patient assessment/oxygenation/gas exchange indices dictated need for escalation to MV.

Instrumentation

All patients enrolled in the study were treated and monitored in the intensive care unit and had an intravenous catheter. If an arterial catheter was in place or could be placed without incurring additional stress for the patient, then arterial blood samples were collected. If arterial sampling was not feasible or deemed unsafe for the patient, then venous blood sampling was utilized.

HFNC. Patients were fitted with an Optiflow™ HFNC[c] interface by the emergency and critical care veterinarian that determined suitability for enrolment. Prior to placement, nares were instilled with 5-10 drops of proparacaine[d] bilaterally. The HFNC interface was selected so as to occlude no more than 50% of the patient's nares based on manufacturer/standard human recommendations; circuit tubing was accordingly selected based on the size of the interface selected (adult vs pediatric). The adult interface frequently required the application of a small piece of modeling clay at the nasal philtrum for appropriate angling of the interface and a securing suture on the lateral aspect of the face at the zygomatic arch. Pediatric interfaces remained in place by using the sliding clip to cinch the tubing at the back of the head, as well as the adhesive Wigglepads™ adhered to fur adjacent to the nares bilaterally (Figure 2), and with a very small amount of Krazy Glue[e] as needed.

Data Collection

Vital parameters and blood gas analyses. Data was collected at T0, 30 minutes, 60 minutes and every 6 hours thereafter (pending patient progress), using a standardized data collection sheet. Patient identification and signalment, body weight, and interface type (adult vs. pediatric) were documented. The

following variables were recorded at each time point while the patient was receiving HFNC support: FiO_2, flow rate, patient temperature, heart rate, respiratory rate, blood pressure (systolic, diastolic and mean), and pulse oximetry. Heart rate was measured by auscultation and respiratory rate was measured by visualizing the number of breaths over one minute. When respiratory rates were recorded as 'pant', a value of 120 breaths per minute was substituted for data analysis. Direct blood pressure measurements were recorded if an arterial catheter was in place, otherwise, an oscillometric recording was obtained.[f] If an oscillometric blood pressure measurement was unable to be obtained, a Doppler monitor[g] was used. If a range of pulse oximetry readings were recorded, the average value was used. Arterial or venous blood gas analyses were performed at each time point. The PvO_2, $PvCO_2$ or PaO_2, $PaCO_2$, along with pH were measured.[h] Calculated values included a PaO_2/FiO_2 ratio (P/F) if an arterial catheter was in place, and an SpO_2/FiO_2 ratio (S/F) was calculated when the patient's SpO_2 was between 80-97%.[16]

Scoring systems. Three predefined scores were used to subjectively evaluate patient tolerance, WOB and level of sedation (Tables 1-3, respectively) at each data collection time point. The interface tolerance score was used as described in a previous study, with a lower value representing improved tolerance of the system.[a] A dyspnea score was adapted from the preceding pilot study to assess clinical respiratory failure.[b] This score was adapted from a human pediatric respiratory score that assesses breathing rate in combination with use of accessory muscles of respiration, ability to rest, play, drink and eat;[17] a lower value represents lower WOB. Lastly, a sedation assessment score was used to trend requirement for anxiolysis with HFNC use. A lower value represented a lower level of patient sedation.

Outcomes. The primary outcome included changes in respiratory rate, dyspnea score and blood gas parameters. Secondary outcomes included survival to discharge, need for intubation, and HFNC success/failure. Survival to discharge was documented as yes or no based on discharge after hospitalization

for that incident of respiratory failure. Intubation was recorded as yes or no if the patient was intubated after a trial with a HFNC had been attempted. A positive HFNC responder status was allocated to patients that had improvement in respiratory vitals (RR, SpO_2) and blood gas parameters (PO_2, PCO_2) as well as lack of increase in dyspnea or tolerance scores. High flow nasal cannula success status (success vs. fail) reflects the overall outcome of the HFNC intervention in that patient. Failure was defined as lack of tolerance of the system, or deterioration or lack of improvement that resulted in death or euthanasia of the patient. These outcomes were used to determine whether patients that responded would also survive, and to capture those that responded favourably to HFNC but, were euthanized based on a diagnosis with poor prognosis or due to progressive critical illness. High flow nasal cannula responder and success status were assessed at time 30 minutes, and 60 minutes by consensus of three investigators (TJ, AB, CK).

Statistical Analyses

Parameters of interest were modelled in a commercially available software program[i] using ANOVA for repeated measures with the fixed effect of time and random effect of the animal. Data was checked for normality with a Shapiro-Wilk test and examination of the residuals. The correlation structure with the best fit for repeated measures was autoregressive (AR1) error structure. If the overall F-test was significant a post-hoc pairwise T-test was conducted. Spearman's correlation was used to look for associations between PaO_2, PvO_2, $PaCO_2$, $PvCO_2$, SpO_2, scoring systems, and heart rate, respiratory rate and blood pressure versus HFNC flow dose. The variable S/F ratio was modelled as an ANOVA as there was not enough data to run a repeated measures model.

Sample size determination. Sample size was calculated using respiratory rate as the outcome parameter of interest and power to detect a difference of seven breaths per minute between traditional oxygen supplementation and HFNC support, was 97% with 10 animals. Data was based on human patients

failing traditional oxygen therapy. An estimated sample size of 20 dogs was selected based on similar published human studies comparing HFNC use to traditional oxygen therapy that have shown significant differences in respiratory rate, SpO_2, and dyspnea score with similar sample sizes (n=17 & n=20).[5,9]

Results

Patient Enrollment and Initiation

A total of 22 dogs were enrolled in the study and received HFNC oxygen therapy. Breeds included: three bulldogs and one of each of the following: French bulldog, German shepherd, mastiff, bloodhound, Shih tzu, Pekingese, Basset hound, Yorkshire terrier, Cavalier King Charles spaniel, Shetland sheepdog, Great Dane, Cane Corso, West Highland white terrier, Jack Russell terrier, Irish wolfhound, English springer spaniel, Border collie, Boston terrier, and a Pomeranian. Baseline characteristics of the dogs and etiologies for oxygen supplementation are reported in Table 4.

All patients received HFNC support after failing traditional oxygen therapy based on primary clinician assessment of oxygenation/ventilation indices and WOB. Initiation of HFNC support was due to hypoxemia in 11/22 dogs, high WOB in 10/22, and due to a combination of hypoxemia and increased WOB in one dog. The initial FiO_2 for patients on HFNC support was 1.0 in 18/22 dogs (82%), with 2 dogs having an initial FiO_2 of 0.80, and one dog each at 0.5 and 0.6.

Thirteen dogs were fitted with a pediatric interface and 9 dogs were fitted with an adult interface. One patient was too small to fit an adequate nasal prong to nare ratio of 50%; nearly 100% nare occlusion was observed with the smallest available neonatal interface leaving insufficient space for proper gas leak. Thus, only one nasal prong was inserted into the nare, with the other nare open to the surrounding air, achieving a 50% occlusive ratio as described above.

For patients who remained on HFNC therapy beyond 1 hour, cumulative duration of HFNC use ranged from 2 - 75 hours with a median of 18 hours. Statistical analysis was limited to data collected up to time 7±1 hour, in order to eliminate the effects of other treatment interventions that may have played a role in improvement of oxygenation parameters during HFNC use (eg. furosemide for congestive heart failure, corticosteroids for eosinophilic bronchopneumopathy, etc.). Results of AHRF dogs on traditional oxygen supplementation and at each time point on HFNC support are reported in Table 5.

Physiologic Variables

The respiratory rate with HFNC support was significantly lower at 1 and 7 hours relative to T0 ($P=0.022$ and $P=0.012$ respectively; Figure 3, Table 5), and decreased significantly over time during the duration of HFNC support ($P <0.05$; Figure 3). There was no significant difference in any other vital parameter: temperature, heart rate, or blood pressure between T0 and any time point of HFNC oxygen administration (30 minutes, 60 minutes, and 7 hours).

Scoring Systems

Dyspnea scores decreased significantly relative to T0 with use of HFNC systems ($P <0.01$; Figure 4, Table 5). During the duration of HFNC use no statistically significant changes were noted in the dyspnea score up to 7 hours post-initiation. There was no significant difference in level of sedation or tolerance between T0 and any time point on HFNC therapy, nor throughout HFNC oxygen delivery (Table 5).

Oxygenation

When comparing SpO_2 in patients on HFNC support to those receiving traditional oxygen therapy (T0), SpO_2 was significantly higher while receiving HFNC support at all time points ($P < 0.01$; Figure 5). Mean oxygen saturation via pulse oximetry was 93% at T0 and 98% on HFNC support. Once HFNC therapy was initiated, there was no difference in SpO_2 over time.

The SpO_2:FiO_2 ratio (S/F) was not assessed for most patients on traditional oxygen systems (T0) given the unknown FiO_2 of a patient receiving

traditional oxygen supplementation (by nasal cannula/nasal prongs). Thus, T0 data was not compared to HFNC data in this analysis. However during HFNC administration, S/F ratios were calculated when the SpO_2 was 80-97%; there was a significant increase in S/F over time, which was noted between 30 and 60 minutes (P = 0.028) and 60 minutes and 7 hours (P = 0.038) respectively (Table 5). There were a total of 10 observations used in this analysis given the criteria for SpO_2.

FiO_2 was significantly reduced over time on HFNC support from 30 minutes to 1 hour (P=0.034), 30 minutes to 7 hours (P<0.001), and 1 to 7 hours (P=0.026) (Table 5). Variable FiO_2 settings made direct comparisons of indices of oxygenation (PaO_2, PvO_2) impossible. Therefore, oxygen tension (PO_2) at T0 was compared to time 30 minutes only if the FiO_2 was set to 100% while the patient was receiving HFNC therapy and the same sample type (arterial or venous) was collected at both time points (n=16; Table 5). Six dogs had arterial sampling wherein the PaO_2 was significantly higher on HFNC therapy at time 30 minutes than T0 (P=0.042). An additional 10 dogs had venous samples taken at T0 and 30 minutes post-initiation of HFNC therapy (Table 5). When performing the same comparison with PvO_2, venous oxygen tension was significantly higher on HFNC support than at T0 (P=0.01; Table 5).

Ventilation

There was no significant difference in $PaCO_2$ or $PvCO_2$ in dogs on traditional oxygen therapy at T0 versus those receiving HFNC support, nor over time while receiving HFNC therapy. There was a moderate correlation between $PaCO_2$ and HFNC flow rate (r = 0.50, P=0.012), but no significant correlation was found with $PvCO_2$.

Flow rates

For analysis purposes, oxygen flow rates were categorized in L/kg/min (range of flow possible in each category shown in parenthesis): 0.5 (<0.7), 1 (0.8-1.25), 1.5 (1.5-1.6), 2, and 2.5 (>2). There was a significant increase in flow rate

at all HFNC time points relative to T0 ($P < 0.001$). There was no difference in flow rate over time once HFNC therapy was initiated.

Correlation with HFNC Flow Rate

There was a moderate positive correlation between HFNC flow rate and PaO_2 ($r = 0.49$, $P = 0.015$) and HFNC flow rate and SpO_2 ($r = 0.51$, $P < 0.001$), and a weak correlation between HFNC flow rate and PvO_2 ($r = 0.34$, $P = 0.033$). As stated above, there was a moderate correlation between flow rate and increasing $PaCO_2$. There was no correlation found between HFNC flow rate and $PvCO_2$, all scoring systems, heart rate, respiratory rate and blood pressure.

Outcomes

The mortality rate in this population of dogs with AHRF was 55% (12/22). Of those that did not survive to discharge, 3/12 died and 9/12 were euthanized. Based on clinician assessment of the patient's overall condition, 13/22 dogs (59%) had MV recommended after a trial with a HFNC. Six dogs were intubated (6/22; 27%), with three dogs (3/22; 14%) proceeding to mechanical ventilation, wherein 1/3 (33%) of mechanically ventilated dogs survived to discharge. Of the remaining dogs that were intubated (n=3): one (bulldog) survived after receiving a temporary tracheostomy, one died and one was euthanized. Intubation and ventilation was declined by one owner wherein additional time on HFNC support resulted in survival without need for further intervention. Overall, out of the 13 dogs that had intubation/escalation therapy recommended, three dogs (23%) survived, eight (62%) were euthanized and two (15%) died.

Of 20 dogs with data collection at 30 minutes, 12 (60%) were considered to have responded to HFNC therapy based on respiratory parameters and dyspnea/tolerance score (Figure 6). By 60 minutes, five dogs died/were euthanized before the recording was captured, and 3 dogs did not have data collected at this time. Thus, 14 dogs had data collection and 11/14 (79%) were considered to be responding to HFNC therapy (Figure 6). Of the eight non-responders at 60 minutes, six were deceased including two that had responded at the 30-minute mark. Only 1 dog was considered a non-responder due to

intolerance of the interface by time 60 minutes. Conversely, three patients that had not responded (lack of improvement) at 30 minutes, were considered responders by their 60-minute data recording. Data was missing for 2/8 of these dogs at the 60-minute mark, one of which survived after being mechanically ventilated, and another that was euthanized for financial implications of continued care. Based on assessment of the responders at 30 and 60 minutes, 6/12 (50%) and 8/11 (73%) dogs ultimately survived to discharge.

Complications

There were no clinical air-leak syndromes noted in the patients enrolled in this study, nor observation of additional complications.

Discussion

Based on the findings of this study, HFNC oxygen therapy appears to have a role as a non-invasive respiratory support modality that can bridge the gap between traditional oxygen supplementation and invasive MV. As hypothesized, there was a notable effect on oxygenation in patients failing traditional oxygen support, and significant improvements in respiratory parameters. Our positive results in dogs with AHRF concur with those shown in a previous veterinary study and several human clinical trials.[a,5,7,9,11-13,18,19] Further, HFNC use is associated with reduced cost relative to MV and acceptable patient tolerance.

In this group of dogs with AHRF, 6/22 (27%) were intubated after an HFNC trial and mechanically/manually ventilated; and six additional dogs were euthanized at the request of the owner, given need for escalation therapy. However, without the availability of an alternative oxygen support modality, all 22 dogs failing traditional oxygen supplementation would have had MV recommended as the next therapeutic intervention. Moreover, 10/22 respiratory failure patients survived to discharge with 8 dogs (36%) avoiding intubation as a result of a HFNC trial. In a previously published prospective canine study using a

Vapotherm® HFNC system in hypoxemic patients, similar results were found with 45% of dogs surviving to discharge and 30% of dogs escalating to MV.[a] Despite both studies having a small sample size relative to human studies, comparable results exist in people with AHRF. In a large multicenter, randomized controlled trial by Frat et al, in-hospital ICU mortality in hypoxemic adults was 11% with a 38% intubation rate in the group receiving HFNC support.[10] The comparison of mortality rates between human and veterinary literature is difficult due to the accepted veterinary practice of euthanasia and concurrent implications of comorbidities/financial resources, which play a part in end-of-life decision-making for clients.

In this study, the use of HFNC therapy resulted in a significant improvement in respiratory parameters. Dyspnea scores and respiratory rates decreased significantly relative to traditional oxygen therapy. This finding is similar to human studies evaluating HFNC use in patients with AHRF.[5,9,18] In several human studies, respiratory rate and dyspnea evaluations were improved within 30 minutes,[5,9,18] and 60 minutes of therapy.[10,19] There are several mechanisms thought to contribute to the efficacy of HFNC therapy which include: positive airway pressure (PAP) provision, washout of nasopharyngeal deadspace, increased inspiratory flow, and the preconditioning of gas (heated/humidified).[1] Primarily, the provision of constant high gas flows results in an increased resistance to exhalation, and maintenance of positive pressure within the airways throughout the respiratory cycle, which is referred to as continuous positive airway pressure (CPAP). The associated positive end-expiratory pressure (PEEP), results in recruitment of lung units; with both invasive and non-invasive (nasal prongs/mask) forms of mechanical ventilation.[20] The provision of PAP by HFNC systems has been demonstrated in numerous adult human studies.[20-23] In healthy adult volunteers there is a linear increase in PAP with increasing flow rate, such that at 30 L/min the PAP was 3 cmH_2O, at 40 L/min the PAP was 4 cmH_2O, and at 50 L/min the PAP was 5 cmH_2O.[23] Electrical impedance tomography has been able to demonstrate that end-expiratory lung

volume indeed increases with use of HFNC by about 25% and airway pressure by 3 cmH_2O when compared to traditional oxygen therapy, resulting in improved oxygenation, dyspnea scores and respiratory rate.[14] One experimental canine study (in press) demonstrated this linear increase in positive expiratory pharyngeal pressure with increasing flow rate, such that CPAP was provided at flow rates of 1-2 L/kg/min, similar to rates that are recommended in adults (30-60L/min, ~0.5-1 L/kg/min) and neonates (2-8 L/min, ~1-2.3 L/kg/min).[b,1,24] However, another experimental veterinary study was not able to demonstrate PAP using a HFNC system in dogs based on transpulmonary pressures as measured by an esophageal balloon catheter.[8] The authors of this report suggest this may be due to the small sample size (6 dogs) and limited assessment of breathing pattern (open versus closed mouth respiration).[8] However, the selected flow rates of 20 and 30 L/min may have been insufficient to cause PAP in dogs of the size assessed in their study (mean 28kg).[8]

Nasopharyngeal washout is an additional mechanism for the reduction in dyspnea scores with HFNC oxygen support.[1,22] Nasopharyngeal washout involves elimination of deadspace by flushing the airways with high oxygen flows and reducing CO_2 rebreathing by ensuring the airways are constantly filled with the prescribed FiO_2.[22] The high flow rates also cause a decrease in the resistance to inhalation and thus, reduce WOB. This may in part explain improved dyspnea scores relative to traditional oxygen supplementation systems. While the inspiratory resistance may be eliminated when using HFNC therapy, the high flows cause a high resistance to exhalation. Due to the washout within the airways, hypercapnia is infrequently observed with use of a HFNC in cases of pulmonary pathology, in the human literature.[22,24,25] Lastly, the metabolic cost of conditioning the gases and resultant physiological advantage of warmed, humidified air, should not be overlooked as an important component of patient tolerance and thus permits the use of high gas flows that facilitate the above mechanisms.[24]

High flow nasal cannula systems offer the clinician the advantage of reliably setting the FiO_2,[b] unlike some of the standard methods of oxygen supplementation. In the current study, the FiO_2 was decreased over time on HFNC support. Prompt reduction in FiO_2 to the lowest level that will maintain PaO_2 or surrogate measures, is recommended to reduce the potential for additional lung injury incurred by oxygen toxicity, as well as to facilitate maintenance of recruited alveoli.[26] Control of the oxygen concentration in this new respiratory support system adds a level of individualized medicine beyond that which is achieved with standard oxygen therapy.

In our study, the SpO_2 on HFNC therapy was increased relative to traditional oxygen support. For patients in which initial FiO_2 was set at 100% on HFNC support, oxygen tensions were significantly higher than with traditional methods at 30 minutes. High flow oxygen systems warm and humidify the gases prior to patient administration, which enables very high flow rates to be provided to the upper airways, as previously noted, and these flow rates achieve desirable physiologic distending pressures while eliminating deadspace.[1] This leads to improvements in oxygenation, as demonstrated in multiple human studies using HFNC systems in both the emergency department and ICU.[5,9,18,19]

Due to our non-invasive and pragmatic approach to obtaining arterial samples, few patients had sequential arterial samples for assessment of P/F ratios. As such, S/F ratios were selected as a surrogate marker. As previously noted, S/F was only calculated when a given SpO_2 was between 80-97% as SpO_2 is unable to assess improvements in oxygenation above 97%.[16] The S/F ratios have previously been shown to correlate well with P/F ratios in dogs and may be considered a noninvasive surrogate for trending oxygenation assessments in canine patients.[16] In our study, an increase in S/F ratio occurred with provision of HFNC support (up to 7 hours); this could be related to the effect of HFNC therapy on pulmonary mechanics, or to an actively resolving underlying respiratory condition. Improvements in respiratory conditions such as cardiogenic pulmonary edema (CPE) is possible in such a short time frame. In the other

etiologies of respiratory distress, it remains likely that HFNC therapy alleviated patient dyspnea and provided time for improvement without the need for invasive intervention.

Interestingly, many studies have found the stabilizing effects of HFNC use to be evident within the first 15-60 minutes of its initiation. [5,9,18,19] In our study, 60% and 79% of dogs demonstrated a positive response at time 30 minutes and 60 minutes respectively, based on improvement in respiratory parameters. Moreover, when evaluating the effect of HFNC oxygen delivery on outcome, at 30 minutes and 60 minutes there was a 50% and 73% rate of discharge from hospital, respectively. Of the 8 non-responders at 30 minutes, three dogs demonstrated favourable improvement with HFNC use at 60 minutes. HFNC response at 30 minutes versus 60 minutes was compared in order to determine if a single time point may best represent patient progress as has been documented in the human literature.[5,9,18] The results of this study do not allow elucidation of the most appropriate time for patient assessment post-HFNC initiation, however, our results support continued assessment of HFNC response beyond 30 minutes, if the patient is not imminently meeting criteria for MV. Conversely, several patients that were responding at 30 minutes, were no longer supported appropriately with the HFNC at 60 minutes. In fact five patients were no longer in the study at 60 minutes because of death/euthanasia. At 60 minutes, the HFNC response and survival to discharge were improved and likely related to a rapid loss of patients with severe respiratory distress who succumbed to their condition prior to the one-hour assessment. These results suggest that overall, while some patients may respond rapidly to initiation of HFNC support, a positive initial response may not lead to a successful outcome.

Etiologic cause of respiratory distress and the associated response with HFNC use, has been investigated in human medicine. The present study was not sufficiently powered to investigate different etiological categories. However, HFNC use has been recommended in human medicine for patients with CPE. A retrospective study in 75 human AHRF patients demonstrated that the

improvement in PaO_2 at 1 and 24 hours, along with a diagnosis of CPE, were prognostic indicators for success with HFNC oxygen therapy.[12] In our study, only two dogs had severe heart failure. In both cases, HFNC use was able to improve oxygen saturation and reduce WOB as diuretic therapy was given time for effect.

While oxygenation is supported by HFNC use and PAP provision reduces WOB, the system is not a primary means of ventilation. Since no mechanical assistance occurs with HFNC support, it is not indicated as a non-invasive modality for hypercapnic respiratory failure. Moreover, a correlation between HFNC flow rate and rise in $PaCO_2$ was noted in this study, although $PaCO_2$ levels were not significantly different from measurements on traditional oxygen supplementation. Physiologically, this correlation between increasing flow rate and $PaCO_2$ are not unlike the effects of PEEP provision by a ventilator. In lung protective ventilation, permissive hypercapnia may be required based on the need for higher PEEP to maintain alveolar recruitment and oxygenation parameters.[27] As well, with HFNC use there is increased resistance to exhalation due to the high inspiratory flows, which can lead to hypercapnia in the absence of an adequate nasal leak. Though the partial pressure of CO_2 may increase with increasing HFNC flow rates, most human studies of AHRF do not demonstrate significant changes in PCO_2 with use of a HFNC.[10] In AHRF, the risk of causing hypercapnia seems to be ameliorated by a lower requirement for ventilation due to nasopharyngeal washout of CO_2 and deadspace elimination as well as the improvement in WOB for hypoxemic patients.[14,22] This was supported in a prospective randomized control trial conducted by Mauri et al., where HFNC use was compared to facemask oxygen therapy in 15 AHRF patients.[11] The authors speculate that AHRF patients with a higher deadspace fraction may particularly benefit from the washout effect of HFNC support, lowering previous concerns for hypercapnia with this modality. In the veterinary literature, there is one AHRF canine case series that demonstrates an increase in $PaCO_2$ by 3 mmHg, without clinically relevant changes or alteration in pH.[7] Though PCO_2 in our study did not change significantly, it should be monitored as is appropriate for any critical

respiratory patient but, particularly at higher than standard flow rates of 2 L/kg/min. It should be noted that no additional benefits, with regards to reliability of FiO_2 or provision of CPAP, occur beyond 2 L/kg/min and healthy dogs were found to be intolerant to rates above this level.[b]

A secondary objective of this study was documenting clinical complications, as this pertains to the utility of this modality. There were no known pneumothoraces requiring clinician intervention observed during the provision of HFNC therapy in the 22 dogs enrolled in this study. As thoracic radiography was not specifically performed following HFNC initiation, the rate of subclinical air-leak syndromes are unknown. In the veterinary literature, air leak syndromes secondary to HFNC support have been reported in 2 dogs and include one pneumothorax in a hypoxemic dog after HFNC use and persistence of a pre-existing pneumothorax (that resolved on discontinuation of HFNC support).[a,7] Human studies likewise report a low rate of 1% or less for pneumothorax secondary to HFNC.[28,29,30] While there is a risk of air-leak syndromes, these rates are likely lower than those associated with mechanical ventilation (generally 4-15% ventilated people).[31] The study was likewise not designed to interrogate the degree of aerophagia caused by HFNC therapy, a finding that has been documented in other veterinary studies, albeit without need for clinical intervention.[8,b] Following manufacturer's recommendations to ensure that the correct nasal interface is selected to maintain a nasal leak (50% nare occlusion)[32] appears critical to reduce the risk of overpressurization and aerophagia.

There are several limitations to this study. Inconsistencies in blood sampling site during provision of HFNC oxygen therapy led to blood gas parameter analysis difficulties and poor statistical power. Future studies should ideally select one consistent sampling site. Another limitation of the study was the inherent difficulty of consistent categorization using the dyspnea scoring system. The scoring system was determined prior to study initiation. A respiratory rate cut off of 40-60 breaths/min was used as one factor within the scoring

categories, however some patients remained tachypneic (> 40 breaths/min) despite a noticeable change/apparent improvement in respiratory character, or conversely did not meet the respiratory rate qualification of a given category but the respiratory effort and WOB remained increased. Trends were monitored and reflected in the scores attributed to the patients. Although this was a limitation, statistical analysis of respiratory rate also supports the trend in respiratory scores. Another limitation is that the outcome for the patients in this study may have been affected by the etiology or severity of respiratory disease. Severe respiratory insufficiency was an inclusion criteria for initiating support with a HFNC, however this pre-selected patients for whom MV was potentially necessary and thus clients may have been more likely to select euthanasia based on severe morbidity and its financial implications. The decision to euthanize likely had a significant impact on outcome measures (responders to HFNC use, need for mechanical ventilation and survival to discharge) in this study. In fact, 5 patients did not survive to the 60-minute HFNC assessment point. In addition, the diagnosis of terminal illness did not preclude study inclusion (dogs were included prior to establishing a diagnosis). Terminal illness negatively impacts survival to discharge and as such this outcome measure does not directly reflect success or failure of HFNC support at alleviating respiratory signs. For this reason, a separate responders variable was assessed that did not rely on survival/mortality. For patients with suspected terminal illness, eg. cases of severe refractory pulmonary arterial hypertension (3/22 dogs), HFNC support was ultimately used as a palliative option. Palliative use of HFNC oxygen support has also been reported in people. Patients with do-not-intubate orders have benefitted from HFNC use during episodes of respiratory crisis, avoiding transition to other support options (NIV) in 82% of patients.[15] High flow nasal cannula oxygen therapy may be shown in future studies to have benefit in veterinary patients for non-invasive crisis management or alleviation of patient distress prior to death.

Conclusion

High flow nasal cannula oxygen administration employed after failure of traditional oxygen therapy to stabilize dogs with AHRF resulted in improved respiratory rate, WOB, and oxygenation parameters in a significant number of dogs without causing clinically relevant air-leak syndromes or hypercapnia. Oxygen flow rate and FiO_2 can be adjusted with HFNC systems and permit relevant improvements in AHRF patients while minimizing the risk of oxygen toxicity. Based on the findings of this study, the Optiflow^{TM} HFNC system is a viable, potentially life-saving option available to canine patients as a therapeutic modality prior to pursuit of invasive ventilation in AHRF. Further studies should seek to determine the optimal timing for initiation of HFNC therapy, the optimum time point for assessing patient success with HFNC support, and determine if specific etiologies may have higher positive response rates.

Footnotes

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b. Jagodich TA, Bersenas AME, Bateman SW, Kerr CL. Comparison of high flow nasal cannula oxygen administration to traditional nasal cannula oxygen therapy in healthy dogs. J Vet Emerg Crit Care *In press.*
c. Fisher-Paykel Optiflow™ HFNC System, Fisher-Paykel Healthcare, East Tamaki, Auckland.
d. Alcaine, proparacaine hydrochloride ophthalmic solution 0.5% w/v, Alcon Canada Incorporated, Mississauga, ON.
e. Krazy Glue, Elmer's Products Inc., Westerville, OH.
f. Cardell® veterinary monitor model 9401 BP, Midmark, Tampa, FL.
g. Ultrasonic doppler flow detector model 811-AL, Parks Medical Electronics Inc., Aloha, OR.
h. ABL800 FLEX, Radiometer Canada, London ON, Canada
i. SAS Institute Inc 2004, Cary, NC.

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Table 1. Tolerance scoring system

Score	Parameter
0	Did not ever bother at interface
1	Paw/rub interface 1x
2	Paw/rub interface 2x
3	Paw/rub interface >2x

Table 2. Dyspnea scoring system

Score	Parameter
0	Normal RR, no to mild effort
1	RR ~40-48, able to eat/sleep/rest, no use of accessory muscles
2	RR~40-48 and/or: focused on respirations, mild abdominal component to breathing, occasionally will lie down, +/- willing to eat
3	RR 48-60 and/or: lips retracted, neck extension present, moderately increased respiration with abdominal component, paradoxical breathing
4	RR >60 with marked respiratory effort and/or: extreme restlessness, abducted elbows, unwilling to lie down despite sedation

Table 3. Sedation assessment scoring system

Score	Parameter
1	Bright, alert, no discernable sedation
2	Mild sedation, appears sleepy or quiet
3	Moderate sedation, appears very sleepy, +/- recumbent but rousable
4	Heavy sedation, recumbent and difficult to rouse
5	Profound sedation, recumbent and cannot be roused

Table 4. Characteristics of AHRF subjects

Characteristic	**Event**
Age (years)	5.5* (0.3-12)
Gender (number of dogs):	
Spayed female	6
Intact female	2
Castrated male	8
Intact male	6
Body weight (kg)	22.1* (1.9-74)
Etiology of AHRF (number of dogs):	
Pneumonia	7
Inflammatory	3
Pulmonary artery hypertension	3
Congestive heart failure	2
Trauma	1
Other	6

Mean is denoted by (*). Ranges are represented within parentheses.

Table 5. Results of AHRF dogs according to time point

Characteristic	Time 0 Traditional oxygen	Time 30 minutes HFNC	Time 60 minutes HFNC	Time 7±1 hour HFNC
Number of patients with data available (n)	n=22	n=20 n_{alive} =22 $n_{missing\ data}$=2	n=14 n_{alive} =17 $n_{missing\ data}$=3	n=9 n_{alive} =14 $n_{missing\ data}$=1
Dyspnea score*$^{\lambda}$	3 (1-4)	3 (1-4)	2.5 (1-4)	2 (1-3)
Tolerance score	0.3 (0-3)	0.6 (0-3)	0.6 (0-3)	0.4 (0-2)
Sedation score	2.4 (0-5)	2.7 (1-5)	2.6 (1-5)	2.6 (1-4)
Respiratory rate*$^{\lambda}$ (brpm)	65 (28-120)	53 (20-132)	36 (20-120)	36 (24-60)
Heart rate (bpm)	129 (92-190)	125 (77-170)	124 (96-178)	116 (71-140)
Temperature (Celsius)	38.0 (35-39.5)	38.2 (36.4-39.7)	38.4 (37.3-39.7)	38.2 (37.2-39.1)
Mean arterial pressure (mmHg)	111 (68-137)	97 (68-157)	97 (69-116)	95 (67-115)
SpO_2*$^{\lambda}$ (%)	94 (85-100)	99 (92-100)	99 (92-100)	98 (90-100)
Number of arterial; venous samples	5; 15	8; 11	6; 8	4; 5
PvO_2*(mmHg)	41.5 (24.9-78.7)	57.7 (35.7-93.5)	53.9 (37-84.4)	47 (46.5-61.6)
PaO_{2*} (mmHg)	65.6 (53-142)	121.3 (77.8-295)	98.9 (77.9-349)	83 (61.3-121)
$PvCO_2$* (mmHg)	49.1 (22.7-68.1)	47.9 (37.3-86)	50.8 (36.9-78)	43.3 (35.5-47.2)

$PaCO_2$* (mmHg)	38.8 (25-45.7)	38.4 (31-45.8)	43.8 (30.9-53.4)	37.4 (25.3-45.4)
Clinician-directed: **FiO_2*** **	NA (NA-100%)	0.96 (0.5-1.0)	0.84 (0.5-1.0)	0.65 (0.4-1.0)
Clinician-directed: **Flow rate (L/kg/min)***	0.44 (0.03-1)	1 (0.5-2.3)	1 (0.5-2.3)	1 (0.7-2.3)
Calculated variable (n=10): **SpO_2:FiO_2** **	NA	94 (92-95)	102 (92-119)	196 (90-243)

*For characteristics that were normally distributed the mean was reported, and if not, the median (*) was reported. Ranges are represented within parentheses. (**) The SpO_2:FiO_2 was calculated when SpO_2 was 80-97% and was significantly different between 0.5 & 1h and 1h & 7h ($P<0.05$). (***) The FiO_2 was significantly decreased over time ($P<0.05$). Remaining significant characteristics (**λ**) are denoted in Figures 3-5 such that others did not demonstrate a significant difference.*

Figure 1. High flow nasal cannula delivery system.

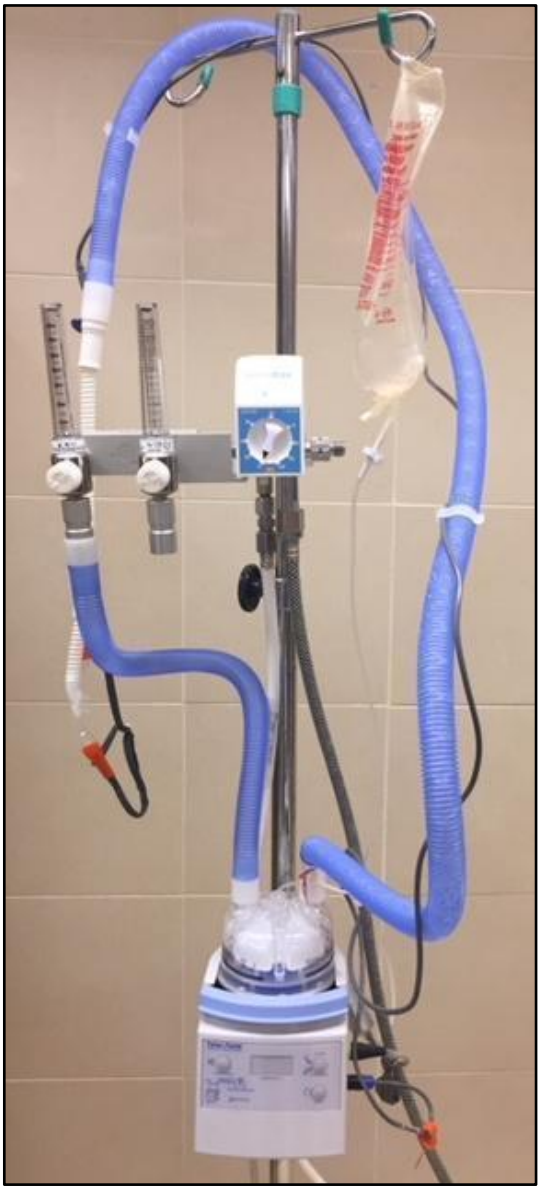
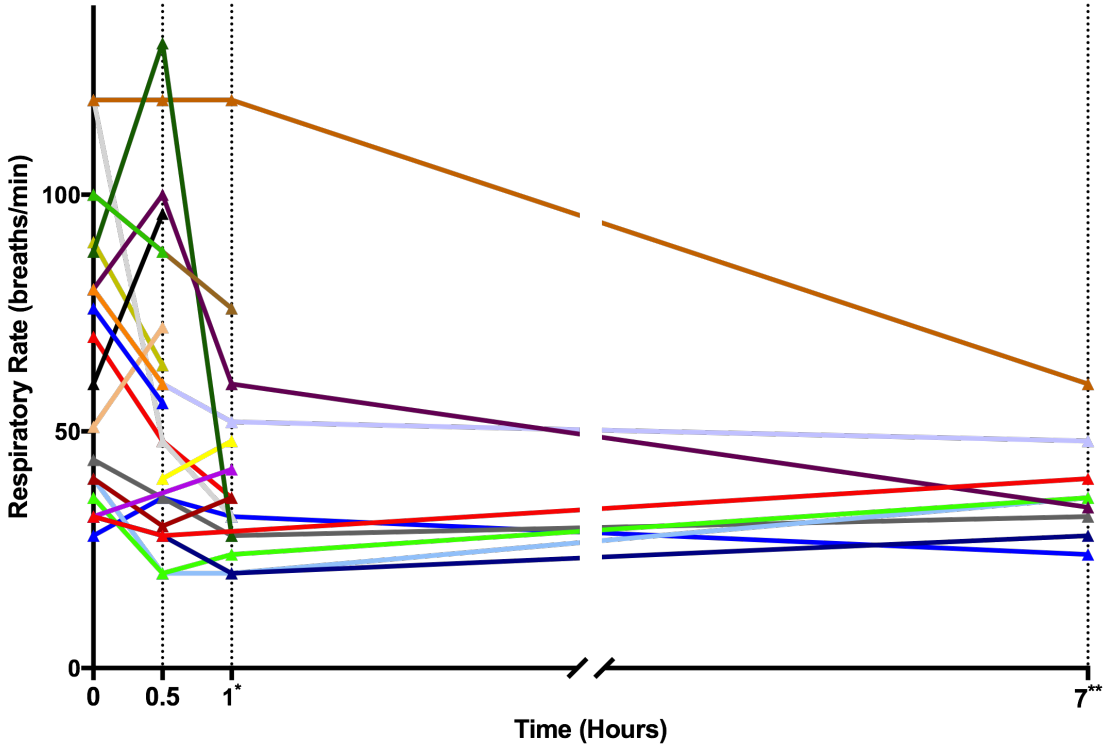


Figure 2. Pediatric interface with adhesive Wigglepads™.

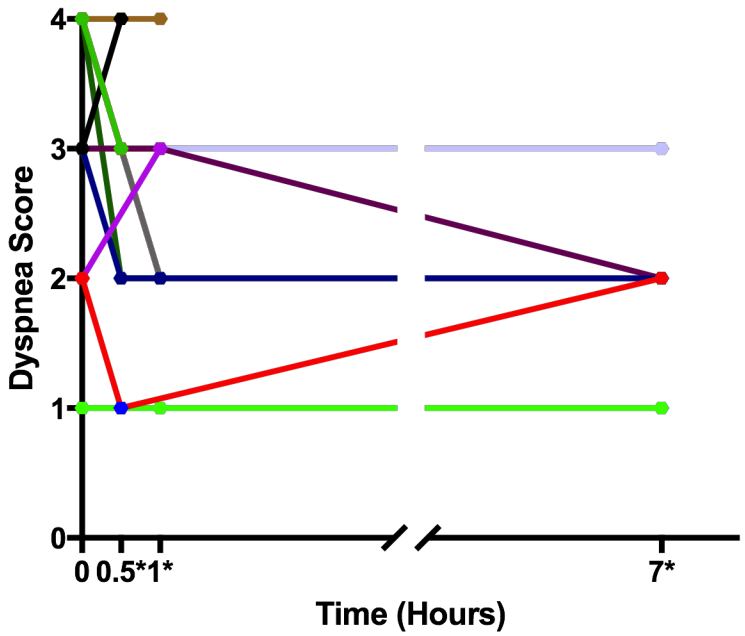
Figure 3. Respiratory rates over time with transition from traditional oxygen therapy (time 0) to HFNC at all other times.



(*) denotes time 1 hour significance relative to baseline and 30 minutes P <0.05

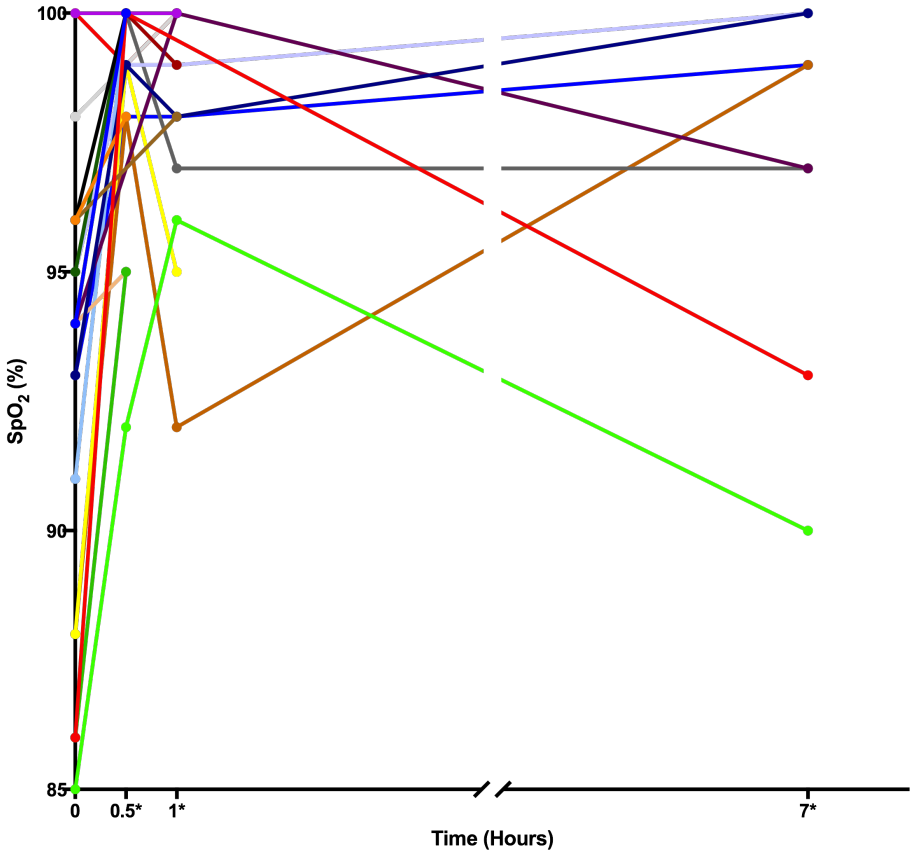
(**) denotes time 7 hour significance relative to baseline and 30 minutes P <0.04

Figure 4. Dyspnea scores over time comparing traditional oxygen therapy (time 0) to HFNC at all other times.



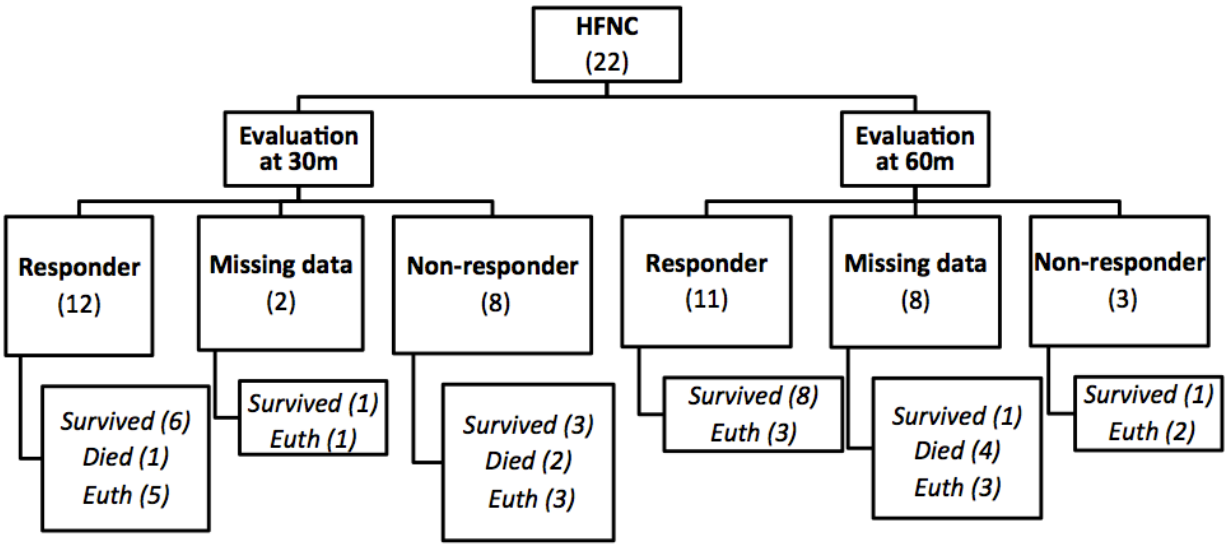
(*) denotes significance relative to time 0 (P<0.01)

Figure 5. SpO_2 over time comparing traditional oxygen therapy (time 0) to HFNC at all other times.



(*) denotes significance relative to time 0 (P<0.01)

Figure 6. Patient enrollment, response to HFNC and outcome



Number of dogs represented in parentheses; Euth = euthanized.

CHAPTER 4

Preliminary evaluation of the use of high flow nasal cannula oxygen therapy during recovery from general anesthesia in dogs with obstructive upper airway breathing

Abstract

Background – Brachycephalic airway syndrome can pose a risk of complicated recovery from anesthesia as a result of irritation to the excess pharyngeal and laryngeal tissue present in affected dogs. High flow nasal cannula oxygen therapy (HFNC) is a respiratory support modality that offers provision of continuous positive airway pressure (CPAP) via high gas flow rates. The system has shown high tolerance due to active warming and humidification of inspired gases to physiologic conditions by HFNC systems. High flow oxygen therapy was applied to dogs that developed increased work of breathing and/or hypoxemia in the recovery phase of anesthesia, to determine if this device would be tolerable and effective for relief of upper respiratory difficulty.

Key Findings – The HFNC nasal prong interface is well suited to the brachycephalic facial structure. The application of HFNC was found to reduce dyspnea scores in patients with signs of upper airway obstruction after general anesthesia.

Significance –Application of HFNC in the recovery period may result in improved airflow during times of somnolent obstructive breathing, not unlike use of CPAP therapy in human sleep-disordered breathing.

Key Words – Continuous positive airway pressure, high flow, brachycephalic airway syndrome, oxygen therapy

This study was funded by the Ontario Veterinary College Pet Trust Fund.

Abbreviation List

BOAS	Brachycephalic obstructive airway syndrome
CPAP	Continuous positive airway pressure
FiO_2	Fraction of inspired oxygen
HFNC	High flow nasal cannula oxygen therapy
MV	Mechanical ventilation
UAO	Upper airway obstruction
WOB	Work of breathing

Introduction

Canine brachycephalic obstructive airway syndrome (BOAS) results in structural changes such as medial collapse of the nasal cartilage and stenosis of the nares, elongated soft palate, and everted laryngeal saccules.[1,2] As a result, there are increases in negative inspiratory pressures and resistance to breathing in brachycephalic patients.[1,2] The altered pressure dynamics of respiration can culminate in secondary consequences of airway obstruction via pharyngeal and laryngeal edema, laryngeal collapse and eventual acute respiratory distress. Gastrointestinal abnormalities have been found in 97% of brachycephalic dogs with upper respiratory signs.[1,3] These abnormalities may explain the high frequency of regurgitation in brachycephalic patients and may be coupled to the large inspiratory negative pressure (resulting in retrograde flow of stomach contents) when upper airway obstruction (UAO) is experienced. Aspiration pneumonia is common and is the leading cause of endotracheal intubation and mechanical ventilation (MV).[4] In a patient population with a high prevalence of both gastrointestinal and upper airway abnormalities, the post-extubation recovery period is critical. Early intervention and prevention of respiratory distress is paramount to avoiding further respiratory complication.

High flow nasal cannula oxygen therapy (HFNC) is a novel non-invasive respiratory support modality that offers advantages similar to continuous positive airway pressure (CPAP). Previous reports of CPAP delivered using helmets and facemasks in tranquilized and post-anesthesia brachycephalic dogs, demonstrated improvement in pulmonary function, [5,6] however these methods have not gained favour in clinical practice. HFNC is a simple, inexpensive, mobile, oxygen delivery unit that blends air and oxygen to meet a prescribed fraction of inspired oxygen (FiO_2).[7] The gas is warmed and humidified to 100% relative humidity and 37°C via a heated water chamber/cartridge system, and the system delivers the blended oxygen/air to the patient via wire-heated tubing at flow rates of 1-2 L/kg/min.[a,7] These flow rates are approximately 10 times the flow

rates considered tolerable by traditional nasal oxygen catheters, and are thought to be more comfortable due to the preconditioning of gases.[a,b,7,8]

Our objective was to assess the effects of HFNC on respiratory noise/work of breathing and oxygenation/ventilation in dogs with signs of UAO or hypoxemia during recovery from general anesthesia. We hypothesized that in dogs experiencing upper respiratory difficulty during recovery, that HFNC would decrease work of breathing (WOB) and support oxygenation without negatively impacting carbon dioxide levels.

Methods

Dogs were prospectively enrolled from July 2016 to August 2017 in this preliminary evaluation of Optiflow™ HFNC use for palliative relief of UAO in the recovery period from general anesthesia.[c] Consent was obtained prior to patient enrolment. This pilot trial was approved by the University of Guelph Institutional Animal Care and Use Committee.

Patients were eligible for inclusion if, in the immediate post-anesthesia period (2 hours following extubation), signs of UAO (stertor/stridor accompanied by increases in respiratory rate or effort) or hypoxia (SpO_2 <96%) were identified, during breathing of room air or traditional methods of oxygen supplementation. Patients were treated with sedation at the attending clinician's discretion. The HFNC nasal prong interface size was selected to provide 50% occlusion of the nares. The flow rates were initiated at 0.5-1.5 L/kg/min.[a] The FiO_2 was set at the discretion of the attending clinician and could be adjusted depending on the dog's oxygenation status.

Patient information including signalment, body weight, body condition score (5-point scale), and reason for anesthesia were recorded. Vital parameters (heart rate, respiratory rate, oscillometric or Doppler blood pressure), SpO_2, and scores for sedation, tolerance, and dyspnea (adapted from a human pediatric respiratory score)[9] were recorded (Table 1) immediately prior to HFNC (time 0)

and post-HFNC initiation at 30 min, 60-90 min, and again at 7+/-1 hours if the patient was still receiving HFNC. Arterial or venous blood samples were also collected at these times. HFNC was discontinued when no longer required as determined by the attending clinician, or in the event urgent re-intubation was deemed necessary. Descriptive statistics were reported for all parameters due to the small sample size.

Results

Animals. A total of six dogs met the criteria for UAO requiring respiratory assistance in the post-anesthesia period, five within the 2-hour period post-anesthesia and one at 24 hours due to ongoing upper airway obstructive signs following extubation. Five dogs were brachycephalic breeds including two bulldogs, two French bulldogs, one pug; the non-brachycephalic patient was a Jack Russell terrier. Median age was 10.4 years (range 1.1 to 14.8 years). Median body condition score was 3.5/5 (range 3-4), with median body weight of 12.7 kg (range 8.3-23.6 kg). Sedatives/analgesics used during HFNC administration included: buprenorphine, hydromorphone, butorphanol, gabapentin, trazodone, acepromazine, propofol.

Surgery and recovery. The type of procedure, prior to HFNC application, included: three dogs for BOAS correction (staphylectomy, sacculectomy +/- wedge resection alarplasty), one C2-C3 ventral slot for intervertebral disc disease, one brain MRI, and one parathyroidectomy + thyroidectomy. In the non-brachycephalic dog, everted laryngeal saccules were discovered in the post-parathyroidectomy recovery period, due to prominent UAO post-extubation. A laryngeal sacculectomy was subsequently performed.

Five dogs were receiving supplemental oxygen post-extubation, and 5/6 dogs had HFNC initiated for non-hypoxemic signs of UAO. Four of these dogs were receiving non-invasive traditional oxygen supplementation, and no dog had

a SpO_2 below 96%. One French bulldog was enrolled due to immediate desaturation upon attempts at extubation and thus, was extubated directly to HFNC. Origin of samples for blood gas analysis were arterial for one dog throughout data collection, arterial for one dog at 60 minutes post-initiation of HFNC, and venous for all remaining samples.

Parameters of Interest. The HFNC interface was easily adapted to the brachycephalic facial structure (Figure 1). Results at each time point (median and range) on HFNC are listed in Table 2. Dyspnea scores tended to decrease over time (Table 2). The median PCO_2 was similar at all time points (Table 2), however one patient experienced a $PvCO_2$ >60 mmHg after 30 minutes that resolved in one hour, only to return by the 7 hour recording. Another patient had a rise in $PvCO_2$ from 54.8 to 57.7 mmHg from time 1 hour to 7 hours. The remaining four dogs had stable or improved PCO_2 measurements relative to baseline. The dog that had a ventral slot performed experienced frequent goose-honk coughing (10 coughs in 30 minutes) during recovery that worsened at the 24-hour mark. After initiation of HFNC, the frequency was reduced to 2 coughs in the next 30 minutes and no coughing at 60 minutes. Subsequently, when HFNC was removed to determine if the cough had resolved, the patient resumed coughing (12 coughs in the 30-minute trial off HFNC).

Outcome. The HFNC system was discontinued at 1.5 hours in one dog, 3 hours in two dogs, 8.75 hours in one dog, and >12 hours in two dogs. All six dogs were discharged from hospital.

Complications. One dog required orogastric intubation for relief of severe aerophagia at 1.5 hours after HFNC initiation at a flow rate of 0.6 mL/kg/min. Following decompression, the patient was maintained on 0.8 mL/kg/min HFNC flow rate for 19 hours with no further complications. There were no clinical air-leak syndromes identified.

Discussion

This is the first described use of HFNC for palliation of canine upper respiratory difficulty in the post-anesthesia recovery period. The HFNC interface was easily adapted to the brachycephalic facial structure and well tolerated in dogs with stridor. In the authors' opinion, there was clinical improvement in the degree of stridor and upper respiratory obstructive breathing patterns when HFNC was initiated, based on dyspnea scores. The discussion of HFNC availability has become a part of the presurgical consultation for brachycephalic patients at this institution.

Due to the high gas flows created by HFNC at 1-2 L/kg/min, HFNC may be a novel modality for providing non-invasive CPAP to dogs.[a,7,10] The flow-dependent positive airway pressure may allow for constant splinting of the upper airway in an open position, alleviating obstruction caused by excess tissue mass in the pharynx.[1,10] The high flows may also reduce the inspiratory resistance in brachycephaly, resulting in improved efficiency and WOB.[1,10] This may explain the trend of decreasing dyspnea scores with HFNC in this series.

Intervention with HFNC also appeared to reduce the severity of stridor in these dogs. In a study of 20 people post-cardiac surgery with prophylactic post-extubation HFNC, its use was found to reduce respiratory rates and dyspnea scores compared to patients receiving standard oxygen supplementation, and resulted in a 25% increase in end-expiratory lung volume.[11] It is possible that the CPAP provided by HFNC provides nasopharyngeal splinting, while also improving post-anesthesia atelectasis and overall respiratory efficiency.[10,11] Early intervention with HFNC may lessen the inflammation caused by the traumatic nature of obstructive breathing, often potentiated by recent endotracheal intubation in BOAS.

In these dogs, respiratory rates initially increased in 50% of patients at 30-90 minutes post-HFNC initiation, prior to improving. This phenomenon was also noted with experimental use of HFNC in dogs with normal lungs.[a] Flow rates in HFNC can meet or exceed the patient's peak inspiratory flow rate and patients

require time to adjust. In human patients, cervicothoracic discomfort has been described,[7] though this is difficult to assess in these dogs given the use of sedation/analgesia in this study. A slower titration of optimal flow may ameliorate the sensation experienced in the conscious patient.

Relative to their initial dyspnea scores, 5/6 dogs improved over the trial period, with one dog showing no change. Although the lack of control group eliminates the ability to claim superiority of HFNC over standard recoveries, HFNC in these dogs with UAO, may have added comfort and relief as is seen in human patients.[7,10] No conclusions regarding the ability of early intervention with HFNC to avert gastrointestinal or respiratory sequelae can be drawn from this non-randomized, uncontrolled study. However, early alleviation of obstruction and improved respiratory mechanics may reduce potential consequences of obstructive breathing patterns. The authors speculate that decreasing the inspiratory resistance and the provision of CPAP is likely to account for the palliative effect of HFNC in this population of dogs.

In this study, two dogs developed hypercapnia. One dog was transiently hypercapnic post-HFNC initiation ($PvCO_2$ 62.3 mmHg after 30 minutes and 50.7 mmHg at 60 minutes). This increase was likely secondary to the increased resistance to exhalation that occurs with the high gas flows. Alternatively, sedation or opioid use in the brachycephalic patient may have played a role in the transient rise in $PvCO_2$. Interestingly, current human literature suggests that a significant rise in PCO_2 is rarely encountered, although small increases in PCO_2 may be noted.[7] Nasopharyngeal washout is likely the mechanism by which hypercapnia is avoided during the application of HFNC.[10] However, proper interface fitting allowing for adequate nasal leak, or presence of open-mouth breathing, is imperative for elimination of CO_2 and relief of excessive distending pressures.[10]

One brachycephalic dog in this case series developed severe aerophagia after initiating HFNC. The authors hypothesize that inappropriate interface fitting (reduced opportunity for nasal leak) accounted for air trapping within the stomach

causing inadequate pressure-release. In this case, the nasal prongs did not occlude more than 50% of the external nares, however internal nasal anatomy cannot be evaluated externally and may be more delicate in the brachycephalic dog, as has been demonstrated in neonates and women.[10] Alternatively, if the prongs are seated deeply within the nares, eliminating space for leakage, the pressure provided by the high flows may be more than anticipated.[10] Viable options in this event include using a smaller interface, insertion of only one nasal prong (50% overall nare occlusion), reduction in flow rate, or ensuring an air leak via open-mouth breathing. In a recent experimental study of HFNC in healthy dogs, aerophagia was present in all post-HFNC radiography, however, no dog required clinical intervention.[a]

Although this case series included a very small number of dogs, it demonstrates the potential role for HFNC during post-anesthetic recovery in dogs with signs of UAO. In conclusion, HFNC appeared to reduce the severity of stridor and WOB in select patients with UAO during recovery from general anesthesia. Future prospective, randomized, controlled, clinical trials are necessary to confirm the utility of this respiratory support modality in this patient population, and the effect on outcome variables.

Footnotes

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c. Fisher-Paykel Optiflow™ HFNC System, Fisher-Paykel Healthcare, East Tamaki, Auckland.

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Table 1. Scoring systems

Score	Parameter
Dyspnea Score	
0	Normal RR, no to mild effort
1	RR ~40-48, able to eat/sleep/rest, no use of accessory muscles
2	RR~40-48 and/or: focused on respirations, mild abdominal component to breathing, occasionally will lie down, +/- willing to eat
3	RR 48-60 and/or: lips retracted, neck extension present, moderately increased respiration with abdominal component, paradoxical breathing
4	RR >60 with marked respiratory effort and/or: extreme restlessness, abducted elbows, unwilling to lie down despite sedation
Sedation Score	
1	Bright, alert, no discernable sedation
2	Mild sedation, appears sleepy or quiet
3	Moderate sedation, appears very sleepy, +/-recumbent but rousable
4	Heavy sedation, recumbent and difficult to rouse
5	Profound sedation, recumbent and cannot be roused
Tolerance Score	
0	Did not ever bother at interface
1	Paw/rub interface 1x
2	Paw/rub interface 2x
3	Paw/rub interface >2x

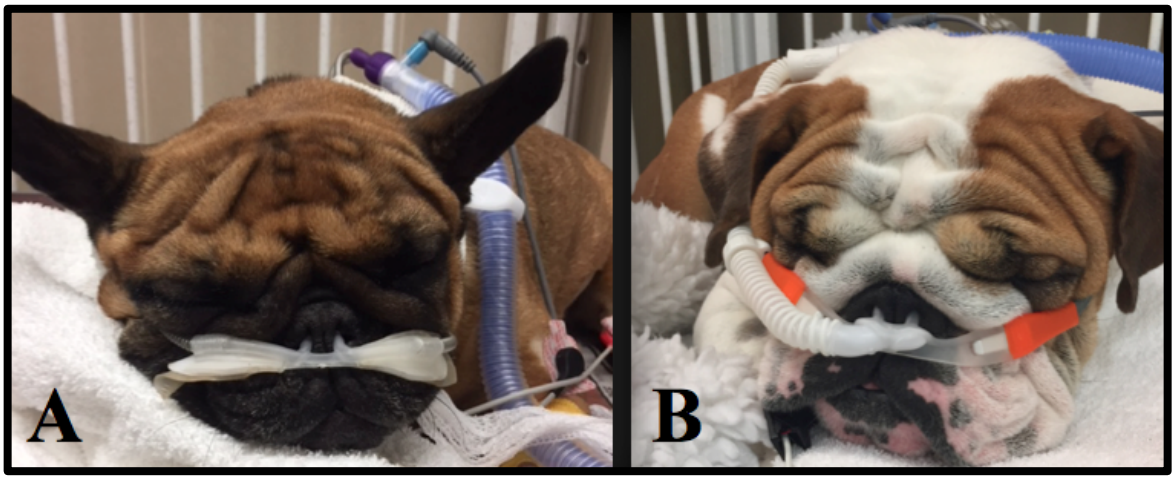
Table 2. Data collected at each time point on HFNC (median and range*)

Characteristic	0	30 min	60-90 min	7±1 hours
Number of dogs	6	6	6	3
Prescribed Variables				
Flow rate (L/kg/min)	0.23 (0.1-0.3)	1 (1-1.5)	1 (0.6-1.5)	0.8 (0.8-1)
FiO_2 (%)	NA (NA-100)	60 (30-100)	43 (30-80)	40 (35-40)
Vital Parameters				
SpO_2 (%)	98 (92-100)	100 (99-100)	99 (98-99)	100 (99-100)
Respiratory rate (brpm)	24 (20-144)	32 (12-180)	28 (12-180)	12 (12-16)
Heart rate (bpm)	125 (60-170)	108 (45-174)	106 (50-200)	88 (70-100)
Temperature (°Celsius)	37.8 (36.7-38.1)	38.1 (34.2-38.9)	37.8 (34.9-40)	36 (35.1-37.6)
Mean blood pressure (mmHg)	111 (102-167)	110 (92-113)	101 (90-134)	93 (87-147)
Scoring Systems				
Dyspnea Score (0-4)	3 (1-4)	2 (0-3)	2 (0-4)	0 (0-1)
Sedation Score (1-5)	2 (0-2)	2 (0-3)	2.5 (0-3)	3 (1-3)

Tolerance Score (0-3)	0 (0-3)	0 (0-3)	0 (0-2)	0 (0-1)
Blood Gas Analysis				
Number of arterial and venous samples	1 arterial 4 venous	1 arterial 4 venous	2 arterial 4 venous	0 arterial 3 venous
PaO_2 (mmHg)	100	145	182 (94.3-270)	-
PvO_2 (mmHg)	49.2 (37.6-63.9)	49 (45.4-71.1)	50 (49.4-66.3)	47.9 (42.9-53.3)
$PaCO_2$ (mmHg)	62	50.1	49 (46.4-51.6)	-
$PvCO_2$ (mmHg)	50 (41.6-57)	50.2 (43.5-62.3)	46.6 (41.8-54.8)	57.7 (50.7-64.1)

**Range is presented within parentheses.*

Figure 1. Pediatric (A) and adult (B) HFNC interface in brachycephalic dogs.



CHAPTER 5

Summary & Conclusions

General Discussion

The aim of this thesis was to determine whether high flow nasal cannula (HFNC) oxygen therapy could be used to ameliorate dyspnea in dogs, with acceptable feasibility and safety. High flow nasal cannula oxygen therapy has demonstrated promising results in respiratory care in adult, pediatric, and neonatal human medicine,[1] and this thesis has demonstrated similar findings in dogs. Overall, HFNC use has been considered more comfortable, simple to set-up, and highly effective in improving respiratory parameters in emergent human patients struggling to breathe.[2] The use of HFNC as established in healthy dogs, canine acute hypoxemic respiratory failure and inflammatory upper airway obstruction supports these findings, in that the system is accepted by dogs, is easy to set up, and provides improved oxygen delivery to veterinary patients.

The first study sought to determine whether Optiflow^{TM} HFNC oxygen supplementation was feasible, tolerable and safe in dogs. Secondary objectives included evaluating its potential to provide continuous positive airway pressure (CPAP), as well as the effects of high flow oxygen delivery on blood gas and vital parameters. Indeed, both the adult and pediatric HFNC nasal prong interfaces were adequately fitted to dolicocephalic dogs. Although HFNC systems are adapted for the human face, their application to the facial structure of dogs was possible. The pediatric interface design was better suited for dogs than the adult design, as it remained in place without modification. The pediatric prong design is ideal for brachycephalic patients whose overall head and facial structure are flattened and more similar to that of people. For similar reasons, the system likely has great potential in cats. However, concerns exist for appropriate sizing in feline patients due to their small nare size. Occlusion of a single nare with the smallest currently available prongs, to achieve the recommended nasal prong to

nare ratio of 50%, may be feasible. The design of the adult interface however, with its weight distributed unilaterally to one side of the face, required a securing suture over the zygomatic arch for support, as well as a piece of modeling clay at the nasal septum to better seat the prongs. The latter modification was required to direct the flow of gas into the nares given the marked difference in anatomical structure of the human nose and dolicocephalic muzzle. Ideally modifications to the adult interface involving the elimination of the slight prong curvature designed for the human nose and redirection of gas flow into the nares at an upwards angle, would be more suitable for the dolicocephalic dog. Since the completion of this study, Fisher & Paykel Healthcare has redesigned the contour of the pediatric interface with Waveflex^{TM} technology, which still holds all benefits of the previous design, however, enhances prong security and offers a wider range of sizes for neonates and pediatric human patients.[a] Since this prong design was not tested in our canine pilot study, it is uncertain whether our results apply to these prongs, though we suspect that the findings would be unchanged.

High flow nasal cannula oxygen support was considered successful in healthy dogs, based on providing a reliable FiO_2 with CPAP provision at flow rates ≥ 1 L/kg/min. Several dogs receiving flow rates of 1 L/kg/min had positive airway pressures recorded on expiration, however, negative oropharyngeal pressures were encountered during inspiration in about half of the dogs. While some dogs did not achieve CPAP at this moderate gas flow, when 2 L/kg/min was provided, nearly all dogs demonstrated CPAP on oropharyngeal pressure tracing. In the clinical setting, the degree of CPAP is unknown, though these studies suggest that trials of increasing flow rates are required to achieve this benefit of HFNC therapy. It should be noted that a flow rate of 2.5 L/kg/min was trialed for margin of safety assessment, and failed to demonstrate additional CPAP benefits. This very high flow rate resulted in severe behavioural intolerance in some dogs, as well as a change in respiratory pattern and a decrease in systemic blood pressure at its initiation, and for these reasons this flow rate cannot be recommended. Conversely, a low HFNC gas flow rate of 0.4

L/kg/min (below recommended flow rates in human medicine), did not demonstrate sufficient positive airway pressure, and produced a more variable and inconsistent FiO_2. The findings from the first study ultimately lead to recommended HFNC flow rates of 1-2 L/kg/min, on the basis of FiO_2 reliability, the provision of CPAP, and improved tolerance without the need for heavy sedation.

This study in healthy dogs, also highlighted that using traditional nasal cannula (TNC) oxygen supplementation at previously recommended flow rates produced unreliable FiO_2 and, as expected, did not provide CPAP. The veterinary standard oxygen rate of 100 mL/kg/min did not provide a FiO_2 that was different from that of room air. For patients with hypoxemic respiratory failure, effective administration of oxygen is paramount to the therapeutic plan, and the results of this study suggest that TNC flow rates are sub-optimal for oxygen supplementation in dogs. Realistically, flow rates above 100 mL/kg/min are necessary to increase FiO_2 consistently above room air and methods to achieve rates above 100 mL/kg/min (eg. bilateral nasal catheter oxygen administration) should be considered.

With regards to complications, HFNC therapy demonstrated minimal risk despite trials of flow rates above those established in pediatric and adult human medicine. In all healthy dogs, aerophagia was documented radiographically on completion of the HFNC trial, however, no dog required clinical intervention for this finding. In patients with clinical respiratory signs, aerophagia is often identified. The potential effects of HFNC use on pre-existing aerophagia cannot be commented on based on the findings of the first study. Additionally, there was a small rise in $PaCO_2$ found in healthy dogs with the application of HFNC oxygen support. This rise in CO_2 was small and it was noted in dogs without pulmonary compromise nonetheless, this finding warrants further investigation especially in dogs with pulmonary pathology, given the lack of active ventilation provided by HFNC devices. Overall, the Optiflow^{TM} HFNC system designed for use in people,

was adaptable for use in dogs, and complications that would prevent its use in dogs were not encountered.

The second study assessed the application of HFNC oxygen therapy to patients with respiratory disease, in a prospective, sequential, pragmatic trial. At the outset of this study, concern existed for implementing HFNC in patients with an elevated $CO_{2,}$ based on the above findings in healthy dogs and previously published human literature.[1] Throughout the 18-month trial period and with further experience, minimal change in PCO_2 was noted, as was supported by the current human literature.[3,4] Despite the lack of ventilation provided by this non-invasive oxygen support modality, increases in CO_2 may be prevented during the application of HFNC therapy due to nasopharyngeal washout and thus, elimination of deadspace. Patients with mild hypercapnia were therefore considered for HFNC therapy in this second study, as improvements in work of breathing (WOB) may further improve hypercarbia. However, at the completion of the study, when evaluating the effects of flow rate of HFNC therapy, there was a positive correlation between flow rate and $PaCO_2$, indicating the need for continued monitoring of this variable, especially as increasing flow rates are applied. This fact is not surprising, and echoes the need to monitor blood gas variables when a patient is provided with positive-end expiratory pressure by a mechanical ventilator. Given the previously demonstrated CPAP achieved by HFNC therapy at higher flow rates, similar monitoring is required when implementing HFNC oxygen therapy.

Ultimately, HFNC oxygen supplementation in 22 acutely hypoxemic dogs failing TNC oxygen support had a 45% patient survival to discharge. High flow oxygen therapy offered a new modality that obviated the need for mechanical ventilation in a modest cohort of patients. Moreover, it should be noted that though half of the dogs died or were euthanized, the option for non-invasive respiratory palliation with HFNC while awaiting owner arrival to the hospital, demonstrated an unexpected place for HFNC in veterinary critical care. Escalation from traditional oxygen to HFNC has been integrated into standard

practice in the veterinary intensive care unit hosting this clinical trial, since the availability of additional support measures, especially for clients that cannot financially pursue invasive ventilation, can be life-saving. Overall, this study demonstrated improved WOB and oxygenation with the use of HFNC in a subset of dogs with hypoxemic respiratory failure, and revealed that this new modality may bridge the gap between traditional oxygen therapy and mechanical ventilation (MV).

The third study was a brief investigation of the feasibility and effect of HFNC use on dogs with evidence of upper airway obstruction in the post-anesthetic period. The anatomical changes associated with brachycephaly are the most common reason for obstructed airflow during times of somnolent breathing, and thus, brachycephalic dogs were primary candidates for inclusion. Subjectively, HFNC use reduced the extent of stridor, which was demonstrated by a trend in decreasing dyspnea scores. In these patients with upper airway obstruction, hypercapnia is often present due to the obstruction to airflow due their anatomy +/- exacerbated by inflammation of pharyngeal/laryngeal tissues due to recent intubation and/or surgery. In this study, all but one dog demonstrated similar or improved CO_2 measurements with use of HFNC. However, since hypercapnia did occur with use of HFNC, a larger randomized, controlled trial is needed to determine the incidence of CO_2 changes in this patient population.

The importance of proper nasal or mouth leak was exemplified with HFNC application in one dog in the third study. Despite appropriate external nasal prong to nare occlusion ratio, the brachycephalic facial structure may be internally more stenotic or delicate. Though aerophagia was subclinical in the two earlier studies, this was not the case for one dog in the post-anesthetic upper airway obstruction group that required orogastric decompression. The anatomical changes associated with brachycephaly alter the pressure and airflow distribution and caution should be exercised when applying HFNC empirically to novel patient populations. This brief report served to demonstrate an additional place for the

use of HFNC to alleviate respiratory distress in veterinary medicine, while relaying important possible sequelae.

Limitations

The authors acknowledge several limitations in this project. The majority of the limitations centre around pragmatic study designs, despite the intention to demonstrate clinically applicable findings in the veterinary literature.

With use of HFNC oxygen therapy in people, clinical air-leak syndrome has been infrequently reported but, can lead to fatalities.[5] In the veterinary clinical trials included in this project, routine imaging was not included in study design and precluded the ability to definitively refute the possibility for subclinical air-leak syndromes (pneumomediastinum, pneumothorax). In the study investigating HFNC oxygen support in healthy dogs, no air-leak syndromes were detected on post-HFNC radiography, however, due to the incomplete randomized block design, radiographs were taken only after completion of HFNC trials (and radiography was not performed on completion of TNC oxygen supplementation). In the AHRF and post-anesthetic canine patients, HFNC did not result in any known clinical pneumothoraces, however, scheduled imaging throughout use of HFNC oxygen supplementation was not standardized, with repeat imaging being at the discretion of the attending clinician. Moreover, in human pediatric patients, the rate of air-leak syndrome is 1%,[6] thus the power in our studies was insufficient to detect such a rate of complication. However, we believe there remains a low risk to canine patients. Future studies seeking evaluation of the incidence of any air-leak associated with use of HFNC should include standardized radiography during use of HFNC oxygen administration.

Arterial blood gas analysis is paramount for studies assessing the efficacy of oxygen administration on gas exchange. Due to pragmatic design of this project, an arterial catheter was not required and venous sampling could be performed. While this is more practical, comparisons between venous and arterial samples are not possible. Alternative, surrogate oxygenation parameters

(eg. oxygen saturation and SpO_2:FiO_2 (S/F) ratios) were assessed for practical purposes. However, for future studies, consideration for consistent sampling (i.e. only venous or arterial) should be made for improved analysis of this variable. Inconsistency in sampling method lead to difficulties in trending of oxygenation variables. Based on this limitation, S/F ratios were incorporated into the analysis, and significant changes in pulse oximetry proved more useful than PO_2. With use of S/F ratios however, the oxyhemoglobin dissociation curve dictates that this ratio can only be trended as a surrogate for PaO_2:FiO_2 when the SpO_2 is between 80-97%.[7] As such, trending of S/F ratio during HFNC oxygen therapy was limited. Ideally, arterial sampling would be an inclusion criteria in future trials. However, arterial line placement can add undue stress to dyspneic patients, and may be especially difficult to establish in the critically ill, small breed dog. Such stringent criteria would have a significant negative impact on case acquisition and study completion.

Scoring systems were employed in these studies to add a more objective measure of clinical assessments, though they are not without inherent bias. The dyspnea score used in the clinical trials was created at the time of study development, based on current human literature.[8] However, with score implementation, a discrepancy between the set respiratory rate and other descriptors within a score category became obvious. Further work on optimizing respiratory scores remains necessary, with consideration to exclude respiratory rate from the scoring system to better capture the effort or distress that patients are experiencing (eg. open mouth breathing, use of accessory muscles, ability to lie down, ability to eat / sleep, ability to respond to caregiver).

Another limitation encountered in the AHRF trial, was euthanasia and its impact on patient outcome when assessing the effect of HFNC oxygen supplementation. It is possible that etiology affected the ultimate outcome or decision of owners to continue therapy (eg. if a diagnosis with poor prognosis was established). Euthanasia is a major hindrance to exploring the true effect of HFNC. Unfortunately, the emotional and financial commitment associated with

hospitalization and care for a patient with respiratory distress often affects the owner's decision to continue care. Euthanasia impacts outcome analysis even in cases that are considered amenable to treatment. Despite the effect of this influence on our results, this is a realistic part of practicing veterinary medicine and, though a limitation in evidence-based medicine, it is the current nature of the profession and thus clinical research will continue to be affected. Furthermore, survival to discharge was not the only measure of HFNC success. For this reason, response to HFNC was assessed based on: acceptable tolerance, improved oxygenation, lack of significant change in PCO_2 or presence of hypercapnia, decreased respiratory rate and dyspnea score, and was determined by three investigators (one which did not participate in clinical administration of HFNC). Regardless, bias may have affected results in this form of evaluation. Evidence-based examination of objective measures (respiratory rate, SpO2, PO_2, PCO_2) limited response bias, however subjective assessments (eg. scoring systems) may have added a degree of bias.

In the third study investigating HFNC therapy in cases of upper airway obstruction during recovery from anesthesia, limitations involve the fact that the post-anesthetic period is fraught with multiple confounding variables, including sedative administration, variable recovery time (eg. recovery regardless of HFNC use) and HFNC oxygen administration. Strict inclusion criteria including the specific post-anesthetic time period would be beneficial for patient comparisons. The immediate post-extubation period was selected in this study, however, when clinical signs persisted or even worsened within the first day after anesthesia, need for use of HFNC resulted in one dog being included due to clinician-assessed requirement for assistance with upper airway obstruction. This may have led to exclusion of other patients that had difficulty after the 2-hour post-extubation time period. Selection of this short time period was made in an effort to reduce the potential contribution of new onset of pulmonary parenchymal disease, such as is seen with aspiration pneumonia secondary to regurgitation.

Though each study is not without limitations, these preliminary studies on HFNC form the foundation for future, specific question-based trial designs.

Future Directions

The importance of designing future HFNC trials around a predetermined research question cannot be overemphasized given the findings of this project. Our studies support further investigation into the use of HFNC in the post-extubation period for patients with upper airway obstruction, ie. in the brachycephalic patient. A formal randomized, controlled, clinical trial in brachycephalic dogs could confirm the suspected benefit of this new respiratory support modality in difficult anesthetic recoveries due to upper airway obstruction. Though blinding is not possible, this study would ideally involve a control group with randomization, to allow for conclusions to be drawn regarding superiority, or lack thereof, of HFNC relative to standard of care. Data collection of regurgitation events, onset/presence of aspiration pneumonia, return of stridor at discontinuation, need for sedation, arterial $PaCO_2$ monitoring, and post-HFNC radiography for documentation of aerophagia and air-leak, should be strongly considered as outcome variables of interest.

High flow nasal cannula oxygen support may have a place during and following small animal bronchoscopy. Bronchoscope diameter may preclude the use of an endotracheal tube and oxygen saturation is often maintained via standard flow-by oxygen therapy, however, desaturation events may limit completion of this diagnostic test. Applying HFNC therapy may offer superior oxygen supplementation and provide CPAP support during bronchoscopy. Further, should patients experience peri-procedural desaturation events, HFNC support may be continued until adequate respiratory status is regained. A prospective, randomized, controlled trial is worthwhile in this setting.

High flow nasal cannula oxygen therapy may also have a role as non-invasive respiratory support in the post-MV period, as is noted in human medicine.[9] The administration of HFNC oxygen support in the post-extubation

period may have an effect on need for re-intubation and success with HFNC in this area, may offer earlier extubation and reduced cost to clients. Such a study, including a control group, may involve a long trial period. Consideration of involving multiple centers to increase sample size, along with strict 'weaning success' definitions are strongly recommended.

An additional future study might also evaluate the use of HFNC oxygen support as a first-line therapy for use in the emergency department, in cases of severe respiratory distress. Ideally this would investigate whether enhanced patient stability could facilitate time for diagnosis and discussion with owners and lead to improvements in patient care or outcome. The evaluation of the effect of HFNC on outcome in specific etiologies, for instance, in cases of cardiogenic pulmonary edema (CPE), may also be worthwhile. There may be a distinct role for HFNC support in CPE, particularly for patients presenting to the emergency department with respiratory distress. The provision of standard oxygen therapy may not offer enough support, and through the addition of low-level CPAP provision, HFNC may help alleviate dyspneic sensations as diruetic therapy takes effect. In people, use of HFNC therapy in CPE is associated with success in avoiding intubation.[10]

The optimal timing for initiation of HFNC is also a question worth exploring. Initiation of HFNC at the point where MV is being considered, as was done in the AHRF study, may in fact lower response rates due to the severity or progression of disease to a critical state. The active humidification and heating offered with HFNC may lessen the energy demand for the critically ill patient, and may offer added comfort. Providing HFNC therapy at admission as stated above, prophylactically after anesthesia, to patients requiring standard oxygen rates >4L/min, or even instead of standard oxygen therapy, are questions that may be worth future investigation. It is clear that the studies in this thesis have only demonstrated the infancy of HFNC therapy in veterinary medicine.

Conclusion

In conclusion, use of Optiflow™ HFNC oxygen therapy is feasible and well tolerated in dogs. It offers the advantage of being able to non-invasively provide CPAP to conscious, spontaneously breathing dogs requiring assistance beyond that which is provided by traditionally used oxygen supplementation techniques. The HFNC system also affords the clinician the ability to prescribe the FiO_2, while the high gas flows ensure the patient is receiving a reliable FiO_2, as well as allowing for FiO_2 tapering in avoidance of the negative potential consequences of resorption atelectasis and pulmonary oxygen toxicity. The use of HFNC may improve patient comfort and WOB beyond the improvements seen in oxygenation, as a result of the heating and humidification of the gases. Similar to the widespread utility of HFNC in human medicine, this new modality has a life-saving place in veterinary practice in alleviating dyspnea in canine patients.

Footnotes

a. Optiflow FP Junior 2 Nasal Cannula Manufacturer information accessed 05/19/2018 https://www.fphcare.ca/hospital/infant-respiratory/optiflow-junior/understand/optiflow-junior-interfaces/optiflow-junior-2-interface/

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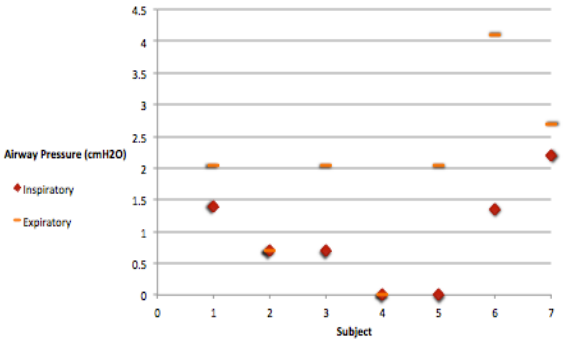
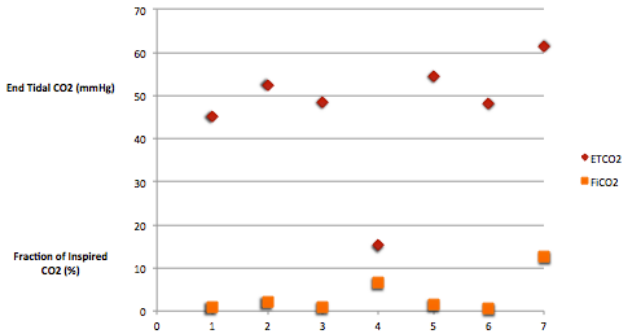
APPENDIX

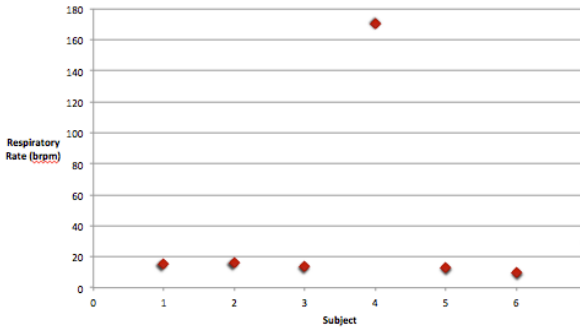
CHAPTER 2 Raw Data

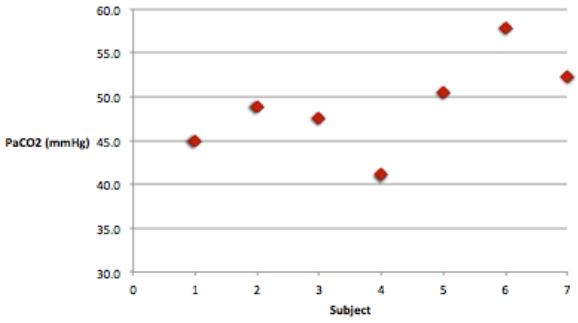
- Airway Pressure, Respiratory Rate, Airway Oxygen, Airway CO_2, $PaCO_2$, PaO_2 vs. Subject

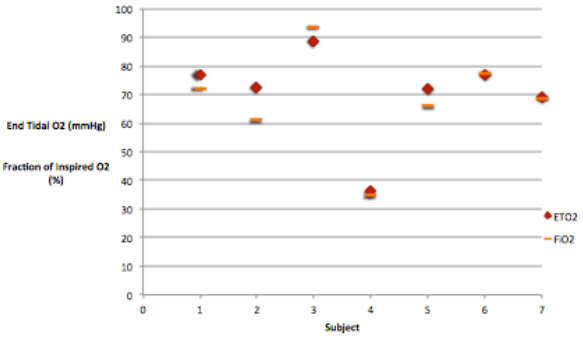
HFNC 0.4 mL/kg/min in Awake Dogs

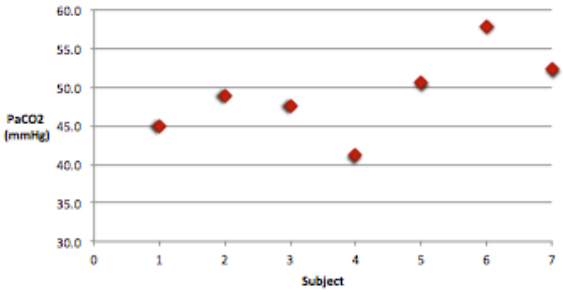




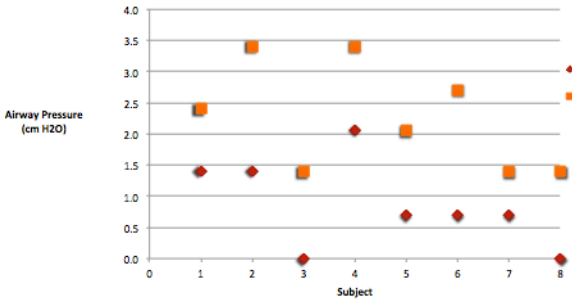


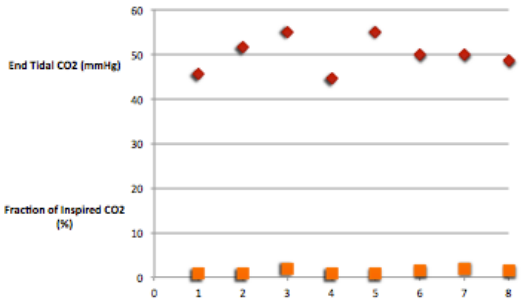


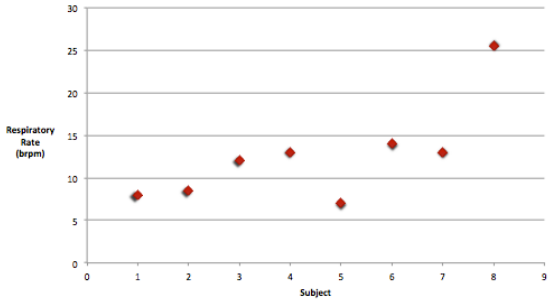


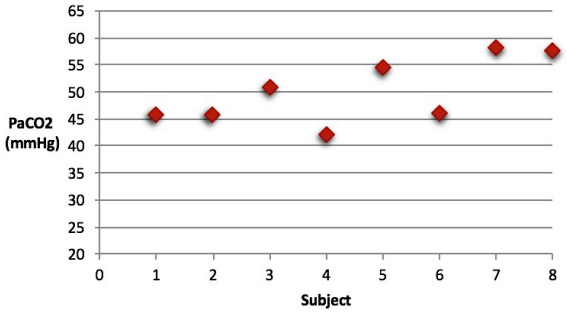


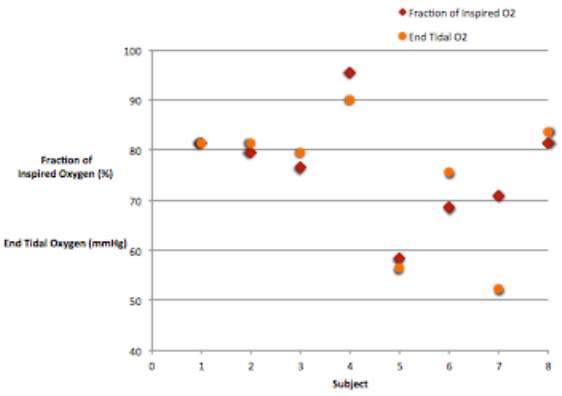
HFNC 0.4 L/kg/min in Sedated Dogs

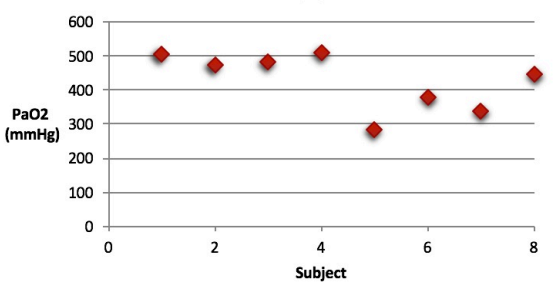




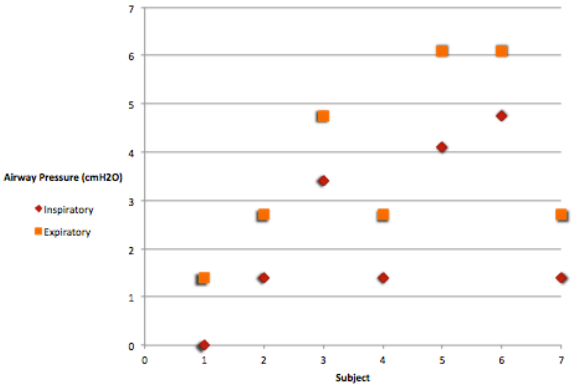


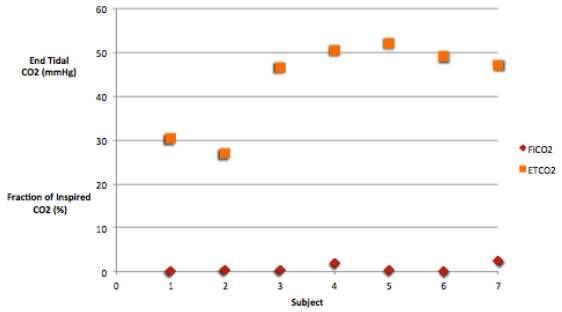


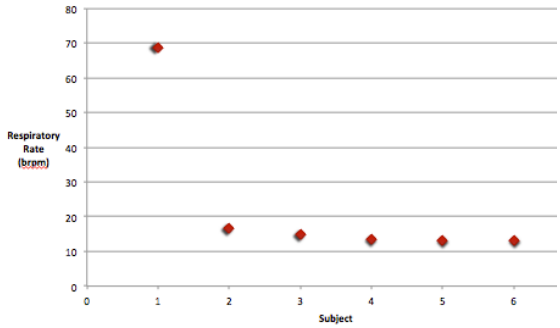


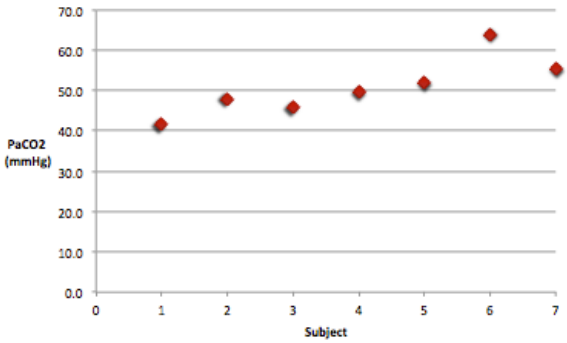


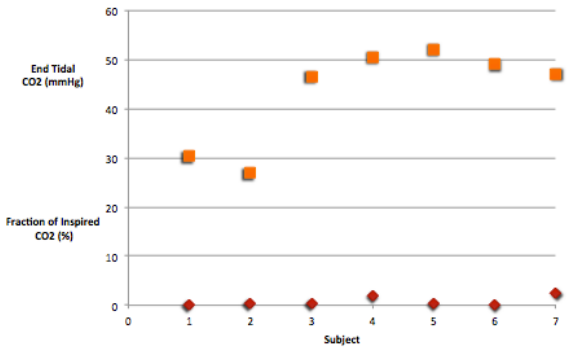
HFNC 1 mL/kg/min in Awake Dogs

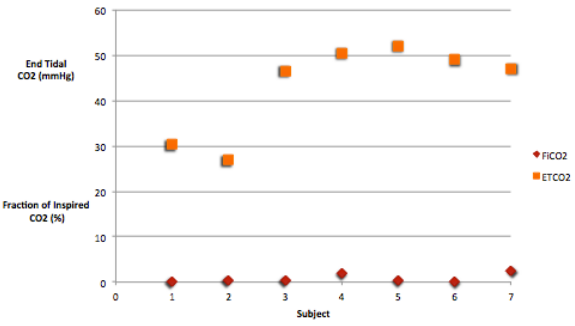




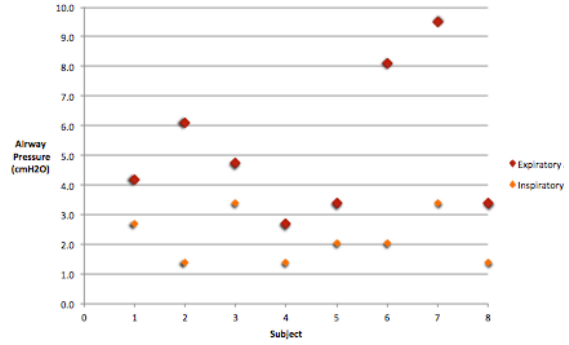


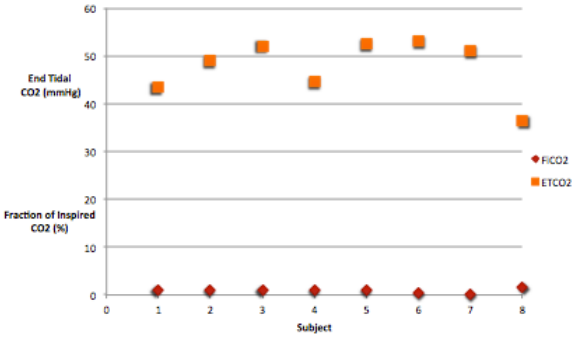


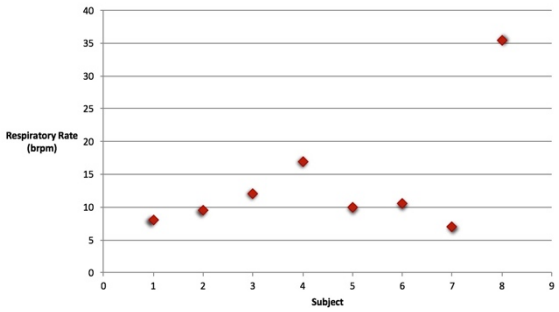


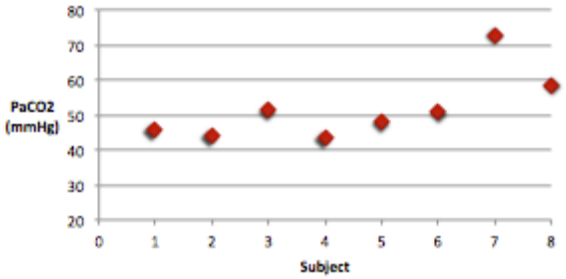


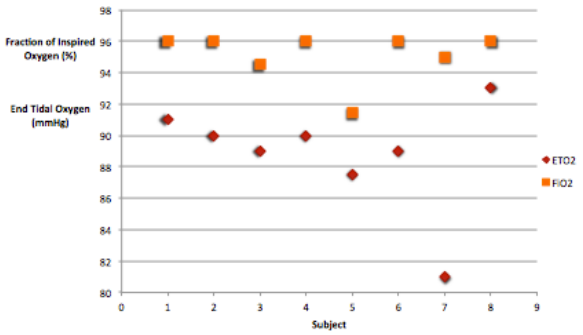
HFNC 1 L/kg/min in Sedated Dogs

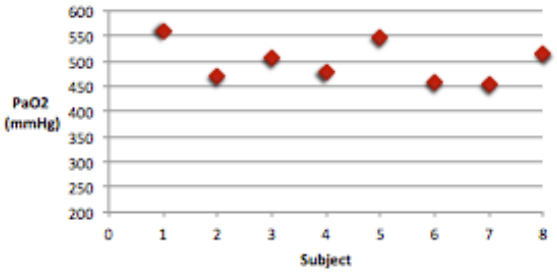












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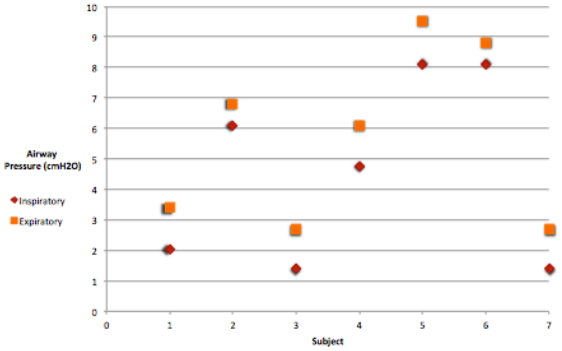
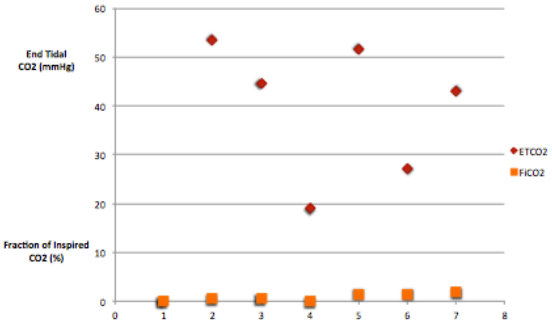
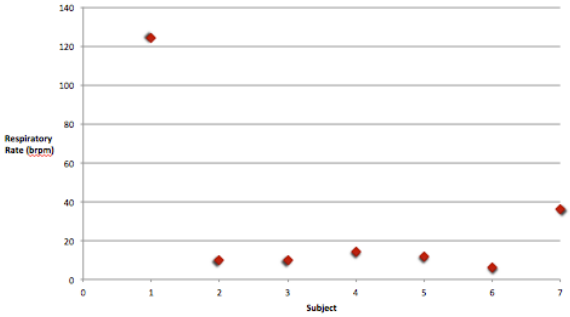
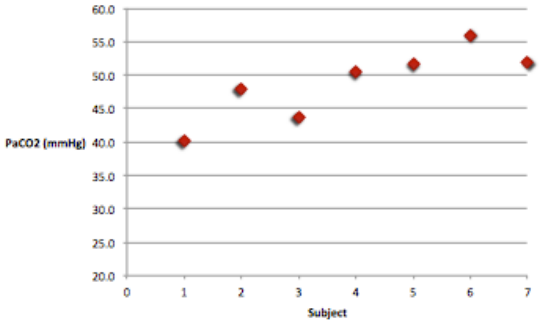
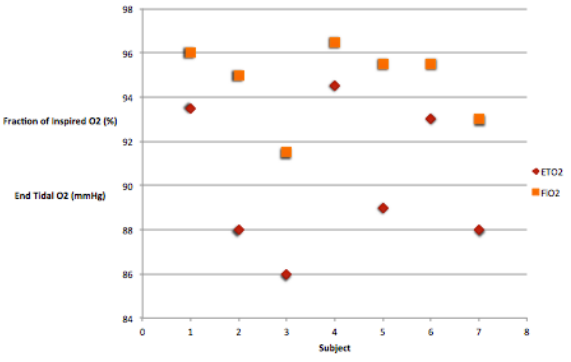
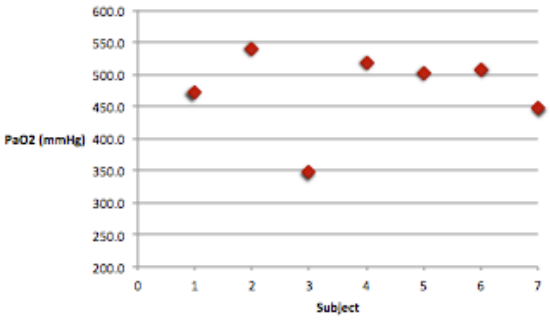




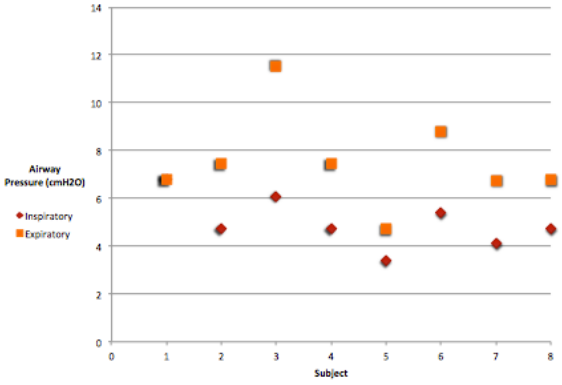


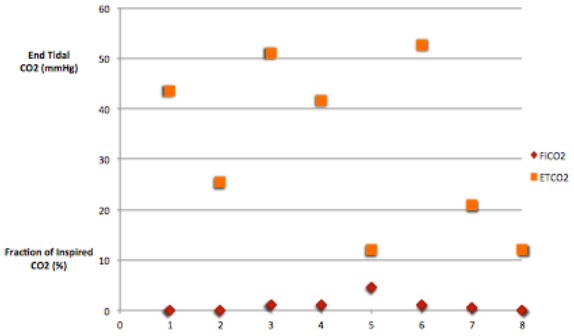


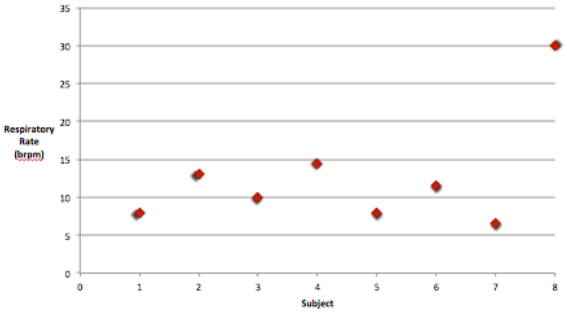


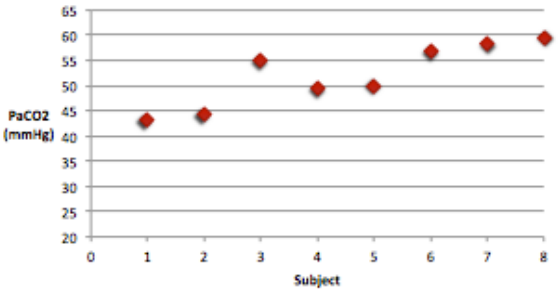


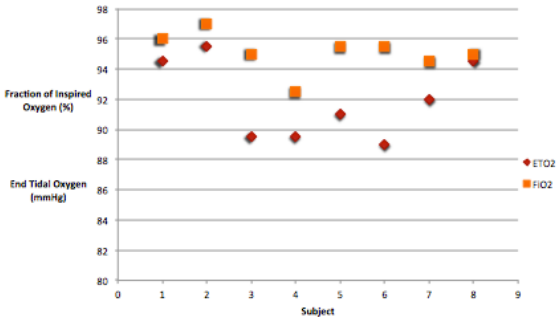
HFNC 2 L/kg/min in Sedated Dogs

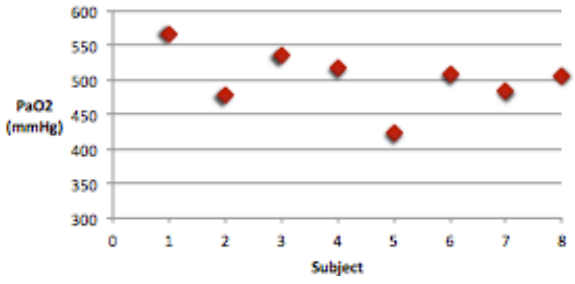




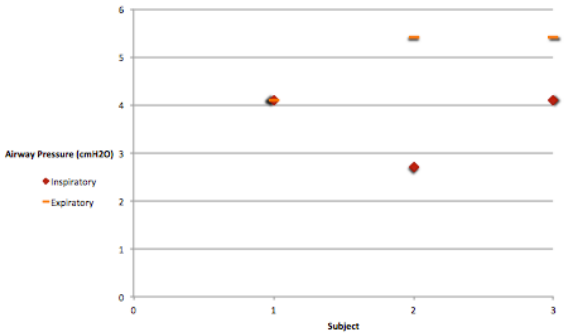


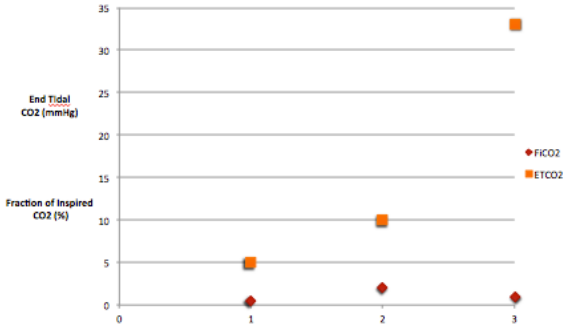


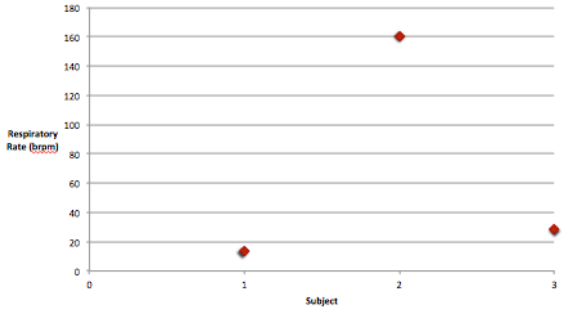


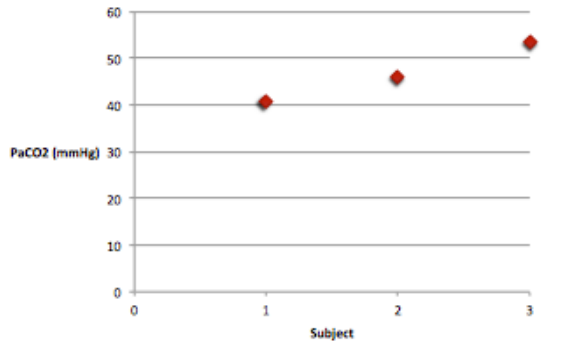


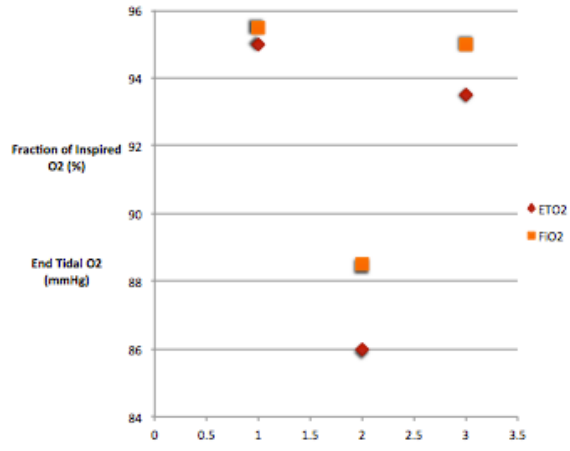
HFNC 2.5 L/kg/min in Awake Dogs

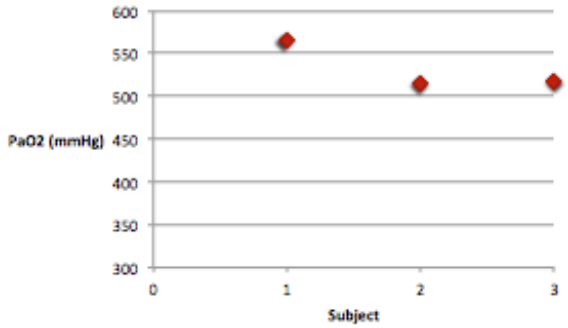




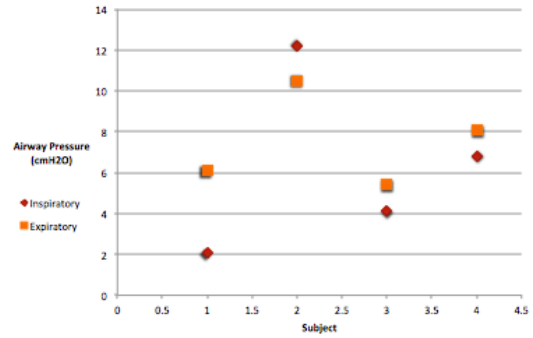


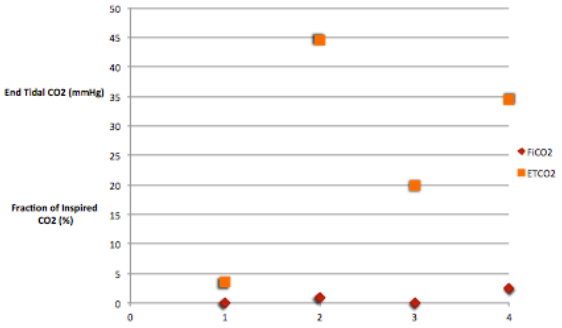


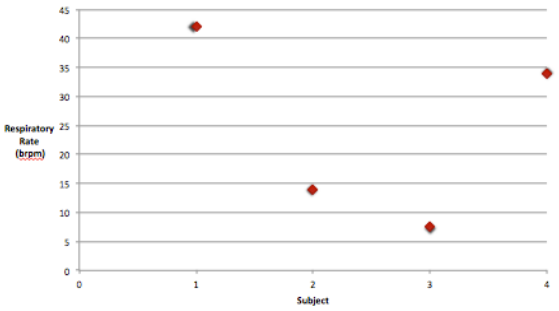


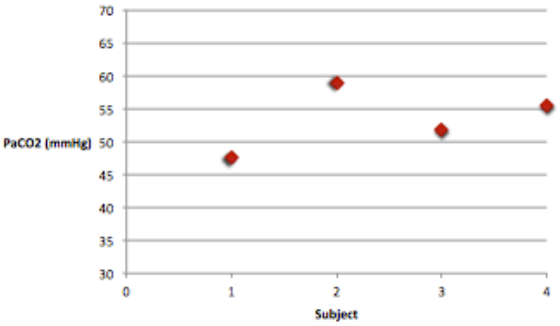


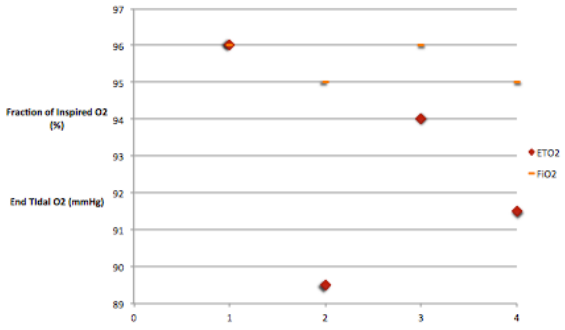
HFNC 2.5 L/kg/min in Sedated Dogs

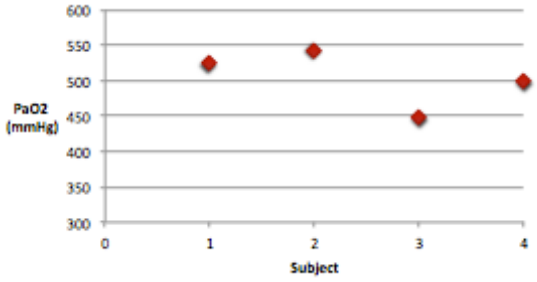




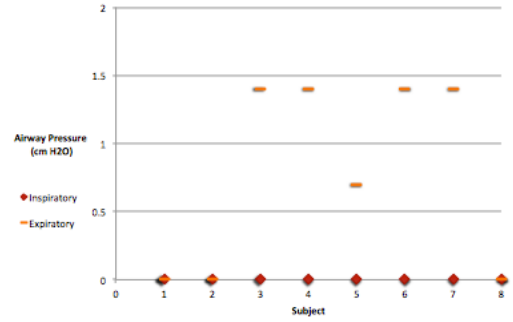


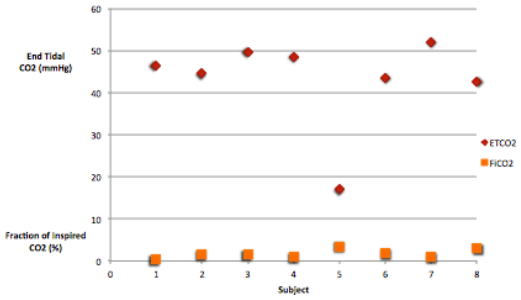


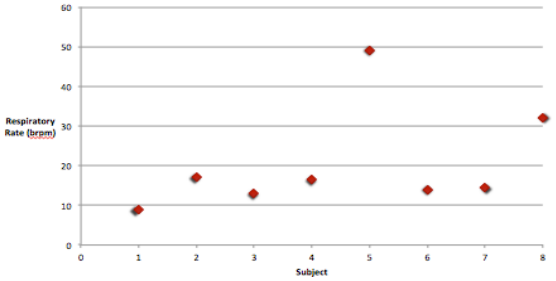


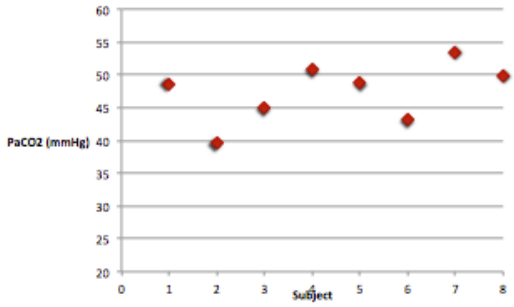


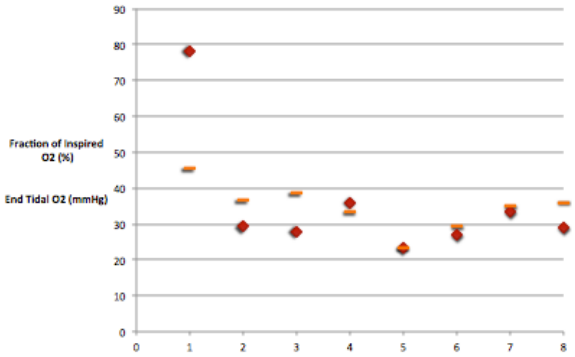
TNC 0.1 mL/kg/min in Awake and Sedated Dogs

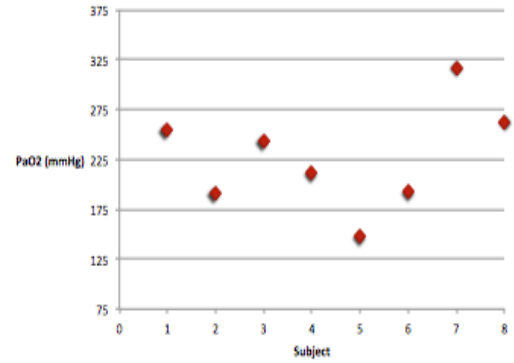




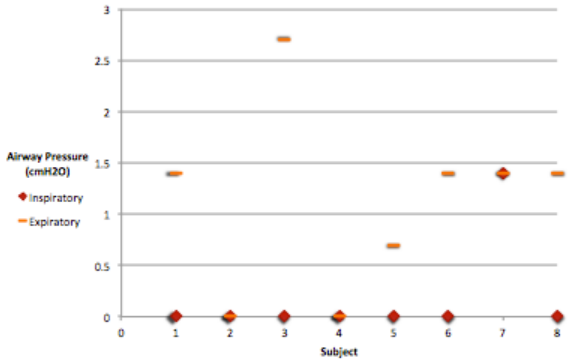


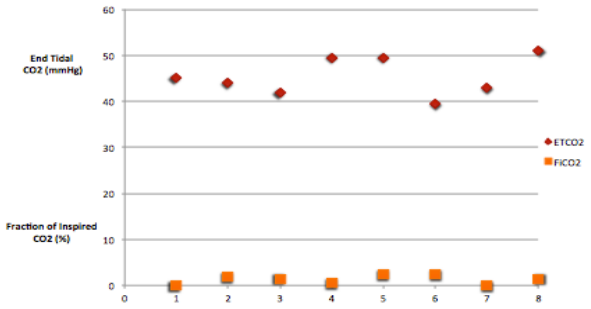


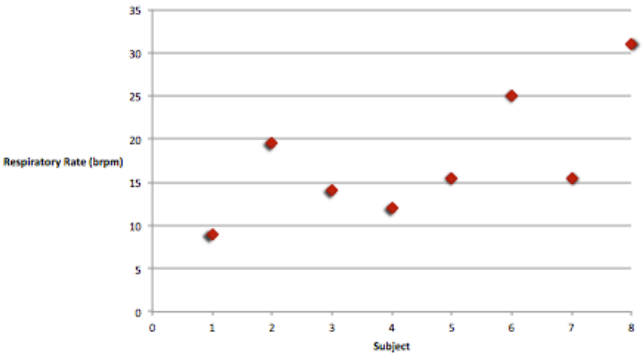


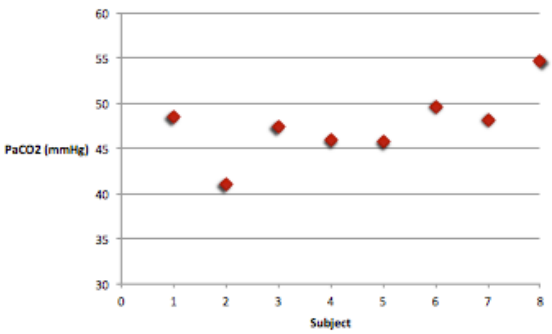


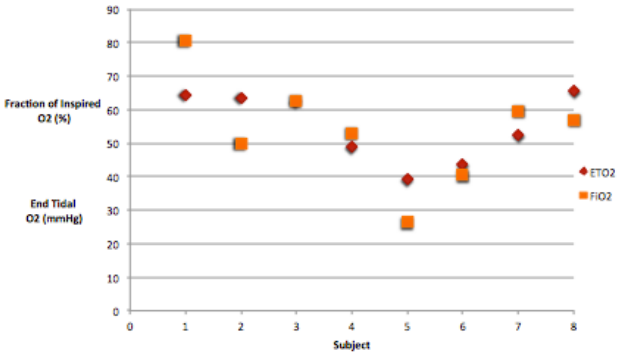
TNC 0.2 mL/kg/min in Awake and Sedated Dogs

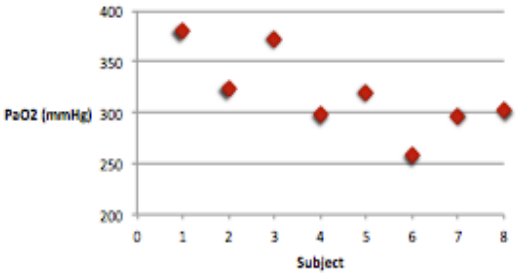




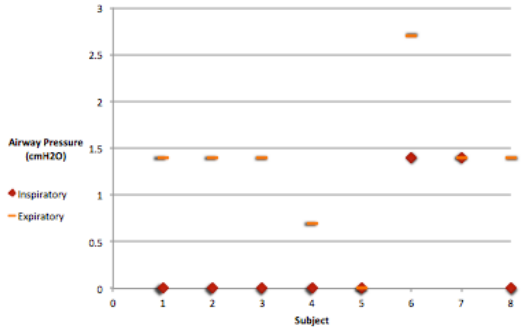


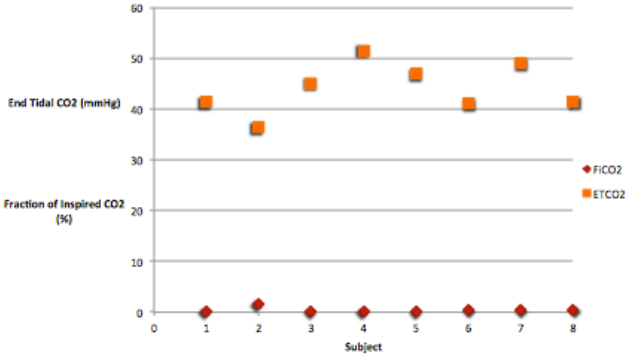


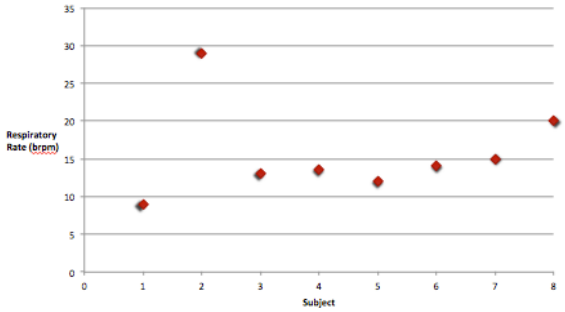


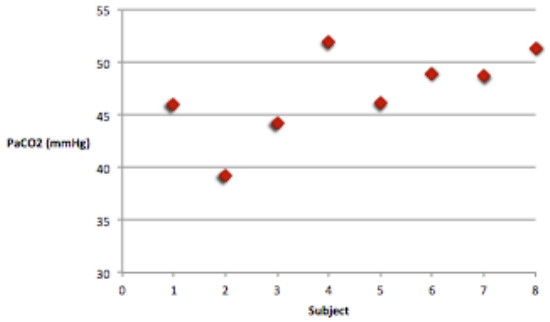


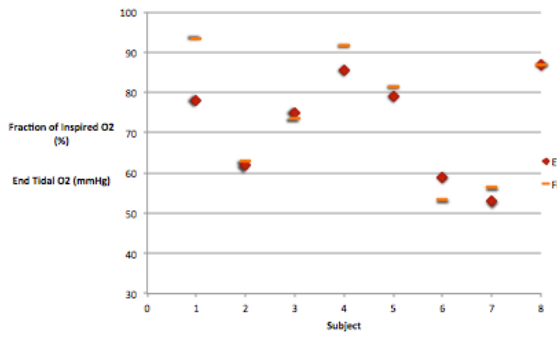
TNC 0.4 mL/kg/min in Awake and Sedated Dogs

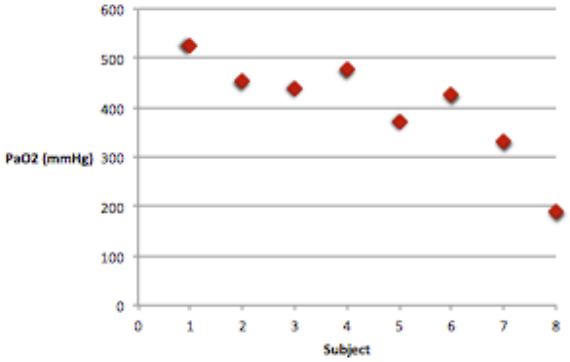






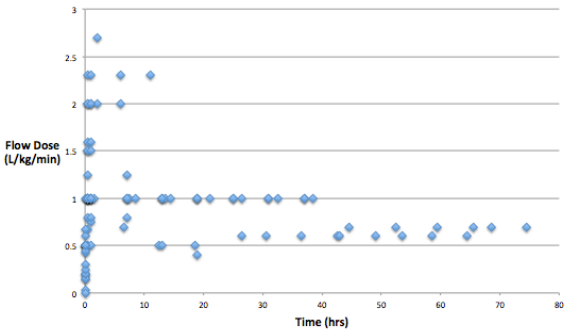


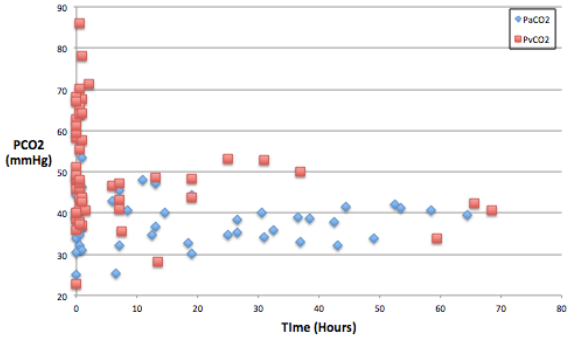


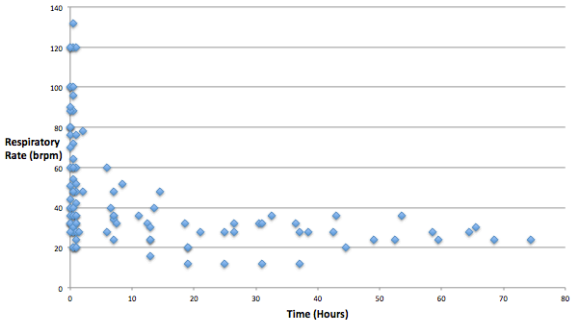


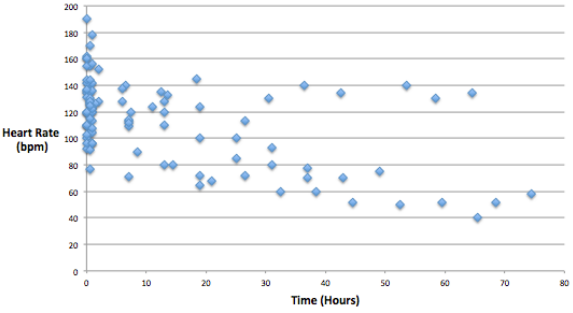
CHAPTER 3 Raw Data

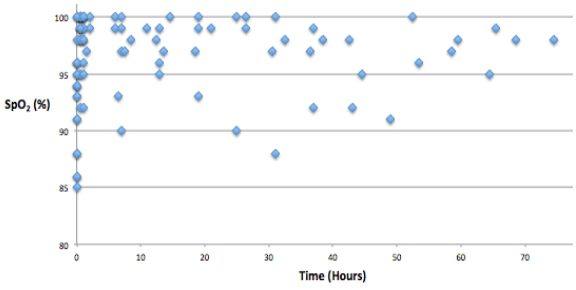
- HFNC Flow Dose, Respiratory Rate, SpO_2, PCO_2, Heart Rate, PO_2, vs. Time

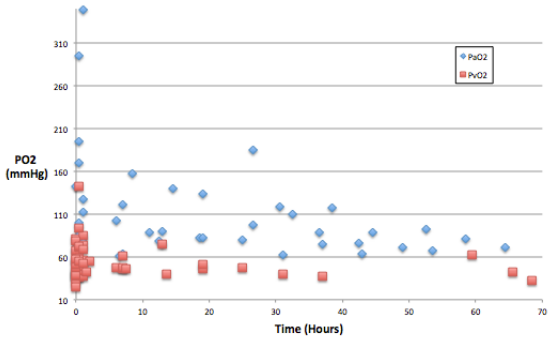




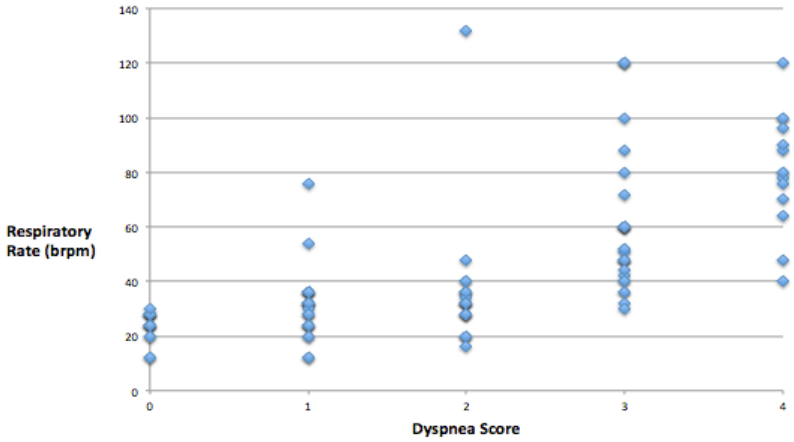








- Respiratory Rate vs. Dyspnea Score



- Heart Rate vs. Dyspnea Score