Impact of flow and temperature on non-dyspnoeic dogs' tolerance undergoing high-flow oxygen therapy

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Title

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Authors

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Abstract

Objectives: To prospectively describe the impact of gas flow rate and temperature on dog's tolerance of high-flow nasal oxygen therapy (HFNOT) during recovery from anaesthesia, hypothesizing that higher flow rates and temperatures will decrease tolerance.

Methods: Twelve non-dyspnoeic client-owned dogs recovering from general anaesthesia were included in this study. After extubation, a nasal cannula was positioned and HFNOT was initiated. Two flow rates (two or four time the theoretical minute ventilation: HF2 and HF4), each of them combined with two temperatures (31 and 37°C: T31 and T37), were randomly applied (four conditions *per* dog). For each condition, cardiovascular and respiratory parameters (heart rate, respiratory rate, arterial systolic blood pressure, and pulse oximeter oxygen saturation), sedation score, and tolerance score were recorded at initiation (T_0) and after 10 minutes of accommodation (T_{10}).

Results: Sedation scores were not significantly different between the four conditions. Cardiovascular and respiratory parameters were not significantly different between any condition at both T_0 and T_{10}. Tolerance scores were good and not significantly different between any flow rate or temperature (HF2-T31: 4 (2-4), HF4-T31: 4 (2-4), HF2-T37: 4 (2-4), HF4-T37: 4 (1-4)).

Clinical significance: The gas flow rates and temperatures studied have no impact on tolerance during the recovery period of non-dyspnoeic dogs, and HFNC is well tolerated. Further studies are required to confirm these results in dyspnoeic dogs.

Keywords: Hypoxaemia, High-flow oxygen therapy, Dyspnoea, Mechanical Ventilation, Nasal cannula

Introduction

Oxygen supplementation is often the first line, lifesaving, treatment for hypoxaemic dogs. 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). They deliver oxygen as a cold dry gas, and can achieve variable fractions of inspired oxygen (FIO_2) ranging from 30 to 70% (Guenther 2018). Delivery of cold gas could cause patient discomfort at higher rates, desiccation of the nasal mucosa, airway constriction, impairment of the mucociliary function, and increased risk of infection (Dunphy *et al.* 2002; Kallstrom 2002; Kopelman & Holbert 2003; Kilgour *et al.* 2004).

Since the early 2000s, an advanced oxygen delivery method, called high flow nasal oxygen therapy (HFNOT) has received growing attention in human medicine (Guenther 2018). High-flow nasal oxygen therapy uses an air-oxygen blender connected to a flow meter, an active humidifier and heater, a warmed breathing circuit, and a specific bilateral nasal cannula (Pouzot-Nevoret *et al.* 2019). Respiratory support delivered with HFNOT machines is achieved by administration of humidified air/oxygen blends, using high flow rates up to 60 L/min, adjustable fraction of inspired oxygen (FIO_2) from 21 to 100%, and precise temperature, between 31 and 37°C (Mauri *et al.* 2018). Heated and moistened air inspired through the high flow nasal cannula (HFNC) improves comfort and compliance of the dyspnoeic human patient (Stefan *et al.* 2018).

High-flow nasal oxygen therapy recommendations settings for paediatric patients are a flow rate from 1 to 2 L/kg/min and a temperature of 34°C (Milési *et al.* 2018; Yurtseven *et al.* 2019). In adult patients, clinicians use flow rates from 50 to 60 L/min, independently of the weight, considering that lung capacities are almost equivalent from one individual to another. Several studies have suggested that an increase in the flow rate may decrease the work of breathing in patients with acute respiratory distress, although this may also impact the patient's comfort (Milési *et al.* 2013; Weiler *et al.* 2017). Recently, the influence of flow rate and temperature on patient comfort using HFNOT was evaluated (Mauri *et al.* 2018). In this study, adult dyspnoeic patients were more comfortable with the temperature set at 31°C than 37°C, with the HFNOT set at both 30 and 60 L/min. However, in the subgroup of patients with $FIO_2 \geq 45\%$, both lower temperature (31°C) and higher flow rate (60 L/min) led to higher comfort, highlighting the importance of flow rate and temperature on patient's comfort.

In veterinary medicine, feasibility, tolerance and safety of HFNOT have already been proven in healthy and hypoxaemic dogs (Daly *et al.* 2016; Keir *et al.* 2016; Daly *et al.* 2017; Pouzot-Nevoret *et al.* 2019; Jagodich *et al.* 2020). Its efficacy in increasing the arterial partial pressure of oxygen (PaO_2) compared to COT has also been demonstrated (Daly *et al.* 2016; Keir *et al.* 2016; Jagodich *et al.* 2019; Pouzot-Nevoret *et al.* 2019; Jagodich *et al.* 2020). Described flow rates in dogs range from 0.2 to 2.5 L/kg/min (Jagodich *et al.* 2019; Pouzot-Nevoret *et al.* 2019; Jagodich *et al.* 2020) or predefined flow rates of 20 to 30 L/min (Daly *et al*. 2017) all derived from human medicine (Kernick & Magarey 2010; Mayfield *et al.* 2014; Mauri *et al.* 2018; Yurtseven *et al.* 2019). However, a flow rate above 2 L/kg/min is not well tolerated in healthy dogs (Jagodich *et al.* 2019). A search on the Pubmed Database with the following keywords: “High flow oxygen” and “dog” was performed on 19th August 2020 and revealed no study reporting the impact of temperature on dogs’ tolerance of HFNOT.

The objective of this study was to evaluate the impact of the combination of two different flow rates and temperatures on the tolerance of HFNOT in healthy dogs. We hypothesized that higher flow rates and temperature might reduce tolerance in healthy dogs.

Material and methods

Ethical statement

This study protocol was approved by the VetAgro Sup Ethics committee (number 1849).

Study design and inclusion criteria

Written owner informed consent was obtained during the pre-surgery consultation. Client-owned dogs undergoing general anaesthesia for surgery or diagnostic procedures were enrolled in this prospective blinded randomized crossover study, from January to April 2019. All dogs were deemed healthy prior to the study on the basis of a complete physical examination.

At the end of the procedure, all dogs were transferred into the emergency and critical care unit (SIAMU, VetAgro Sup) for experimental convenience and were extubated when the swallowing reflex was recovered. In all dogs, type of procedure, duration of anaesthesia (from induction to discontinuation of isoflurane administration) and extubation time were recorded.

The person assessing patient tolerance scores was blinded to the machine settings which were determined through random order draws and set by another person.

Exclusion criteria

Exclusion criteria at enrolment included dogs below 9.5 kg. This exclusion criteria was due to paediatric manufacture settings of the HFNOT equipment, as paediatric mode of the Airvo^{TM} 2 System is preset to 34°C and thus, did not meet the study model. Other exclusion criteria at enrolment were abnormal findings at physical examination, aggressive or agitated dogs.

High-flow nasal cannula settings

The HFNOT was provided with the Airvo^{TM} 2 System in adult mode (Fisher & Paykel Airvo^{TM} 2 System, Fisher & Paykel Healthcare), using soft silicone bilateral nasal cannula (Optiflow^{TM+} nasal high flow canula, Fisher & Paykel Healthcare) as the interface to the patient. Nasal cannulas are available in 7 sizes (4 paediatrics and 3 adults). Depending on the dog size and morphology, a cannula was chosen as to occlude a maximum of 50% of the opening of the nares (Figure 1). The adult mode allows adjustable flow rates from 10 to 60 L/min, with a possible increase by steps of 1L from 10 to 25L, and by steps of 5L from 25 to 60L, and with adjustable temperature of 31, 34 or 37°C. The FIO_2 was maintained at 21% as all study dogs were deemed healthy.

Experimental procedure

In order to assure the delivery of the predetermined FIO_2, the flow rate of HFNOT should be set above the minute ventilation (MV) of the dog (MV = respiratory rate (bpm) x tidal volume (mL/kg)) (Helviz & Einav 2018, Pouzot-Nevoret *et al.* 2019). For each dog, theoretical MV was calculated with a standard respiratory rate of 20 bpm and a tidal volume of 20 mL/kg considering these dogs were healthy (Testa *et al.* 2014; Helviz & Einav 2018; Milési *et al.* 2018; Jagodich *et al.* 2019). The MV was then multiplied by 2 (High Flow x 2: HF2) or by 4 (HF4), depending on the tested flow rate. When calculated flow rate was under 10 L/min (minimum limit of the Airvo™ 2 System), flow rates of 10 L/min (HF2) and 20 L/min (HF4) were selected. Each dog underwent, in a random order, four 10-minutes steps:

A. Flow rate MV x 2 and temperature 31°C (HF2-T31)
B. Flow rate MV x 4 and temperature 31°C (HF4-T31)
C. Flow rate MV x 2 and temperature 37°C (HF2-T37)
D. Flow rate MV x 4 and temperature 37°C (HF4-T37)

Transition between each step was done automatically and gradually by the Airvo™ 2 System, and equilibration at each flow rate and temperature couple occurred for 10 minutes prior to each subsequent recording.

Monitoring

Three-lead electrocardiogram, pulse oximetry (SpO_2), and non-invasive systolic arterial blood pressure (SBP) were monitored during the whole study protocol (Dynascope DS-7100, Fukuda Denshi) (Figure 1).

Data collection

Immediately after extubation, baseline parameters (heart rate (HR), respiratory rate (RR), SBP, SpO_2 and temperature) were recorded by the same operator (CH). Then, the nasal cannula attachment was gently tightened behind the neck. Sedation score (SS, Table S1), tolerance score (TS, Table 1) and vital parameters (HR, RR, SBP and SpO_2) were recorded, before the beginning of HFNOT (PreHF). The tubing of the nasal cannula was connected to the Airvo^{TM} 2 System circuit and the first phase of the protocol was started. For each step, flow rate and temperature were determined by randomized drawing and set by a second operator (AF), different from the one assessing TS and SS. For each separate setting, HR, RR, SBP and SpO_2 were recorded at the beginning (T_0) and at the end (T_{10}) of the ten minutes (Figure 2).

Scoring systems

Dogs were all recovering from general anaesthesia. No additional anaesthetic was used. Given that sedation could influence our results, SS was evaluated at each step of the protocol. The SS was assessed by an experienced observer (CH) using a visual sedation scale validated by Wagner *et al.* (2017), with a score of 0 indicating no sedation, and 21 indicating deep sedation (Table S1). The SS used is based on the dog's mentation, palpebral reflex, ocular position, jaw and tong tone, response to clapping, posture and tolerance of lateral recumbency. Sedation was evaluated during PreHF, at the initiation of each setting (T_0) and after the 10-minutes accommodation period (T_{10}) for each setting.

The TS to HFNOT was blindly assessed by the same experienced observer, using a simple descriptive scale (Table 1; Pouzot-Nevoret *et al.* 2019). This scale ranges from 1 (least tolerant) to 4 (most tolerant). For the specific aim of the study, if a TS of 1 was recorded, there was an immediate change to the next flow rate-temperature setting. If a TS of 1 was recorded a second time, the dog was excluded from the study.

Outcome

Primary outcome of the study was the evolution of TS under the different HFNOT conditions. Evolution of vital parameters (HR, RR, SBP, SpO2) under the different HFNOT conditions was the secondary outcome.

Statistical analysis

Prior to study enrolment, a power analysis was performed to determine minimum sample size to detect a clinically meaningful difference of 2 points TS between HF2 at a temperature of 31°C and HF4 at a temperature of 37°C. Using an effect size of 0.80 (moderate effect) and significance level (α) of 0.05, the inclusion of 4 dogs was estimated to find a significant effect.

Statistical analyses were carried out with JMP version 13.1 (SAS Institute) and envelop number pull was used as randomization method. Data were tested for normal distribution with the Shapiro-Wilk test. For all collected data, the mean ± standard deviation (parametric data) or the median and range (nonparametric data) were calculated. Nonparametric data (duration of anaesthesia, RR and TS) were tested with a Friedman test. Parametric data (HR, SBP, SpO_2 and SS) were compared with a one-way ANOVA. *P* values lower than 0.05 were considered statistically significant.

Results

Animals

Sixteen dogs were initially eligible for the protocol (Figure 2). Two of them had to be excluded at enrolment: one because of aggressiveness and one because the owner declined to participate.

Fourteen dogs were therefore enrolled in the study. Two of them had to be excluded because of a TS of 1 in two successive HFNOT settings, associated with a dysphoric anaesthesia recovery. They were very agitated before placement of the cannula and extra sedation would have been necessary to make them tolerate HFNC.

Twelve dogs were in the final study enrolment: 5 females (2 intact and 3 spayed) and 7 males (1 intact and 6 neutered). Breeds included 2 Mixed Breeds, 2 Labradors retrievers, 1 German shepherd, 1 Dogo Argentino, 1 Beagle, 1 Bernese Mountain Dog, 1 Chow-Chow, 1 American Bully, 1 Britanny and 1 Braque Français. The mean age and mean body weight were 5.8 ± 4.0 years and 29.3 ± 11.8 kg, respectively. Type of procedures included 4 orthopaedic surgeries (2 tibial plate levelling osteotomies, 1 pelvic limb amputation and 1 removal of osteosynthesis implant), 1 ventral slot, 1 perineal hernia repair, 1 mass removal, 2 castrations, 1 ovariectomy, 1 pericardiocentesis and 1 CT scan. Median duration of aesthesia was 137.5 minutes (40-400 minutes).

Eleven dogs completed all phases of the study. One dog did not tolerate HF4-T37, leading to a change to the next step of the protocol and achievement of three conditions over four. Median flow rate was 24 L/min (10-35 L/min) for the HF2 condition (0.8 L/kg/min), and 47.5 L/min (20-60 L/min) for the HF4 condition (1.6 L/kg/min).

Sedation status

Mean ± SD sedation scores were 11 ± 6 for PreHF, 6 ± 3 for HF2-T31, 7 ± 4 for HF4-T31, 8 ± 5 for HF2-T37 and 8 ± 4 for HF4-T37 (Figure 3).

Global mean ± SD sedation score of the HFNOT conditions was 8 ± 4 and there was no significant difference between any of the HFNOT conditions (p = 0.711).

Vital parameters

Median (range) temperature at inclusion was 37.8°C (36.4 – 38.4 °C).

PreHF vital parameters were: HR: 114 ± 38.8 bpm; RR: 40 (16-250) bpm; SBP: 102.8 ± 27.2 mm Hg and SpO2: 95 ± 3%.

There was no effect of flow rate or temperature on vital parameters (HR, RR, SBP, SpO_2) at T_0, and T_{10} (Figure 4 and Table 2).

Effects of flow rate and temperature on tolerance

PreHF TS was 4 (2-4). Tolerance score was not significantly different between any of the HFNOT conditions (Table 3).

Discussion

Based on the literature search performed, this is the first veterinary study evaluating the impact of a combination of different flow rates and temperatures on healthy dogs' tolerance of HFNOT. The study design was based on Mauri et al. (2018)'s clinical trial investigating dyspnoeic human patients. Their study revealed improved patient comfort with the administration of lower gas temperatures. This comparison had never been performed in dogs. In our study, we were not able to show any difference in the dogs' tolerance between HFNOT at 31°C or 37°C, by using a tolerance scale. However, all median scores were high, whatever the setting, confirming the good tolerance of this oxygen therapy technique in dogs. Only one dog did not tolerate the first step of the protocol (HF4-T37) but tolerated every other step. A

dysphoric wakening could have explained this intolerance. Association of highest flow rate and temperature could have also led to this intolerance. Two dogs had to be excluded from the study because of nasal cannula intolerance for 2 conditions. However, these dogs were highly agitated since the beginning of the recovery period and would have needed extra sedation to tolerate nasal cannula. Sedation is often used in dyspnoeic dogs undergoing oxygen therapy.
As this study was conducted during the anaesthetic recovery period and sedation score was part on the initial assessment, no additional interventions were administered.

Absence of difference between conditions could be related to the choice of the tolerance score. This score has never been validated but was described in the clinical trial of Staffieri *et al.* (2014), in which the objectives were comparable to ours. Between the time our study was designed and the end of the clinical trial, Jagodich *et al.* (2019) published a study using another tolerance score, based on the dog's number of attempts to remove the cannula. This score might be more sensitive as long as they were able to highlight an alteration of tolerance with higher flow rates. This scoring system could be used in future studies. Finally, the dogs in this study were not in respiratory distress and therefore did not need HFNOT. Further studies assessing tolerance of differing gas temperatures in dyspnoeic dogs would be useful.

Given the infancy of HFNOT in veterinary medicine, there is no consensus as to ideal flow rate settings. In human medicine, 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 are generally used (Kernick & Magarey 2010; Mayfield *et al.* 2014; Mauri *et al.* 2018; Yurtseven *et al.* 2019; Koga *et al.* 2020). The first studies published in dogs used flow rates without considering a dog's bodyweight or respiratory rate (20 L/min and 30 L/min, (Daly *et al.* 2017)). In order to avoid recruitment of air or oxygen from the surrounding air and assure the delivery of the predetermined FIO_2, the flow rate should be fixed above the MV of the patient (Helviz & Einav 2018). In our study, we have chosen higher flow rates and attempted to determine a limit to tolerance. The calculated flow rates were equivalent to 0.8 and 1.6 L/kg/min in this study. In the recent study of Jagodich *et al.* (2019), tolerance score appears to be worsened only above 2 L/kg/min. This study, not available at the time of protocol conception, could explain our results showing no significant difference in tolerance for our flow rates range. However, the lower flow rates used in this study were based on previous data showing they could be effective in increasing PaO_2 in dyspnoeic dogs (Pouzot-Nevoret *et al*. 2019).

This study was conducted in non-dyspnoeic dogs recovering from anaesthesia, so sedation could have influenced TS. Randomization of machine settings order, median sedation score in the lower range and absence of difference of sedation scores between all conditions suggest that sedation had a minor influence, at most, on our tolerance evaluation. However, further studies in non-sedated dogs would be required.

The 10-minutes period for each setting was chosen based on our clinical experience and previous studies in dyspnoeic dogs. While using HFNOT in dyspnoeic dogs, we noticed that they were generally either compliant from the beginning or never compliant to HFNOT. Tolerance scores stayed the same during the 10-minutes period, confirming this observation. This duration was decided in the light of the various recent studies. In similar protocols, Mauri *et al.* (2018) in human medicine, and Staffieri *et al.* (2014) in veterinary medicine, used 20-minutes steps, whereas Jagodich *et al.* (2019) used 8-minutes periods of time. However, a longer time frame of assessment could have changed the tolerance, especially considering the effect of gas temperature on body temperature. Indeed, Gilardi *et al.* (2020) suggested in a preliminary report that median time of rewarming was shorter in hypothermic non-dyspnoeic patients treated with HFNOT, highlighting the influence of heated air administration on body temperature in people. Tolerance evaluation of different temperature in pyrexic or severely hypothermic dogs is indicated.

We experienced some technical constraints with the AirvoTM 2 System, especially the impossibility to use paediatric cannulas in our protocol. Indeed, they can be used only with the paediatric mode in which temperature cannot be changed. These cannulas have a different shape depending on whether they are adult or junior size. We had an excellent general tolerance to HFNOT in our study, using exclusively adult interfaces. Paediatric cannulas are described to be very comfortable, easier to place and with a better accommodation to the facial structure of dogs (Jagodich et al. 2019, Jagodich et al. 2020), suggesting the same results. Moreover, dog's normal rectal temperature is 38.5°C, and the Airvo™ 2 System temperature set up is optimal for human with a normal temperature of 37.5°C. Setting the temperature of the device at 38.5°C could have changed the tolerance. Although we only had access to the AirvoTM 2 System, other devices are available on the market. For example, Precision Flow® Plus system (Vapotherm® Precision Flow® Plus, Vapotherm® inc) can be adjusted by 1-degree intervals, at all flow rates, independently of the cannula size (paediatric or adult). Further studies would be interesting to determine if a precise regulation of the gas temperature influence dog's tolerance.

There are some limitations in this current study. First, the protocol included only dogs with no respiratory issues, recovering from general anaesthesia. Further studies are required to evaluate the degree of HFNOT tolerance in fully conscious dogs and for longer periods. Moreover, the efficacy of this system in different pathological conditions should be supported by further studies. Second, the impact of flow rates and temperatures on PaO_2 has not been evaluated in this protocol. Daly et al. (2017) showed that HFNOT significantly improved PaO_2 versus COT but there was no significant difference in PaO_2 between rates of 20 L/min and 30 L/min. Jagodich *et al.* (2019) highlighted that HFNOT significantly improved PaO2 compared to baseline and PaO_2 was significantly higher at rate of 1 L/kg/min or more, compared to 0.4 L/kg/min. The potential impact of temperature on oxygenation has never been investigated and further studies will be necessary. Third, clinical complications associated with HFNOT, like gastric dilation, have not been evaluated in our study. However, none of our twelve dogs showed any clinical abdominal distension or discomfort. Finally, non-cooperative or aggressive dogs could not be included in the study because frequent head manipulations were necessary which could represent a bias.

Conclusion

This study is the first in veterinary medicine to evaluate the combined impact of flow rate and temperature on non-dyspnoeic dogs' tolerance of HFNOT and shows no significant difference between 31 and 37°C. It also confirms the high degree of tolerance of HFNOT in healthy dogs of varied body sizes and gives practical information on its use in this species. No clear recommendation for flow rate and temperature settings could be determined based on our results, and user should combine available data in veterinary literature with evaluation of tolerance and efficacy on their patients to guide settings of non-invasive respiratory support by HFNOT.

Conflict of Interest statement: The Authors declare no conflict of interest.

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Figure legends

Figure 1: High-flow nasal oxygen therapy (Fisher-Paykel Airvo^{TM} 2 System, Fisher & Paykel Healthcare) on a dog with full cardiorespiratory monitoring.

Figure 2: Experimental protocol. Conditions 1 to 4 are applied in a randomized order.

SS: Sedation score, TS: Tolerance score, HR: Heart rate, RR: Respiratory rate, SBP: Systolic blood pressure, SpO2: Pulse oximetry.

Figure 3: Sedation scores during PreHF and the end (T_{10}) of the 4 HFNOT conditions.

Figure 4: Mean values of heart rate (A), systolic blood pressure (C) and SpO_2 (D), and median values of respiratory rate (B) in the 12 dogs, at the initiation of each condition (T_0) and after 10 minutes of accommodation (T_{10}).

SEDATION SCORE		Score
Spontaneous posture	Standing	0
	Tired but standing	1
	Lying but able to rise	2
	Lying but difficulty rising	3
	Unable to rise	4
Palpebral reflex	Brisk	0
	Slow but with full corneal sweep	1
	Slow but with only partial corneal sweep	2
	Absent	3
Eye position	Central	0
	Rotated forwards/downwards but not obscured by third eyelid	1
	Rotated forwards/downwards and obscured by third eyelid	2
Jaw and tongue relaxation	Normal jaw tone, strong gag reflex	0
	Reduced tone, but still moderate gag reflex	1
	Much reduced tone, slight gag reflex	2
	Loss of jaw tone and no gag reflex	3
Response to noise (handclap)	Normal startle reaction (head turn towards noise/ cringe)	0
	Reduced startle reaction (reduced head turn/ minimal cringe)	1
	Minimal startle reaction	2
	Absent reaction	3
Resistance when laid into lateral recumbency	Much struggling, perhaps not allowing this position	0
	Some struggling, but allowing this position	1
	Minimal struggling/ permissive	2
	No struggling	3
General appearance/attitude	Excitable	0
	Awake and normal	1
	Tranquil	2
	Stuporous	3
	Total /21	

Table S1: Sedation score (Wagner *et al.* 2017).