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Prospective pilot study for evaluation of High-flow Oxygen Therapy in dyspneic dogs: the HOT-DOG study

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Abstract

Objectives: To describe the use, effectiveness and tolerance of high-flow oxygen therapy in dyspneic dog.

Methods: Prospectively, dogs in acute respiratory distress admitted to the ICU between January and May 2018 that failed to respond to nasal oxygen therapy and medical stabilization after 30 minutes were transitioned to high-flow oxygen therapy and included in the study. High-flow oxygen therapy, delivering an inspired oxygen fraction of 100%, was carried out using an air/oxygen blender, active humidifier, single heated tube, and specific nasal cannula. Respiratory rate (RR), pulse oxymetry (SpO₂), heart rate (HR), and tolerance score were assessed every 15 minutes from T₀ (under nasal oxygen) to 1 hour (T₆₀), and PaO₂ and PaCO₂ at T₀ and T₆₀. Complications were recorded for each dog.

Results: Eleven dogs were included. At T₆₀, PaO₂, flow rate, and SpO₂ were significantly greater than at T₀ (171 ±123 mmHg vs 73 ±24 mmHg; P=0.015; 18 ±12 L minute⁻¹ vs 3.2 ±2.0 L minute⁻¹, P<0.01; 97.7 ±2.3% vs 91.6 ±7.2%, P=0.03, respectively). There was no significant difference in PaCO₂, RR, HR between T₀ and T₆₀. Tolerance score was excellent, and no complication occurred.

Clinical significance: This study established that high-flow oxygen therapy improves markers of oxygenation in dyspneic dogs and confirms that this technique deliver effective oxygen with comfort and minimal complications in this population.
Introduction

Supplemental oxygen administration is the first supportive measure provided to dyspneic dogs upon admission to an emergency facility. In veterinary medicine, oxygen therapy is mostly delivered by non-invasive techniques such as flow-by, nasal prongs, or oxygen cages. These methods are known as conventional oxygen therapy (COT) and can achieve variable fractions of inspired oxygen (FI\textsubscript{O}\textsubscript{2}) ranging from 21 to 70\% (Sumner & Rozanski 2013). When patients remain hypoxemic despite COT, clinicians may choose among more advanced oxygen delivery methods. One option is mechanical ventilation, which however requires prolonged general anaesthesia, continuous advanced care and is associated with frequent complications, high costs, and, depending on the underlying disease, a guarded prognosis - often leading the owner to a decision of euthanasia (Hopper \textit{et al.} 2007, Mueller 2007). In human medicine, non-invasive ventilation (NIV) is a popular method to avoid intubation. Continuous positive airway pressure (CPAP) is a NIV mode that has been validated in dogs (Briganti \textit{et al.} 2010, Staffieri \textit{et al.} 2014, Meira \textit{et al.} 2018). Continuous positive airway pressure is effective to improve arterial partial pressure of oxygen (PaO\textsubscript{2}) in companion animals when used with devices such as masks or helmets (Briganti \textit{et al.} 2010, Staffieri \textit{et al.} 2014, Meira \textit{et al.} 2018) and can be used in dyspneic animals.

In human medicine, a non-invasive oxygen delivery technique known as high-flow oxygen therapy (HOT) has emerged as an alternative to COT (Helviz \textit{et al.} 2018). This system allows for delivery of heated and fully humidified gas with high flow rates of up to 60 L minute\textsuperscript{-1} through a specific high-flow nasal cannula, with a FI\textsubscript{O}\textsubscript{2} ranging from 21\% to 100\% (Frat \textit{et al.} 2015). Such high flow rates are not achievable with COT because of technical limitations (flowmeters rates, diameter of the nasal prongs). Furthermore, administration of a partially humidified, cold gas could cause patient discomfort, desiccation of the nasal mucosa, airway constriction, impairment
of the mucociliary functions, and increased risk of infection if delivered at similar rates (Kallstrom

High-flow oxygen therapy uses an air-oxygen blender connected to a flow meter, an active
humidifier and heater, a heated breathing circuit, and a specific nasal cannula (Nishimura 2016)
(Figure 1). Warm and adequately humidified gas delivered at high flow rates has apparent
beneficial physiological effects that are increasingly recognized in humans. These include: good
tolerance (Sztrymf et al. 2012) and comfort (Roca et al. 2010, Frat et al. 2015), decreased
mismatch between the oxygen flow and the patient’s inspiratory flow (Sztrymf et al. 2012),
allowing precise setting by the clinician; generation of a low level of positive airway pressure
(Groves & Tobin 2007, Parke et al. 2011), decreased anatomical dead space by washing the
expired volume of carbon dioxide from the airway and replacing it with oxygen-enriched gas
(Helviz et al. 2018, Hernández et al. 2017, Millar et al. 2014), and decreased ventilatory drive and
work of breathing in obstructive human patients (Di Mussi et al. 2018), allowing the use of HOT
in hypoxemic and hypercapnic respiratory failure.

High flow oxygen therapy has recently been studied in veterinary medicine. It has been
shown to be a safe and effective method for oxygen delivery in sedated and awake healthy dogs
(Daly et al. 2017; Jagodich et al. 2019), and a preliminary retrospective study described its
successful use in six hypoxemic dogs (Keir et al. 2016). No prospective study reporting the use of
HOT in dyspneic dogs has been conducted. The objective of this pilot study was to prospectively
describe the use, tolerance and potential complications of HOT in dyspneic dogs.

Materials and Methods

Ethical statement

The study protocol was approved by the VetAgro Sup Ethics committee (number 1730).
This prospective pilot study was conducted between January and May 2018 in the emergency and critical care unit (SIAMU, VetAgro Sup) on client-owned dogs admitted for acute respiratory distress. Respiratory distress at admission was defined as a respiratory rate (RR) above 40 breaths minute$^{-1}$ associated with an abnormal respiratory pattern or laboured breathing at rest.

After admission, all respiratory distressed patients received 100% oxygen delivered via a single nasal cannula at 150 mL kg$^{-1}$ minute$^{-1}$ (Dunphy et al. 2002, Mazzaferro 2015), using a standard wall water humidifier (COT). Standard therapy for stabilization of the respiratory distress was administered based on the most likely diagnosis, at the discretion of the attending clinician, independently from the study. After 30 minutes of medical stabilization, dogs non-responsive to nasal oxygen therapy were transitioned to HOT and prospectively enrolled in the study. Dogs non-responsive to nasal oxygen therapy (inclusion criteria) were defined as persisting respiratory distress as previously defined or a SpO$_2$<95% under nasal oxygen at the end of the 30-minute stabilization period. Owner consent was obtained prior to transition from nasal oxygen therapy to HOT.

The exclusion criteria were a body weight below 2 kg, adequate response to COT defined as respiratory distress improvement and SpO$_2$>95%, or criteria for immediate intubation, defined as excessive respiratory effort with impending respiratory fatigue or failure, severe hypoxemia despite oxygen therapy (SpO$_2$<90% or PaO$_2$<60 mmHg), or a severe hypercapnia (arterial partial pressure of carbon dioxide (PaCO$_2$)>60 mmHg).
Early termination criteria were failure to tolerate HOT (defined by a tolerance score (TS) equal to 4, Table 1) and fulfilment intubation criteria (as defined above). Dogs with a do-not-intubate order remained on HOT despite being intubation candidates.

**High-flow oxygen technique description**

High flow oxygen therapy was delivered by a commercially available unit connected to a specific nasal cannula interface (Optiflow®, Fisher&Paykel Healthcare). The system is composed of an air-oxygen blender connected to oxygen wall source, a flow meter, an active humidifier and heater, a heated breathing circuit, and a specific nasal cannula (Figure 1). The nasal cannula is a soft silicone bilateral nasal prong with tubing that connects to the heated breathing circuit (Figure 2). The system allows for administration of humidified and warmed gas with a FIO$_2$ between 21 and 100%. Continuous humidification was ensured by a water chamber connected to a sterile water bag. Temperature was set at 37°C and administered to the patient via the heated breathing tube.

The nasal cannula was chosen according to the size of the dog’s nostrils, so that the cannula diameter would not exceed 50% of the diameter of the nostril and therefore allowed exhalation with minimal resistance (Daly *et al.* 2017). Seven different sizes were available (4 junior, 3 adult). Once the size of the nasal cannula was chosen, they were gently tightened behind the neck, and eventually secured with tape and sutured in place next to each nare (Figure 2).

In order to avoid recruitment of oxygen from the surrounding air and assure the delivery of the predetermined FIO$_2$, the oxygen flow rate was set to be equivalent to the dog’s minute ventilation (MV=RR*tidal volume) (Helvis *et al.* 2018). For homogeneity, tidal volume was set at 10 mL kg$^{-1}$ (Grimm *et al.* 2015). For example, a 30 kg dog with a RR of 80 breaths minute$^{-1}$ had a flow rate with HOT of 10*30*80=24 L minute$^{-1}$ (compared to a flow rate of 4.5 L minute$^{-1}$ with nasal oxygen therapy). The FIO$_2$ was set at 100% and the gas temperature at 37°C during the 60-
minute protocol. Once setting was ready, the patient was connected to the heated breathing tube.

At the end of the 60-minute protocol period, the FIO₂ was adjusted to the lowest level possible to maintain SpO₂>95%.

**Data recording**

The RR, SpO₂, heart rate (HR), TS (Table 1), flow rate, need for additional sedation, type and dose of sedative agent used and complications during HOT were recorded by the same operator (LH). Each of these parameters was recorded right after the 30-minute stabilization period (T₀), when dogs were still receiving nasal oxygen therapy. The oxygen delivery technique was then changed from nasal oxygen therapy to HOT and the parameters were recorded immediately at 15, 30, 45 and 60 minutes after T₀ (T₁₅, T₃₀, T₄₅, and T₆₀, respectively). A catheter was inserted in the dorsal pedal artery to allow drawing of arterial blood samples and evaluate PaO₂ and PCO₂ at T₀ (under nasal oxygen therapy) and T₆₀ (under HOT). Arterial blood gases measurements were performed on fresh whole arterial blood collected in a heparinized syringe according to the manufacturer’s instructions using an on-site VetStat (IDEXX Laboratories Inc.).

An APPLEfast scale (0-50 score, calculated from glucose, albumin, lactate, platelet count, and mentation score) was used in each dog at inclusion to stratify illness severity by mortality risk as previously described (Hayes *et al.* 2010).

**Outcomes**

The evolution of PaO₂, PaCO₂ and flow rate between T₀ and T₆₀, and evolution of RR, tolerance score, SpO₂ and HR every 15 minutes during the 60-minute protocol were recorded. The occurrence of complications due to the oxygen delivery technique during the protocol, requirement for escalation to intubation within 24 hours after admission and in-hospital mortality were also recorded.
Statistical method

Statistical analyses were carried out with JMP® version 13.1 (SAS Institute). All individual data were described with a spaghetti plot graphic. Data were tested for normal distribution with the Shapiro-Wilk test. Continuous variables were compared with paired t-tests. Data were expressed as mean ± standard deviation (SD) with 95% confidence intervals (CI). A value of P<0.05 was considered as statistically significant.

Results

Animals

During the study period, 11 dogs were included in the high flow oxygen therapy protocol. The breeds of dogs included were three Golden Retriever, two King Charles Spaniel, two Dachshunds and one each of Australian Shepherd, German Wirehaired Pointer, Jack Russell Terrier and Pomeranian. Four dogs were female neutered and seven were male neutered, with mean ±SD weights of 28.3 ±12.3 kg (range, 4.8 to 43.0 kg) and ages 7.8 ±3.8 years (range, 2 to 13 years).

Five dogs had a diagnosis of aspiration pneumonia, and one of each: cardiogenic pulmonary oedema, non-cardiogenic oedema following cluster seizures, leptospirosis infection, pulmonary haemorrhages following a car accident, pulmonary hypertension of unknown origin, and pericardial effusion. The mean ±SD APPLEfast score was 27.0 ±4.4

Recorded data

Dogs were receiving nasal oxygen therapy at T₀ and HOT at T₁₅, T₃₀, T₄₅ and T₆₀.

\[
PaO₂
\]
High-flow oxygen therapy allowed a significant increase in mean PaO$_2$ at T$_{60}$ (171 ±123 mmHg) compared to nasal oxygen therapy at T$_0$ (73 ±24 mmHg; P=0.015, 95% CI: 23 to 172 mmHg).

Individual data are presented in Figure 3. For every dog, PaO$_2$ increased after HOT initiation. Of the 7 dogs with PaO$_2$<80 mmHg at COT, 5 had a resolution of their hypoxemia one hour after HOT initiation.

Flow rate (Figure 4)

The mean oxygen flow rate was significantly greater with HOT (18 ±12 L minute$^{-1}$) than in nasal oxygen technique (3.2 ±2.0 L minute$^{-1}$, P<0.01, 95% CI: 8.0 to 22.5 L minute$^{-1}$). Flow rate with HOT ranged from 2 to 37 L minute$^{-1}$. Flow rate with nasal oxygen technique ranged from 0.7 to 6.5 L minute$^{-1}$.

Respiratory rate

Individual data are presented in Figure 5. Six dogs had a decrease in RR between T$_0$ and T$_{60}$. However, only 2 dogs reached our criteria of respiratory distress of less than 40 breaths minute$^{-1}$ at T$_{60}$ despite the use of HOT.

SpO$_2$, HR and PaCO$_2$

The mean SpO$_2$ was significantly greater at T$_{60}$ (97.7 ±2.3%) than at T$_0$ (91.6 ±7.2%, P=0.03, 95% CI: 0.7 to 11.5%). There was no significant difference at any time for HR or PaCO$_2$. All individual data are showed in figure 6, 7, and 8 (supplemental material).

Tolerance score
The TS remained low during the entire protocol. Only one animal displayed a TS of 3 when setting the HOT device, requiring additional sedation that lowered its TS to 2 or 1 depending on the protocol time. Another dog displayed a TS of 2 at two occurrences but did not need any additional sedation. Every other dog had a TS of 1 at every protocol time.

Complications

No complications due to the oxygen delivery technique occurred during the study. Nasal cannulas were easy to fix and to use. No injuries occurred due to the nasal cannula.

Intubation within 24 hours and mortality in hospitalisation

Five of the 11 dogs (45%) developed a need for intubation within 24 hours after admission. Due to financial reasons, only 3 of them (27%) were intubated. Six of 11 dogs (54%, including the 5 that presented intubation criteria) died during hospitalization. Death were due to deteriorating clinical state leading to cardiac arrest in 5 dogs and 1 euthanasia for prognostic reason.

Discussion

This is the first prospective clinical trial evaluating the effectiveness and tolerance of HOT in respiratory distress dogs. Our study shows the potential for HOT to be an efficient, safe and well-tolerated alternative to COT with nasal oxygen therapy to deliver oxygen. This technique allows for a significant increase in PaO₂ in dogs, with the PaO₂ more than doubling between nasal oxygen therapy and HOT within only one hour. This finding is consistent with the human (Sztrymf et al. 2012, Frat et al. 2015, Makdee et al. 2017), and the veterinary literature. Indeed, Daly et al. (2017) and Jagodich et al. (2019) in healthy dogs, and Keir et al. (2016) in hypoxemic dogs showed this PaO₂ improvement after HOT. With such an increase in PaO₂ during a short
period of time, HOT raised concern for oxygen toxicity if continued for a long time. For homogeneity in the study design, the authors chose to keep the FIO\textsubscript{2} up to 100% during the 60-minute protocol, but FIO\textsubscript{2} was decreased immediately at the end of the protocol to the lowest required FIO\textsubscript{2} to reach a SpO\textsubscript{2}>95%. As high-flow devices offer multi-configurable solutions for flow and FIO\textsubscript{2}, these two parameters can be changed easily to fit patient’s demand. Once the targeted oxygenation parameters are reached and plateaued, the FIO\textsubscript{2} should be decreased under 60% as soon as possible to avoid oxygen toxicity (Guenther 2019).

In the present study, flow rates with HOT ranged from 2 to 37 L minute\textsuperscript{-1} and resulted in an increase in PaO\textsubscript{2} in all cases (Figure 3). By delivering higher flow rates, HOT systems are less prone to allow inhalation of room air during patient inspiration than traditional oxygenation systems (Helvis \textit{et al.} 2018). Different systems exist for high-flow delivery: Precision flow (Vapotherm), Optiflow (Fisher&Paykel Healthcare), Airvo system (Fisher&Paykel Healthcare). Each of them has specific characteristics and has to be used with their specific nasal cannula to ensure appropriate flow rate, temperature, and FIO\textsubscript{2}. In our study, we used the Optiflow system which was easy to use and offer a multi-configurable solution for patients requiring HOT. This system relies on an O\textsubscript{2}/air blender, and FIO\textsubscript{2} of 100% is obtained with use of oxygen wall not mixed with air. No internal system was available to ensure that the delivered FIO\textsubscript{2} at the nasal cannula was at 100%. We were not able to measure the delivered FIO\textsubscript{2} in our study, and some dogs were panting during measurements, so we could not ensure that we were delivering the pre-set FIO\textsubscript{2}. Moreover, a recent study with the same system showed that, when delivering a FIO\textsubscript{2} of 100%, the effective delivered FIO\textsubscript{2} increases with flow rate and varies between 72.2% and 95% for flow rate from 0.4 L kg\textsuperscript{-1} minute\textsuperscript{-1} to 2.5 L kg\textsuperscript{-1} minute\textsuperscript{-1} (Jagodich \textit{et al.} 2019). In our study, flow rate ranged from 0.44 to 1.84 L kg\textsuperscript{-1} minute\textsuperscript{-1}, so we can hypothesise that the effective FIO\textsubscript{2} did not reach 100%. Despite this limitation, our study confirms that HOT allows increase in PaO\textsubscript{2} in clinical settings.
In human medicine, several studies have showed a significant decrease of RR after initiation of HOT (Roca et al. 2010, Sztrymf et al. 2011, Sztrymf et al. 2012, Makdee et al. 2017). In our study, six dogs had a decrease in RR between T₀ and T₆₀, but with very variable evolution among time (Figure 5). The dogs were included in this study because of respiratory distress with failure to respond to nasal oxygen therapy, that could reasonably not resolve in one hour, especially as our population mainly had principally respiratory distress secondary to aspiration pneumonia. Finally, they were treated with HOT early in the course of their respiratory distress (30 min after admission), meaning that other treatments, such as diuretics, antibiotics, etc., did not have time to be effective. Mackdee et al. (2017) showed a significant decrease in RR after one hour in the HOT group compared to COT group in human patients with cardiogenic pulmonary oedema. Another study comparing RR between patients under nasal oxygen therapy or HOT in a more homogeneous population would be of great interest to differentiate between effects of time versus effects of treatment.

By enhancing the heating and humidification of nasal cavities, HOT has been shown to improve patient comfort in human medicine (Roca et al. 2010, Boyer et al. 2011, Sztrymf et al. 2012). In one veterinary study in hypoxemic dogs, HOT intolerance requiring sedation was noticed in 1/6 dogs (Keir et al. 2016). However, no TS was used in this study. Jagodich et al. (2019), using a different TS associated with a respiratory score, showed that HOT tolerance was inversely proportional to flow rate, and flow rate above 2.5 L minutes⁻¹ were not well tolerated. In this study, the HOT administered with specific nasal cannula was easily tolerated and displayed very low TS during all the study period. It would have been interesting to compare tolerance of COT and HOT, but it was not the purpose of this study, and more studies on HOT tolerance are therefore needed. Moreover, one study in human medicine showed that temperature seems to significantly impact the comfort of dyspneic patients with high flows: for equal flow, patient
comfort was significantly higher at 31°C compared to 37°C (Mauri et al. 2018). The impact of temperature was not evaluated in our pilot study and could be assessed in a larger population.

No clinically relevant complications related to the oxygen therapy technique were noted during our study, which therefore supports previously published studies of HOT safety in dogs (Keir et al. 2016, Daly et al. 2017, Jagodich et al. 2019). Jagodich et al. (2019) showed that at flow rates above 2 L kg\(^{-1}\) minute\(^{-1}\), dogs became less tolerant. Our study showed that lower flow rate allowed improvement of oxygen parameters with good tolerance. However, in the study of Daly et al. (2017), one dog had radiographic evidence of gastric distension, and in the study of Jagodish et al. (2019), 8 out of 8 dogs had aerophagia noted on radiographs. As our dogs were dyspneic, we did not perform any abdominal radiographs to evaluate the incidence of gastric distension. Nevertheless, we did not notice any abdominal distension during physical examination. Moreover, the potential long-term complications could not be assessed with our study design.

Given the inclusion criteria of severely dyspneic dogs, the mortality rate in our population was high. In the study of Keir et al. (2016), 3 out of 6 dogs died, of those, 2 died as a result of worsening hypoxemia. Our study population included various primary pulmonary disease processes, that have a different prognosis (Hopper et al. 2007). However, both in Keir et al. (2016) and in our study, aspiration pneumonia was the main diagnosis. Larger population is needed to compare influence on mortality rate of HOT.

Some limitations should be noted in the current study. The biggest limitations are the small sample size and the absence of control group that limits interpretation of the results. Our study was designed as a pilot study for a future randomised controlled study. Adding the result of a control group, treated with standard medical stabilisation and nasal oxygen therapy would have been of great interest to provide context for the magnitude of improvement in recorded parameters (i.e. effects of time versus treatment type). However, the dogs included in our study were severely dyspneic, and not adding HOT to their therapeutic plan could have raised ethical concerns.
Second, HOT has been showed to have several physiological effects allowing improvement of PaO$_2$. In dogs, Jagodish et al. (2019) showed that HOT provides CPAP and predictable oxygen support in healthy dogs. As our study was a clinical study, it was not possible to use more invasive monitoring to differentiate between a positive effect on PaO$_2$ related to a therapeutic effect of the HOT on respiratory mechanic or related to enrichment of inspired oxygen. Third, the long-term implications of HOT were not evaluated, and our results (especially tolerance and complication) should be validated in a longer study. Finally, the inclusion of patients with different respiratory distress causes could have change the results, as some patients could benefit more or less from HOT.

**Conclusion**

This study is the first in veterinary medicine to prospectively confirm that HOT could deliver effective oxygenation and comfort with minimal complications in dyspneic dogs, and gives practical information on HOT use in dogs.
Bibliography


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<th>Description</th>
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<tr>
<td>1</td>
<td>The patient is calm, comfortable; no agitation; no attempts to remove the nasal cannula</td>
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<tr>
<td>2</td>
<td>The patient tolerates the nasal cannula, but looks stressed and afraid; no attempts to remove the nasal cannula</td>
</tr>
<tr>
<td>3</td>
<td>The patient is agitated and tries to remove the nasal cannula; it is still possible to keep the nasal cannula on by gently restraining the patient</td>
</tr>
<tr>
<td>4</td>
<td>The patient does not tolerate the nasal cannula, is agitated, attempts to pull the nasal cannula; additional sedation is required to tolerate the oxygen delivery device</td>
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Table 1: Oxygen delivery device tolerance score (adapted from Staffieri et al. 2014)
Figure 1: Schematic representation of a high-flow oxygen device and its components (Drawing Dr Mathieu Taroni).

Figure 2: Dog with the specific high-flow nasal cannula

Figure 3: Change in Arterial Partial Pressure of Oxygen ($\text{PaO}_2$) for individual patients. HOT: High-flow oxygen therapy. In figures 3, 4, 5 and supplemental material, the same dog is represented by the same colours.

Figure 4: Change in flow rates for individual patients. HOT: High-flow oxygen therapy.

Figure 5: Change in respiratory rates (RR) for individual patients. HOT: High-flow oxygen therapy. *Data from one dog are missing.*

Supplemental material

Figure 6: Change in pulse oxymetry ($\text{SpO}_2$) for individual patients. HOT: High-flow oxygen therapy. *Data from one dog are missing.*

Figure 7: Change in heart rates (HR) for individual patients. HOT: High-flow oxygen therapy. *Data from one dog are missing.*
Figure 8: Change in arterial partial pressure of CO₂ (PaCO₂) for individual patients. HOT: High-flow oxygen therapy.
Conflicts of interest statement

No conflicts of interest have been declared.