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C Pouzot-nevoret, L Hocine, J Nègre, I Goy-thollot, A Barthélemy, et al.. Prospective pilot study for evaluation of high-flow oxygen therapy in dyspnoeic dogs: the HOT-DOG study. *Journal of Small Animal Practice*, 2019, 60, pp.656 - 662. 10.1111/jsap.13058 . hal-03242644v2

HAL Id: hal-03242644

<https://vetagro-sup.hal.science/hal-03242644v2>

Submitted on 16 Jun 2021 (v2), last revised 5 Jul 2021 (v3)

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Prospective pilot study for evaluation of high-flow oxygen therapy in dyspnoeic dogs: the HOT-DOG study

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OBJECTIVES: To describe the use, effectiveness and tolerance of high-flow oxygen therapy in dyspnoeic dogs.

MATERIALS AND METHODS: Prospectively, dogs in acute respiratory distress admitted to an intensive care unit between January and May 2018 that failed to respond to nasal oxygen therapy and medical stabilisation after 30 minutes were transitioned to high-flow oxygen therapy. High-flow oxygen therapy, delivered an inspired oxygen fraction of 100% using an air/oxygen blender, active humidifier, single warmed tube and specific nasal cannula. Respiratory rate, pulse oximetry (SpO₂), heart rate and a 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 versus 73±24 mmHg; P=0.015; 18±12 L/minute versus 3.2±2.0 L/minute, P<0.01; 97.7±2.3% versus 91.6±7.2%, P=0.03, respectively). There was no significant difference in PaCO₂, respiratory rate or heart rate between T₀ and T₆₀. Tolerance was excellent, and there were no complications.

CLINICAL SIGNIFICANCE: High-flow oxygen therapy improves markers of oxygenation in dyspnoeic dogs and is an effective means to deliver oxygen with comfort and minimal complications.

Journal of Small Animal Practice (2019)

DOI: 10.1111/jsap.13058

Accepted: 2 July 2019

INTRODUCTION

Supplemental oxygen administration is the first supportive measure provided to dyspnoeic 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 and can achieve variable fractions of inspired oxygen (FIO₂) ranging from 21 to 70% (Sumner & Rozanski 2013). When patients remain hypoxaemic despite conventional oxygen therapy, clinicians may choose among more advanced oxygen delivery methods. One option is mechanical ventilation, but this

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 *et al.* 2007, Mueller 2007). In human medicine, non-invasive ventilation is a popular method to avoid intubation. Continuous positive airway pressure (CPAP) is a non-invasive ventilation mode that has been validated in dogs (Briganti *et al.* 2010, Staffieri *et al.* 2014, Meira *et al.* 2018). CPAP is effective to improve arterial partial pressure of oxygen (PaO₂) in companion animals when used with devices such as masks or helmets (Briganti *et al.* 2010, Staffieri *et al.* 2014, Meira *et al.* 2018) and can be used in dyspnoeic animals.

In human medicine, a non-invasive oxygen delivery technique known as high-flow oxygen therapy (HOT) has emerged as an alternative to conventional oxygen therapy (Helviz & Einav 2018). This system allows for delivery of warmed and fully humidified gas with high flow rates of up to 60 L/minute through a specific high-flow nasal cannula, with a FIO_2 ranging from 21 to 100% (Frat *et al.* 2015). Such high flow rates are not achievable with conventional oxygen therapy 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 mucociliary function and increased risk of infection if delivered at similar rates (Kallstrom 2002, Dunphy *et al.* 2002, Kilgour *et al.* 2004, Kopelman & Holbert 2003).

HOT uses an air-oxygen blender connected to a flow meter, an active humidifier and heater, a warmed breathing circuit, and a specific nasal cannula (Nishimura 2016) (Fig 1). Warm and adequately humidified gas delivered at high flow rates has apparent beneficial physiological effects that are increasingly recognised in humans. These include: (1) good tolerance (Sztrymf *et al.* 2012) and comfort (Frat *et al.* 2015); (2) decreased mismatch between the oxygen flow and the patient's inspiratory flow (Sztrymf *et al.* 2012), allowing precise delivery; (3) generation of a low positive airway pressure (Groves & Tobin 2007, Parke *et al.* 2011); (4) decreased anatomical dead space because the expired volume of carbon dioxide is washed from the airway and replaced with oxygen-enriched gas (Millar *et al.* 2014, Hernández *et al.* 2017, Helviz & Einav 2018) and (5) decreased ventilatory drive and breathing effort in obstructive disease (Di Mussi *et al.* 2018), allowing the use of HOT in hypoxaemic and hypercapnic respiratory failure.

HOT has recently 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 hypoxaemic dogs (Keir *et al.* 2016). No prospective study reporting the use of HOT in dyspnoeic dogs has been conducted. The objective of

this pilot study was to prospectively describe the use, tolerance and potential complications of HOT in dyspnoeic dogs.

MATERIALS AND METHODS

Ethical statement

The study protocol was approved by the VetAgro Sup Ethics committee (number 1730).

Animals

This prospective pilot study was conducted between January and May 2018 in an 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 above 40 breaths *per* minute associated with an abnormal respiratory pattern or laboured breathing at rest.

Inclusion

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

Exclusion criteria

The exclusion criteria were: (1) bodyweight below 2 kg, (2) adequate response to conventional oxygen therapy, defined as respi-

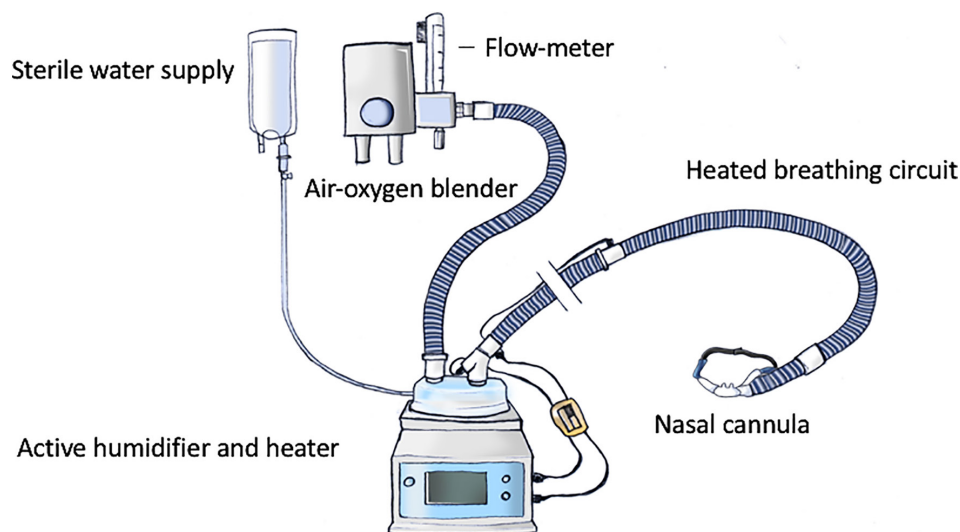


FIG 1. Schematic representation of a high-flow oxygen device and its components (Drawing: Dr Mathieu Taroni)

ratory distress improvement and $\text{SpO}_2 > 95\%$; or, (3) criteria for immediate intubation, defined as excessive respiratory effort with impending respiratory fatigue or failure, severe hypoxaemia despite oxygen therapy ($\text{SpO}_2 < 90\%$ or $\text{PaO}_2 < 60 \text{ mmHg}$), or a severe hypercapnia (arterial partial pressure of carbon dioxide (PaCO_2) $> 60 \text{ mmHg}$). Early termination criteria were failure to tolerate HOT (defined by a tolerance score equal to 4, Table 1) and fulfilment of intubation criteria (as defined above). Dogs with a *do-not-intubate* order remained on HOT despite being intubation candidates.

High-flow oxygen technique description

HOT 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 (Fig 1). The nasal cannula is a soft silicone bilateral nasal prong with tubing that connects to the heated breathing circuit (Fig 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 nares, so that the cannula diameter would not exceed 50% of the diameter and therefore allowed exhalation with minimal resistance (Daly *et al.* 2017). Seven different sizes were available (four junior, three adult). Once the size of the nasal cannula was chosen, the attachment was gently tightened behind the neck, and eventually secured with tape and sutured in place next to each nasal opening (Fig 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 minute ventilation ($\text{MV} = \text{Respiratory rate} \times \text{tidal volume}$) (Helviz & Einav 2018). For homogeneity, tidal volume was set at 10 mL/kg (Grimm *et al.* 2015). For example, a 30 kg dog with a respiratory rate of 80 breaths *per* minute had a flow rate with HOT of $10 \times 30 \times 80 = 24 \text{ L/minute}$ (compared to a flow rate of 4.5 L/minute with nasal oxygen therapy). The FIO_2 was set at 100% and the gas temperature at 37°C during the 60-minute protocol. At the end of the 60-minute protocol period, the FIO_2 was adjusted to the lowest level possible to maintain $\text{SpO}_2 > 95\%$.

Table 1. Oxygen delivery device tolerance score (adapted from Staffieri *et al.* 2014)

1	The patient is calm, comfortable; no agitation; no attempts to remove the nasal cannula
2	The patient tolerates the nasal cannula, but looks stressed and afraid; no attempts to remove the nasal cannula
3	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
4	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



FIG 2. Dog with the specific high-flow nasal cannula

Data recording

The respiratory rate, SpO_2 , heart rate, tolerance score (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 immediately after the 30-minute stabilisation period (T_0), when dogs were still receiving nasal oxygen therapy. The oxygen delivery technique was then changed from nasal oxygen therapy to HOT, and the measurements were recorded immediately and at 15, 30, 45 and 60 minutes after T_0 (T_{15} , T_{30} , T_{45} and T_{60} , respectively). A catheter was inserted in the dorsal pedal artery to allow drawing of arterial blood samples and evaluate PaO_2 and PCO_2 at T_0 (under nasal oxygen therapy) and T_{60} (under HOT). Arterial blood gases measurements were performed on fresh whole arterial blood collected in a heparinised syringe according to the manufacturer's instructions using an on-site VetStat (IDEXX Laboratories Inc.).

An APPLE_{fast} scale (0 to 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 PaO_2 , PaCO_2 and flow rate between T_0 and T_{60} , and evolution of respiratory rate tolerance score, SpO_2 and heart rate 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 \pm standard deviation (SD) with 95% confidence intervals (CIs). 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 retrievers, two King Charles spaniels, 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 \pm 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 haemorrhage following a car accident, pulmonary hypertension of unknown origin and pericardial effusion. The mean \pm SD APPLE_{fast} score was 27.0 ± 4.4 .

Recorded data

Dogs received nasal oxygen therapy at T_0 and HOT at T_{15} , T_{30} , T_{45} and T_{60} .

PaO₂

HOT was associated with a significant increase in mean PaO₂ 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 animal data are presented in Fig 3. For each dog, PaO₂ increased after HOT initiation. Of the seven dogs with PaO₂ < 80 mmHg when using conventional oxygen therapy, five had resolution of hypoxaemia by 1 hour after HOT initiation.

Flow rate

The mean oxygen flow rate was significantly greater with HOT (18 ± 12 L/minute) than when using the nasal oxygen technique (3.2 ± 2.0 L/minute, $P < 0.01$, 95% CI: 8.0 to 22.5 L/minute). Flow rate with HOT ranged from 2 to 37 L/minute. Flow rate with nasal oxygen technique ranged from 0.7 to 6.5 L/minute (Fig 4).

Respiratory rate

Individual data are presented in Fig 5. Six dogs had a decrease in respiratory rate between T_0 and T_{60} . However, only two dogs fulfilled our definition of not having respiratory distress (less than 40 breaths minute⁻¹) at T_{60} despite the use of HOT.

SpO₂, heart rate and PaCO₂

The mean SpO₂ was significantly greater at T_{60} ($97.7 \pm 2.3\%$) than at T_0 ($91.6 \pm 7.2\%$, $P = 0.03$, 95% CI: 0.7 to 11.5%). There was no significant difference at any time for heart rate or PaCO₂. All individual data are shown in Figs S1 to S3.

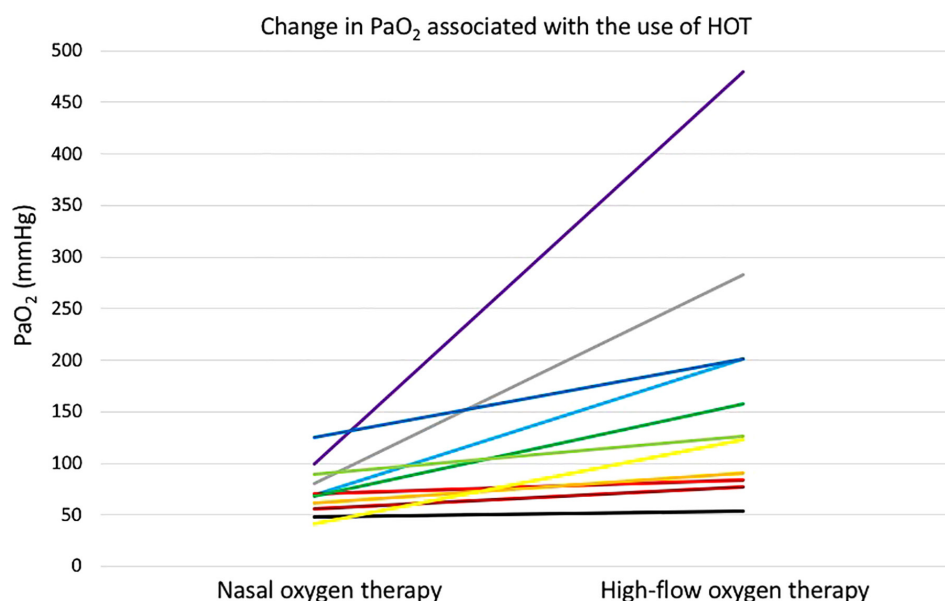


FIG 3. Change in arterial partial pressure of oxygen (PaO₂) for individual dogs. HOT High-flow oxygen therapy. In Figs. 3 to 5 and supplemental material, each dog is represented by the same colour

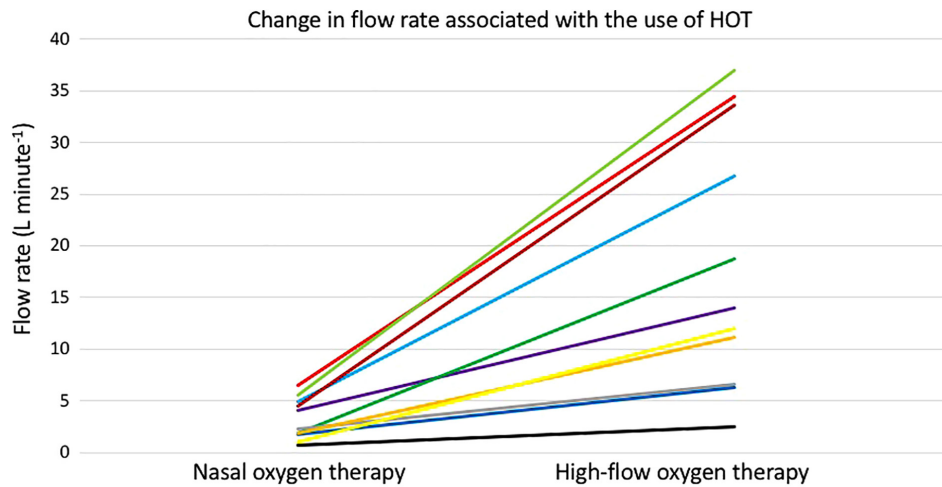


FIG 4. Change in flow rates for individual patients. HOT High-flow oxygen therapy

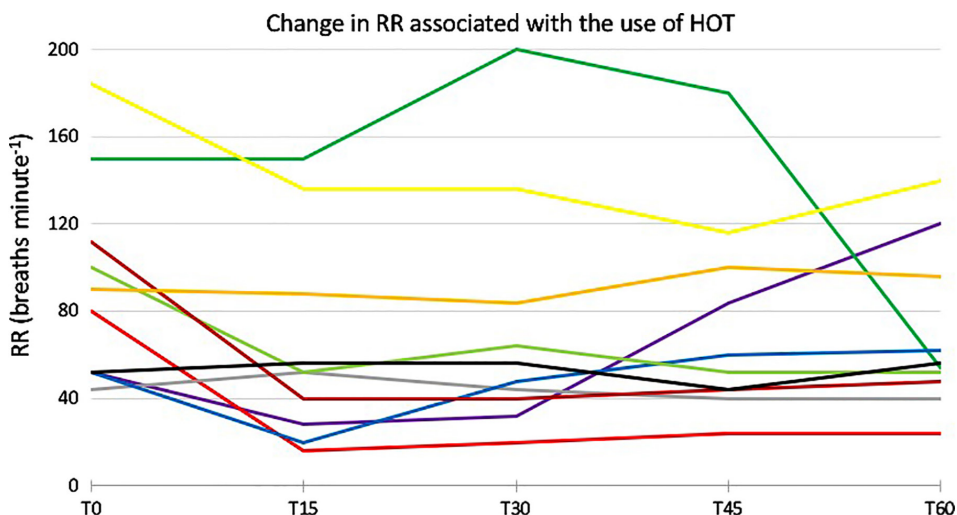


FIG 5. Change in respiratory rates for individual patients. HOT High-flow oxygen therapy. Data from one dog are missing

Tolerance score

The tolerance score remained low (indicating generally good tolerance) during the entire protocol. Only one animal displayed a tolerance score of 3 when setting the HOT device, thus requiring additional sedation which lowered its tolerance score to 2 or 1 depending on the recording time. Another dog displayed two instances of a tolerance score of 2 but did not need any additional sedation. Every other dog had a tolerance score of 1 at each recording.

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 during hospitalisation

Five of the 11 dogs (45%) developed a need for intubation within 24 hours after admission. Due to financial reasons, only three of them (27%) were intubated. Six of 11 dogs (54%, including the

five that fulfilled the criteria for intubation) died during hospitalisation. Death resulted from deteriorating clinical condition leading to cardiac arrest in five dogs and one dog was euthanased because of bad prognostic indicators.

DISCUSSION

This is the first prospective clinical study evaluating the effectiveness and tolerance of HOT in dogs with respiratory distress and shows its potential to be an efficient, safe and well-tolerated alternative to conventional oxygen therapy. This technique allows for a clinically-important increase in PaO_2 in dogs: the PaO_2 more than doubled between nasal oxygen therapy and HOT within 1 hour. This finding is consistent with previous reports in human (Sztrymf *et al.* 2012, Frat *et al.* 2015, Makdee *et al.* 2017) and veterinary medicine. Indeed, Daly *et al.* (2017) and Jagodich *et al.* (2019) in healthy dogs and Keir *et al.* (2016) in hypoxaemic dogs also showed this PaO_2 improvement after HOT. With such an increase in PaO_2 during a short period of time, HOT raises

concern for oxygen toxicity if continued for a long period. For homogeneity in the study design, we chose to keep the FIO₂ up to 100% during the 60-minute protocol, but FIO₂ was decreased immediately at the end of the protocol to the lowest required to maintain SpO₂ > 95%. As high-flow devices offer multi-configurable solutions for flow and FIO₂, these two variables can be changed easily to meet each animal's needs. Once the oxygenation targets are reached, the FIO₂ should be decreased to less than 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 and resulted in an increase in PaO₂ in all cases (Fig 3). By delivering higher flow rates, HOT systems are less liable to allow inhalation of room air during patient inspiration than traditional oxygenation systems (Helviz & Einav 2018). Different systems exist for high-flow delivery: Precision flow (Vapotherm), Optiflow (Fisher & Paykel Healthcare), Airvo system (Fisher & Paykel Healthcare). Each has specific characteristics and has to be used with their specific nasal cannula to ensure appropriate flow rate, temperature, and FIO₂. In our study, we used the Optiflow system which was easy to use and offers a multi-configurable solution for patients requiring HOT. This system relies on an O₂/air blender, and FIO₂ of 100% is obtained by not mixing with air. No internal system was available to ensure that the 100% FIO₂ was delivered at the nasal cannula. We were not able to measure the delivered FIO₂ in our study, and some dogs were panting during measurements, so we could not ensure that we were delivering the pre-set FIO₂. Moreover, a recent study with the same system showed that, when delivering a FIO₂ of 100%, the effective delivered FIO₂ increases with flow rate and varies between 72.2 and 95% for flow rate from 0.4 to 2.5 L/kg/minute (Jagodich *et al.* 2019). In our study, flow rate ranged from 0.44 to 1.84 L/kg/minute, so we think it probable that the effective FIO₂ did not reach 100%. Despite this limitation, our study confirms that HOT allows increase in PaO₂ in clinical settings.

In human medicine, several studies have showed a significant decrease of respiratory rate after initiation of HOT (Sztrymf *et al.* 2011, Sztrymf *et al.* 2012, Makdee *et al.* 2017). In our study, six dogs had a decrease in respiratory rate between T₀ and T₆₀, but with variable changes over time (Fig 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 1 hour, especially as our population consisted largely of dogs with 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. Makdee *et al.* (2017) showed a significant decrease in respiratory rate after 1 hour in the HOT group compared to conventional oxygen therapy group in human patients with cardiogenic pulmonary oedema. Another study comparing respiratory rate 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 warming and humidification of nasal cavities, HOT has been shown to improve human patient comfort (Boyer *et al.* 2011, Sztrymf *et al.* 2012). In one veterinary study in hypoxaemic dogs, HOT intolerance requiring sedation was noticed in one of six dogs (Keir *et al.* 2016). Jagodich *et al.* (2019), using a tolerance score associated with a respiratory score, showed that HOT tolerance was inversely proportional to flow rate, and flow rate above 2.5 L/minutes were not well tolerated. In this study, the HOT administered with specific nasal cannula was easily tolerated and displayed very low tolerance scores (indicating good tolerance) during the whole study period. It would have been interesting to compare tolerance of conventional oxygen therapy and HOT, but we did not aim to measure these differences in this study. Moreover, one study in human medicine showed that temperature appears to significantly impact the comfort of dyspnoeic patients with high flows: for equal flow, patient comfort was significantly higher at 31°C compared to 37°C (Meira *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/minute, dogs became less tolerant. Our study showed that lower flow rate allowed improvement of oxygen variables with good tolerance. However, Daly *et al.* (2017) reported that one dog had radiographic evidence of gastric distension, and Jagodich *et al.* (2019) reported that eight of eight dogs had aerophagia on radiographs. As our dogs were dyspnoeic, we did not perform any abdominal radiographs to determine the incidence of gastric distension. Nevertheless, we did not notice abdominal distension during physical examination.

The most severe limitations of this study are its small sample size and the absence of a control group, both of which limit interpretation of the results. Our study was designed as a pilot for a future randomised controlled trial. Adding 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.* aiding differentiation of the effects of time *versus* treatment type). However, the dogs we studied were severely dyspnoeic, 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 PaO₂. In dogs, Jagodich *et al.* (2019) showed that HOT provides CPAP and predictable oxygen support in healthy dogs. As ours was a clinical study, it was not possible to use more invasive monitoring to differentiate between a positive effect on PaO₂ 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 complications) require validation in a longer study. Finally, the inclusion of patients with different causes of respiratory distress could have changed the results, as some patients could benefit more or less from HOT.

In conclusion, this study is the first in veterinary medicine to prospectively confirm that HOT can deliver effective oxygenation and comfort with minimal complications in dyspnoeic dogs, and gives practical information on HOT use in dogs.

Acknowledgements

The authors would like to thank Dr Mathieu Taroni for the realisation of the Fig 1.

Conflict of interest

No conflict of interest have been declared.

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Supporting Information

The following supporting information is available for this article:

Fig S1. Change in pulse oximetry (SpO₂) for individual patients. HOT High-flow oxygen therapy. *Data from one dog are missing*

Fig S2. Change in heart rates for individual patients. HOT High-flow oxygen therapy. *Data from one dog are missing*

Fig S3. Change in arterial partial pressure of CO₂ (PaCO₂) for individual patients. HOT High-flow oxygen therapy