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Effects of High Flow Nasal Cannula Oxygen Therapy on Oxygenation in Dogs undergoing Diagnostic Bronchoscopy

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eingereicht von

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Abbreviations

$AaDO_2$	Alveolar-arterial oxygen gradient
ABGA	Arterial blood gas analysis
AHRF	Acute hypoxaemic respiratory failure
ARF	Acute respiratory failure
ALI	Acute lunge injury
ARDS	Acute respiratory distress syndrome
AVM	Arteriovenous malformation
BAL	Bronchoalveolar lavage
BGA	Blood gas analysis
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
EIT	Electrical impedance tomography
FiO_2	Fraction of inspired oxygen
HALI	Hyperoxic acute lung injury
HF	High flow
HFOT	High flow oxygen therapy
HPV	Hypoxic pulmonary vasoconstriction
HR	Heart rate
ICU	Intensive care unit
MV	Mechanical ventilation
NIV	Non-invasive ventilation
O_2	Oxygen
P_ACO_2	Partial pressure of alveolar carbon dioxide
P_aCO_2	Partial pressure of arterial carbon dioxide
P_AO_2	Partial pressure of alveolar oxygen
P_aO_2	Partial pressure of arterial oxygen

P_aO_2/FiO_2	Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen
PAP	Positive airway pressure
P_{atm}	Barometric pressure
PEEP	Positive end-expiratory pressure
P_{H2O}	Water vapour pressure
P_iO_2	Partial pressure of inspired oxygen
PO_2	Partial pressure of oxygen
Q	Perfusion
R	Respiratory quotient
ROS	Reactive oxygen species
RR	Respiratory rate
S_aO_2	Arterial oxygen concentration
S_pO_2	Peripheral oxygen concentration
TOT	Traditional oxygen therapy
TTC	Transcutaneous tracheal catheter
V	Ventilation
VILI	Ventilator induced lung injury
VSD	Ventricle septum defect
V/Q	Ventilation/Perfusion
WOB	Work of breathing

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I. Introduction

Hypoxaemia is a common complication in patients undergoing bronchoscopy. It can occur due to many factors, including the need for general anaesthesia, partial occlusion of the airways by the bronchoscope and the administration of lavage fluids. Additionally, underlying respiratory pathologies are the main indication to perform this procedure, and many patients might already be hypoxaemic beforehand. Thus adequate oxygen supplementation during bronchoscopy is necessary to prevent incidents of hypoxaemia and increase patient safety. While different methods of oxygen supplementation exist in human medicine to maintain adequate oxygenation during bronchoscopy, not all can be applicable to small animal patients. Face masks are commonly used in humans and, depending on the design, can even achieve positive airway pressure or non-invasive ventilation. However, they are designed for human facial anatomy and can pose a challenge in terms of fit and tolerance in veterinary patients, especially if in respiratory distress. Nasal, nasopharyngeal and tracheal catheters and endotracheal intubation can also be used. However, these are all invasive methods, and further limitations exist in very small patients where the endotracheal tube diameter can be too small for passage of the bronchoscope. Thus competition for the airways occurs between the bronchoscopist, the anaesthetist and the patient, which can result in hypoxaemic periods and the necessary temporary removal of the bronchoscope to allow for airway management before the procedure can be continued.

High Flow Oxygen Therapy (HFOT) is a newer oxygen supplementation method that provides heated and humidified air and thus allows higher flow rates than traditional oxygen therapy methods. It can quickly be set up as it is administered via soft silicone nasal cannulas, which can easily be attached to the patient and do not require invasive placement or sedation. A special air-oxygen blender allows for FiO_2 settings to be adjusted between 21 and 100% depending on the patient's need. While initially used in neonatal and paediatric medicine, HFOT has found increasing use in other medical areas, including as a way to prevent desaturation during bronchoscopy in human patients. Higher achievable FiO_2, preconditioned air and higher flow rates lead to several beneficial mechanisms that improve oxygenation compared to traditional oxygen supplementation methods. In recent years, HFOT has also gained popularity in veterinary medicine, and first studies showed that it could successfully be used in dogs to improve oxygenation.

This study aims to evaluate the effect of HFOT on oxygenation in dogs undergoing diagnostic bronchoscopy compared to a traditional oxygen supplementation method and assess its safety and efficacy.

II. Literature Review

1. Physiology

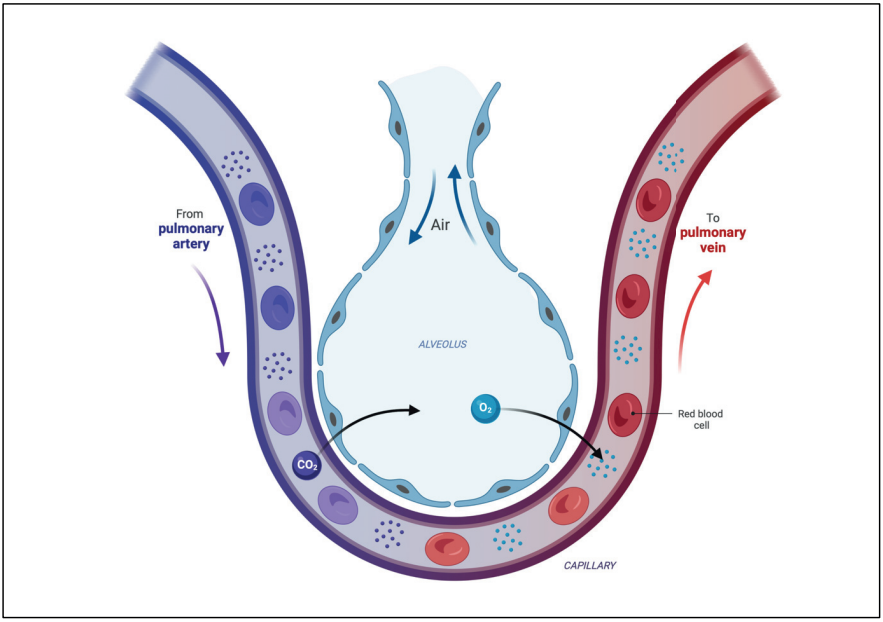
1.1 Anatomy and functions of the airways

Atmospheric air is a gas mixture containing 78% nitrogen, 21% oxygen, and small amounts of trace gases such as carbon dioxide, helium, and argon. Although oxygen constitutes only a relatively small percentage of our air, it is essential for sustaining all aerobic life. Oxygen is supplied to an organism through respiration. The main functions of respiration are ventilation and oxygenation.[1]

Ventilation refers to the process of moving fresh air in and exhaled air out of the body, facilitating the exchange of oxygen with carbon dioxide. The continuous replenishment of oxygen and carbon dioxide removal is essential to obtain a constant oxygen supply for gas exchange. Once ambient air enters the body, it is transported along the respiratory tract. The respiratory tract can be divided into the upper respiratory tract: the nasopharynx, larynx and trachea, and the lower respiratory tract, i.e. the lungs containing the bronchi and alveoli.[1]

Gas exchange, the movement of oxygen into the blood in exchange for carbon dioxide, occurs only in the lower airways. The upper airways only serve as air-conducting pathways and do not participate in gas exchange. Thus the upper airways represent the anatomical dead space, defined as ventilated regions that do not participate in gas exchange.[1, 2] The primary function of the lungs is gas exchange, which occurs primarily in the alveoli. As air travels down the respiratory tract, it enters the lungs filling the alveolar space. The alveoli are separated from the capillary blood system by a thin barrier, the alveolar-capillary membrane. Oxygen from the alveolar space can pass this barrier and enter the pulmonary capillary blood via diffusion. Oxygenation refers to the process of oxygen uptake from the alveolar space into the blood.[1] Once in the blood, most oxygen gets quickly bound by the haemoglobin of the erythrocytes. As a result, only a small amount of oxygen remains dissolved in the plasma.[3] Oxygen is then transported along the arterial system to the target organs fuelled by perfusion and cardiac output. As the blood reaches the organs, oxygen diffuses out of the blood into the tissues. Within the tissues, oxygen fuels cell metabolism producing carbon dioxide, a process termed inner respiration. Oxygen moves out of the blood into the tissues in exchange for the accumulating carbon dioxide. Thus previously oxygenated arterial blood becomes deoxygenated venous blood. Carbon dioxide is then transported back to the lungs and

diffuses through the alveolar-capillary membrane into the alveolar space, from where it is excreted from the body through ventilation.[1]



Picture 1: Gas exchange in the alveoli. Oxygen diffuses into the capillary blood through the alveolar-capillary membrane in exchange for carbon dioxide. Deoxygenated blood becomes oxygenated. (Picture adapted from "Alveolar Gas Exchange", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates).

Disruptions can occur at any point along this respiratory chain, resulting in insufficient arterial oxygenation. An oxygen deficiency of arterial blood is defined as hypoxaemia in patients.

1.2 Hypoxaemia

Hypoxaemia refers to insufficient oxygenation of arterial blood.[1] It is generally defined by the arterial partial pressure of oxygen (P_aO_2), the amount of oxygen dissolved in arterial blood plasma. Normal values of arterial partial pressure of oxygen at sea level while breathing ambient air range from 80 to 110 mmHg.[4, 5] Values of less than 80 mmHg are defined as hypoxaemia, and values of less than 60 mmHg reflect severe and potentially life-threatening hypoxaemia.[5] Since hypoxaemia results from insufficient arterial oxygenation, i.e. not enough

oxygen entering the pulmonary capillary blood, it can be caused by disturbances at any point along the respiratory process. Problems of ventilation, diffusion or perfusion can thus all lead to hypoxaemia.[3]

Hypoxaemia will ultimately lead to hypoxia, defined as insufficient oxygenation of the tissues causing a lack of oxygen needed to perform metabolic cell functions. Hypoxia, however, can also be caused by other mechanisms interfering with oxygen delivery, such as low haemoglobin or cardiovascular dysregulation.[3, 5]

1.2.1 Causes of Hypoxaemia

Hypoxaemia can be caused by any of the following conditions:

1. Low inspired oxygen concentrations (Low FiO_2)
2. Hypoventilation
3. Diffusion impairment
4. Ventilation-Perfusion Mismatch
5. Pulmonary Shunt

Low inspired oxygen concentrations (Low FiO_2)

Abnormally low concentrations of inspired oxygen can only occur either due to a change in barometric pressure, such as at high altitudes or a hostile environment where oxygen is partially or entirely removed.[4, 6]

Increasing altitudes will lead to changes in barometric pressure (P_{atm}). For example, at the summit of Mount Everest, the barometric pressure is only 253 mmHg compared to 760 mmHg at sea level. While the gas composition of ambient air remains the same with 20.93% of oxygen even at the summit, the lower barometric pressure will cause a considerable drop in the partial pressure of oxygen (PO_2) of ambient air from 160 mmHg at sea level to about 53 mmHg at the summit.[1]

A decrease in the fraction of inspired oxygen (FiO_2) can also result from hostile environments or medical complications.[3] Any enclosed space in which the speed of oxygen replenishment does not meet the rate of oxygen consumption will lead to a low FiO_2.[3] Examples can be exposure to fire or gas leaks but also an empty oxygen tank supplying oxygen to a patient. Clinical settings where patients receive oxygen supplementation can thus be common, although unintentional, occurrences of low inspired oxygen concentrations. Low FiO_2 can

result from accidentally disconnected or kinked tubes, dislodged oxygen masks or nasal prongs, mechanical defaults or incorrect settings in ventilators or simply from an unnoticed empty oxygen tank.

A decreased concentration of inspired oxygen will cause a decrease in available alveolar oxygen and ultimately lead to insufficient oxygenation of the arterial blood. Generally speaking, hypoxaemia caused by low FiO_2 is less likely to occur than hypoxaemia due to other mechanisms.[1] It is important to remember that if low FiO_2 is the underlying cause, hypoxaemia is not the result of impaired pulmonary function but simply of a patient's environment and can easily be resolved by supplying oxygen.

Hypoventilation

The primary function of ventilation is to remove carbon dioxide from the lungs in exchange for oxygen-rich, fresh ambient air. Disturbances of ventilation can thus cause an imbalance in the amount of alveolar and thus arterial partial pressure of oxygen and carbon dioxide.

An increase in ventilation is called hyperventilation, while insufficient ventilation is called hypoventilation.[2] Hypoventilation will cause an increase in the alveolar partial pressure of carbon dioxide and a decrease in oxygen. The drop in arterial partial pressure of oxygen is further amplified as oxygen extraction from the alveolar space occurs faster than its replenishment.[3] Normal values for arterial partial pressure of carbon dioxide are between 40 and 45 mmHg. Hypoventilation is defined as an arterial partial pressure of carbon dioxide greater than 45 mmHg in humans and dogs.[2] Hypoxaemia caused by hypoventilation refers to a decrease in P_aO_2 with a simultaneous increase of P_aCO_2 greater than 45 mmHg.

Ventilation is controlled by central and peripheral respiratory centres receiving information from various chemoreceptors.[2] In addition, respiratory muscles conduct the actual mechanics necessary in creating air movement. Any disruption or failure of one of these control and action mechanisms will lead to alterations in ventilation. Anaesthetic drugs are a common cause of hypoventilation as they depress the central regulation of respiratory drive.[1] Other causes include brain or neuromuscular disorders, cerebral and thoracic trauma or paralysis leading to mechanical respiratory restrictions.[2] Consequently, treatment of hypoxaemia resulting from hypoventilation consists of manual or mechanical ventilation until the underlying problem can be resolved.[3] Hypoxaemia due to hypoventilation is again not the

result of impaired lung function and will resolve with oxygen supplementation and assisted ventilation.

Diffusion impairment

Diffusion refers to the movement of oxygen and carbon dioxide molecules between the alveolar space and the capillary blood across the alveolar-capillary membrane.[1]

Fick's law of diffusion states that diffusion of a gas through a membrane is dependent on the surface area and thickness of the membrane and the difference in partial pressure between both sides of the membrane the gas has to pass.[1] Thus, theoretically, alteration of any of these parameters can result in impaired ability of oxygen to reach the blood, resulting in hypoxaemia.

Conditions that can lead to diffusion impairment are primarily the result of a thickened alveolar membrane, e.g. in the case of pulmonary fibrosis.[6] However, diffusion impairment is an uncommon cause of hypoxaemia in clinical settings and is rarely encountered.[1, 3] In resting conditions, the transit time of the erythrocytes through the pulmonary capillaries is still long enough to allow for full arterial oxygenation and can compensate for a thicker membrane. Only during exercise, when cardiac output is increased and thus the transit time of the erythrocytes in the pulmonary capillary is shortened, may hypoxaemia in affected patients become clinically relevant.[1, 6]

Ventilation-Perfusion Mismatch

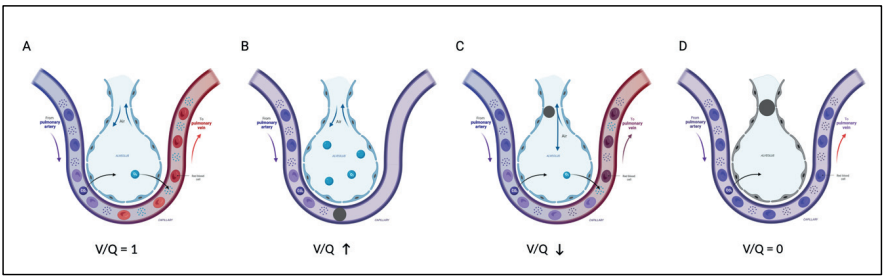
Imbalances in Ventilation (V) and Perfusion (Q) within the lung are the most common cause of hypoxaemia.[1, 3] Such imbalances occur when the amount of ventilation does not match the amount of blood flow in a lung unit. In an ideal lung, the ratio of ventilation to perfusion (V/Q) would equal one, meaning that the amount of ventilation supplying air available for gas exchange is equal to the amount of capillary blood flow receiving and transporting oxygen throughout the body.[1] Lung units with a high V/Q ratio occur when the alveoli of said unit are well ventilated, but experience reduced capillary perfusion. As a result, large amounts of air are wasted as they cannot participate in gas exchange, reflecting an increase in overall dead space. However, the small amount of blood still leaving these units is well oxygenated and does not contribute to hypoxaemia. Low V/Q ratios occur in areas experiencing decreased ventilation while perfusion remains unchanged. Reduced airflow to these units can result

from partial obstruction or atelectasis, among others.[3] Blood leaving such low V/Q regions is only poorly oxygenated. It leads to venous admixture when entering the main circulation, contributing to a reduction in overall partial pressure of arterial oxygen.

In reality, the lung is not homogenous, and physiological imbalances occur. In the upright human lung, apical alveoli receive less blood flow but higher ventilation creating areas with high V/Q ratios. On the other hand, basal regions of the lung experience increased perfusion in relation to ventilation, creating regional low V/Q ratios.[1] Similar physiological regional differences in ventilation and perfusion exist in the animal lung, with ventral areas experiencing more blood flow than the dorsal regions.[5]

A healthy lung can compensate for impaired gas exchange caused by low V/Q regions via the remaining functioning lung units.[1, 6] Additionally, compensatory mechanisms exist, such as Hypoxic Pulmonary Vasoconstriction (HPV). This mechanism causes vasoconstriction of the pulmonary capillaries of underventilated areas leading to reduced perfusion matching the airflow. In turn, this increases the V/Q ratio of the affected unit and blood is diverted to better-ventilated areas.[7, 8] Clinically significant hypoxaemia will, however, occur if the compensatory mechanism fails. This can be due to the administration of vasodilatory drugs [3] or simply if the overall amount of affected areas are too big to compensate.[6]

Perfused lung units with no ventilation at all have a V/Q ratio of zero. These units are called pulmonary right-to-left shunts, as no gas exchange can occur and blood leaving these units remains deoxygenated when joining the arterial circulation.[1, 3]



Picture 2: Ventilation-perfusion ratios. A: normal lung unit with V/Q = 1. B: well ventilated lung unit with decreased perfusion creating an increased V/Q ratio. C: well perfused lung unit with decreased ventilation causing a decreased V/Q ratio. D: Pulmonary shunt. No ventilation takes place while perfusion to the lung unit remains unaltered causing a V/Q ratio of zero. (Picture adapted from "Alveolar Gas Exchange", by BioRender.com (2020). Retrieved from https://app.biorender.com/biorender-templates).

Pulmonary Shunt

Shunt refers to blood entering the arterial system without being oxygenated.[1, 6] Physiologically, shunts exist as small amounts of deoxygenated blood from bronchial circulation and Thebesian veins enter the arterial system.[1] Pathological shunts refer to any vascular abnormality causing venous blood to enter the arterial system without undergoing oxygenation. Pathological shunts can exist intracardial, for example, in the case of congenital defects such as ventricular septal defect (VSD) with right-to-left shunt, or extrapulmonary in the circulatory system such as arteriovenous malformation (AVM).[1, 3]

Pulmonary right-to-left shunts are the most extreme form of V/Q imbalances with a ratio of zero.[1] Although blood still perfuses these alveolar units, no ventilation takes place, and thus, no opportunity for gas exchange exists. Consequently, blood leaving these units will not be oxygenated at all before entering the arterial circulatory system. Therefore lung regions with a V/Q of zero behave equally to pathological shunts as they impair oxygenation due to venous admixture, causing a drop in arterial partial pressure of oxygen. [1, 3]

The main characteristic of hypoxaemia caused by pulmonary right-to-left shunt is its response to oxygen supplementation. While patients suffering from hypoxaemia as a result of low V/Q ratios will show an increase in P_aO_2 when receiving 100% oxygen, in patients with pulmonary shunts, no sufficient increase in P_aO_2 occurs.[1, 3, 6] On the one hand, this is because the shunted blood will have no possibility to access alveolar units with increased P_AO_2, and on the other hand that even a slight depression of capillary P_aO_2 from venous admixture will cause a significant drop in overall P_aO_2 . Patients experiencing hypoxaemia due to pulmonary shunts will still benefit from oxygen supplementation as remaining lung units can help overall arterial oxygenation. However, treatment of hypoxaemia is only possible if the shunt flow is corrected.[3]

1.2.2 Causes of Hypoxaemia during bronchoscopy

Patients undergoing bronchoscopy are at increased risk of developing hypoxaemia.[9-11] Several of the aforementioned mechanisms can be responsible for this.

First, the patients require sedation or, in the case of the veterinary patients, general anaesthesia to undergo bronchoscopy. Respiratory depression caused by the anaesthetic drugs puts the patient at risk of developing hypoxaemia from hypoventilation.[11, 12] Second, the mere presence of the bronchoscope in the tracheal lumen results in a decrease of air

entering the alveoli by partially obstructing the airways.[10, 11] As the bronchoscope is advanced further into the lower respiratory tract, it can block smaller bronchioles completely, hindering ventilation of these units entirely and causing a decrease in oxygenation. The two mechanisms responsible for impaired oxygenation are hypoventilation and V/Q mismatch, as perfusion to these units remains stable while airflow abruptly ceases. Third, applying lavage solution during bronchoalveolar lavage (BAL) sampling can cause transient hypoxaemia in the areas from which the samples are taken. Administrating fluid will temporarily hinder diffusion, while suction to regain lavage solution will also remove air and might even cause alveoli to collapse entirely.[13-16] In general, all encountered episodes of hypoxaemia during bronchoscopy are only temporary, lasting for the moment of the bronchoscopic procedure. However, as respiratory symptoms and suspicion or knowledge of underlying pulmonary disease are indications for bronchoscopy, most patients will already show signs of hypoxaemia before the intervention. For a patient already displaying hypoxaemia, induction of anaesthesia and partially obstructing the airways with a bronchoscope can lead to further respiratory compromise making adequate oxygen supplementation during the procedure essential.

Additional problems exist in veterinary patients regarding patient size adding further risk potential. Due to small anatomic structures, patient size can be a limiting factor for oxygen supplementation techniques.[17-19] Relatively large bronchoscope diameter in relation to the tracheal lumen can cause almost complete obstruction of the conducting airways, further hindering oxygen supplementation.

1.3 Assessing and Monitoring Oxygenation

Adequate assessment of oxygenation is essential to evaluate if a patient is hypoxaemic and in need of oxygen therapy. Furthermore, it helps to monitor a patient's response to oxygen supplementation, showing either improvement or a need for further advanced treatment. Although many different invasive and non-invasive methods for assessing oxygenation have been evaluated, analysis of arterial blood gases remains the gold standard.[4, 5, 20] An arterial blood gas analysis provides direct information about the arterial partial pressures of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) and the pH of the blood sample.[4] As oxygenation and ventilation are defined by the arterial partial pressure of oxygen and carbon dioxide respectively, these parameters can be used to evaluate pulmonary function.[5]

1.3.1 Arterial blood gas analysis

Blood samples for arterial blood gas analysis can most easily be obtained from the dorsal pedal artery in dogs. Alternative sites for blood sampling include the femoral, coccygeal or auricular arteries.[5] Blood collection should always be performed under sterile conditions, and care should be taken to avoid prolonged exposure to air as this can alter the blood gas results. Samples should therefore be measured immediately after collection. An immediate analysis will also prevent interferences due to in vitro metabolic cell changes such as oxygen consumption and carbon dioxide production. Alternatively, samples can be stored in ice water at 4°C for approximately 6 hours.[5] The partial pressure of oxygen depends, among other factors, on the FiO_2 at the time of blood sampling.[4] Therefore, for proper interpretation of the results, samples should ideally be collected either while the patient is breathing room air with a FiO_2 of 21% or when FiO_2 is known, for example, during mechanical ventilation.

Samples are measured using a commercial blood gas analyser incorporating different types of electrodes to measure pH, P_aCO_2 and P_aO_2.[21] A glass electrode is used to measure both pH and carbon dioxide. However, the electrode for carbon dioxide measurement is slightly modified as it contains a bicarbonate buffer solution separated from the sample by a semipermeable membrane. Diffusion of carbon dioxide across this membrane causes pH changes in the buffer, which are recorded by the pH sensor.[21] The partial pressure of oxygen is measured using a Clark electrode. This electrode consists of a platinum cathode and a silver-silver chloride anode separated from the sample blood by an oxygen-permeable membrane. When supplied with a suitable voltage, a current is produced, which draws the oxygen electrons from anode to cathode causing oxygen reduction. The current developed by the oxygen reaction is proportional to the amount of dissolved oxygen in the blood sample.[21]

1.3.2 Partial Pressure of Oxygen

Partial Pressure of ambient oxygen (PO_2)

The partial pressure of any gas in dry air is its percentage in the air times the barometric pressure. The barometric pressure is a function of the weight of the atmosphere above the point of measurement and at sea level averages 760 mmHg. The barometric, or atmospheric pressure, is the pressure of all constituent gases.[4] Atmospheric air contains mostly nitrogen

(78.08%) and oxygen (20.93%), as well as small amounts of carbon dioxide (0.04%) and other gases such as argon, hydrogen or helium in a negligible quantity. According to Dalton's law, the partial pressure of a gas in a gas mixture is the pressure that this gas would exert if it occupied the total volume of the mixture in the absence of the other components.[4] For example, the partial pressure of oxygen (PO_2) in ambient air is 20.93% of the total dry gas pressure. At sea level, this means the partial pressure of oxygen in ambient air is approximately 160 mmHg:

$$PO_2 = \frac{20.93\%}{100} \times 760\ mmHg = 159\ mmHg$$

Changes in altitude will cause changes in barometric pressure. For example, at the summit of Mount Everest, the barometric pressure is only 253 mmHg. While the gas composition of ambient air remains the same with 20.93% of oxygen even at the summit, the barometric pressure change will cause a considerable decrease in the partial pressure of oxygen of ambient air to about 53 mmHg:

$$PO_2 = \frac{20.93\%}{100} \times 253\ mmHg = 52.95\ mmHg$$

Alveolar Partial Pressure of Oxygen (P_AO_2)

Once air is inhaled and enters the upper respiratory tract, it becomes fully saturated with water vapour and is heated to achieve body temperature (37°C).[1] As water vapour exerts its own partial pressure, it must be subtracted from the barometric pressure to obtain the partial pressure of inspired oxygen (P_iO_2).[4] At 37°C, all inspired air has a water vapour pressure of 47 mmHg, so the partial pressure of oxygen of inspired air is approximately 150 mmHg:

$$P_iO_2 = \frac{20.93\%}{100} \times (760\ mmHg - 47\ mmHg) = 149\ mmHg$$

However, the partial pressure of alveolar oxygen (P_AO_2) is not equal to the inspired P_iO_2. The difference is due to the constant gas exchange taking place in the alveoli, whereby oxygen is

removed from the alveolar space into the capillary blood in exchange for carbon dioxide. As inhaled air moves further down the respiratory tract, it mixes with the expired air containing higher amounts of carbon dioxide.[1, 4]

While the partial pressure of alveolar oxygen can technically be measured using end-tidal oxygen measurements, it is usually calculated using the alveolar gas equation and measurements obtained from arterial blood gas analysis.[1]

$$P_AO_2 = FiO_2\left(P_{atm} - P_{H_2O}\right) - \frac{P_aCO_2}{R}$$

With $FiO_2 \times (P_{atm} - P_{H20})$ being the partial pressure of inspired oxygen, the equation can be rewritten as:

$$P_AO_2 = PiO_2 - \frac{P_aCO_2}{R}$$

Where:

P_iO_2 = partial pressure of inspired oxygen; at room air 150 mmHg

P_ACO_2 = partial pressure of alveolar carbon dioxide and can either be obtained by end-tidal gas measurements or substituted with arterial PCO_2. In normal lungs, the alveolar-arterial carbon dioxide gradient is so insignificant that arterial values can be used in exchange. Alveolar PCO_2 in normal conditions is about 40 mmHg.

R = respiratory quotient. The respiratory quotient is the ratio of carbon dioxide production to oxygen consumption, and in healthy humans is about 0.8. The rate of oxygen removal is dependent on metabolic oxygen demand; thus, *R* can vary between 0.7 and 1. The respiratory quotient for dogs has been reported with values ranging from 0.84 to 1.0.[5]

Using the alveolar gas equation above, the alveolar partial pressure of oxygen at sea level comes to 100 mmHg:

$$P_AO_2 = PiO_2 - \frac{P_aCO_2}{R} = 150\ mmHg - \frac{40\ mmHg}{0.8} = 100\ mmHg$$

The alveolar partial pressure of oxygen is thus dependent on the barometric pressure, the fraction of inspired oxygen, and the removal and replenishment of oxygen via ventilation.

Arterial Partial Pressure of Oxygen (P_aO_2)

In the alveoli, continuous gas exchange occurs, and oxygen diffuses into the pulmonary capillary, where it enters the bloodstream, oxygenating the blood. As oxygen is taken up faster than carbon dioxide is released, adequate ventilation is needed to replenish oxygen and remove carbon dioxide from the alveolar space. The undisturbed gas exchange process depends on diffusion, perfusion, and ventilation. Thus problems affecting oxygenation can arise from disturbances in any of these processes, causing a drop in arterial partial pressure of oxygen (P_aO_2).[1]

In an ideal lung, the capillary P_aO_2 would be equal to the alveolar PO_2. In reality, however, arterial partial pressure of oxygen is always lower than alveolar PO_2 due to several factors causing pulmonary venous admixture.[5] Physiological sources of venous admixture are blood perfusing the bronchial system before entering the pulmonary veins and a small fraction of coronary venous blood entering the left ventricle via the Thebesian veins.[1] Incomplete diffusion only makes up a tiny fraction of venous admixture and is negligible. Physiological ventilation-perfusion imbalances cause the largest part of the venous admixture. In the normal upright human lung, changes in ventilation and perfusion exist between the apex and the lung base, creating areas with high and low V/Q units.[1] Although an overall balance between these units exists in the healthy lung, highly ventilated units cannot compensate entirely for less oxygenated units. This imbalance creates a drop in the overall partial pressure of oxygen, causing the physiological drop in arterial partial pressure of oxygen in relation to alveolar PO_2. This physiological difference between arterial and alveolar partial pressure of oxygen represents the alveolar-arterial oxygen difference ($AaDO_2$) and can be used to interpret the efficacy of gas exchange.[1, 22] Physiological venous admixture causes a drop in arterial PO_2 of about 5 to 15 mmHg.[22] At sea level and breathing ambient air, the normal values for arterial partial pressure of oxygen thus range from 80 to 110 mmHg.[5] P_aO_2 is directly correlated to P_AO_2; therefore, values will also change depending on barometric pressure, the fraction of inspired oxygen and ventilation. The standard value of arterial partial pressure of oxygen for a patient breathing 100% oxygen, for example, is 500 mmHg.

Measurement of arterial partial pressure of oxygen is the gold standard for evaluating oxygenation as it reflects the lungs' ability to transfer oxygen from the alveolar space into the blood.[4, 5] An arterial partial pressure of oxygen of less than 80 mmHg while breathing ambient air is defined as hypoxaemia. Values less than 60 mmHg reflect severe hypoxaemia and call for urgent therapeutic interventions and oxygen supplementation.[5] Causes of hypoxaemia are 1. Low FiO_2, 2. Hypoventilation, 3. Diffusion Impairment, 4. Ventilation-Perfusion Mismatch and 5. Shunt.

Besides evaluating P_aO_2, values for arterial partial pressure of carbon dioxide (P_aCO_2) can also be obtained via arterial blood gas analysis.[4] As P_aCO_2 is a measurement for ventilation, knowledge of its value in an arterial blood sample allows to narrow down the causes of hypoxaemia. For example, while a patient suffering from hypoventilation will show a decreased P_aO_2 with an elevated P_aCO_2, hypoxaemia is not caused by an underlying impairment of gas exchange and can be corrected with assisted ventilation.

Causes of hypoxaemia	**P_AO_2**	**P_aO_2**	**P_aCO_2**
Low FiO_2	decreased	decreased	decreased
Hypoventilation	decreased	decreased	increased
Diffusion Impairment	normal	decreased	normal
V/Q Imbalance	normal	decreased	increased/normal/decreased
Shunt	normal	decreased	normal or decreased

Table 1: Causes of hypoxaemia with expected changes in P_AO_2, P_aO_2 and P_aCO_2. P_aCO_2 can be normal, increased or decreased in diseases with V/Q imbalances depending on the respiratory pathology and duration of the clinical symptoms.

Just as the alveolar partial pressure of oxygen is dependent on the barometric pressure, FiO_2 and ventilation so is the P_aO_2. Thus, knowledge of barometric pressure and FiO_2 at the time of arterial blood sampling is essential to properly assess the value of arterial PO_2.[4] A P_aO_2 of 95 mmHg, for example, while normal under ambient air conditions, will be cause for concern while breathing 100% oxygen.

Various oxygenation indices have been established and evaluated to avoid variations caused by changes in FiO_2 and adequately assess a patient's oxygenation ability.[23-25] P_aO_2 obtained

via blood gas analysis can be used to calculate these parameters and aid in further evaluating a patient's pulmonary function.

1.3.3 Alveolar-Arterial Oxygen Difference ($AaDO_2$)

The alveolar-arterial oxygen difference ($AaDO_2$) is used to compare the calculated alveolar PO_2 to the measured arterial PO_2, thereby giving valuable information about the movement of oxygen from the alveolar space into the blood.[22]

Respiratory diseases can cause inefficient gas exchange due to thickening of the alveolar-capillary membrane or increasing lung areas with V/Q mismatch. In theory, the increase in venous admixture caused by such disease processes will reflect in an elevated alveolar-arterial oxygen difference. Normal values of $AaDO_2$ range between 5 and 15 mmHg when breathing ambient air.[1, 4, 22] Values greater than 15 mmHg indicate increased venous admixture due to ventilation-perfusion mismatch, shunt or diffusion impairment.[1, 5, 22] Hence, calculating the alveolar-arterial oxygen difference can help narrow down the causes of hypoxaemia and initiate appropriate diagnostics and treatment.[4, 22, 25]

Causes of hypoxaemia	**P_AO_2**	**P_aO_2**	**P_aCO_2**	**$AaDO_2$**
Low FiO_2	decreased	decreased	decreased	normal
Hypoventilation	decreased	decreased	increased	normal
Diffusion Impairment	normal	decreased	normal	increased
V/Q Imbalance	normal	decreased	Increased/normal/de-creased	increased
Shunt	normal	decreased	normal/decreased	increased

Table 2: Causes of hypoxaemia with expected changes in P_AO_2, P_aO_2, P_aCO_2 and alveolar-arterial oxygen difference ($AaDO_2$).

Calculation of $AaDO_2$ is based on the alveolar gas equation and the measured arterial partial pressure of oxygen using the following formula:

$$AaDO_2(mmHg) = P_AO_2 - P_aO_2$$

The alveolar gas equation is used to calculate the alveolar partial pressure of oxygen:

$$P_AO_2 = FiO_2\left(P_{atm} - P_{H_2O}\right) - \frac{P_aCO_2}{R}$$

Where:

P_{atm} = Atmospheric Pressure at place of measurement (sea level = 760 mmHg)

P_{H20} = Water Vapour Pressure (47 mmHg)

R = respiratory quotient, with a standard value of 0.8

However, two main problems exist in practicality with calculating the alveolar-arterial difference. First, the $AaDO_2$ varies with increasing concentrations of inspired oxygen.[4, 22] For example, in patients breathing 100% oxygen the $AaDO_2$ ranges from 100 to 150 mmHg, and no expected values for oxygen concentrations between 21% and 100% have been established yet, making it difficult to correctly interpret AaDO2 values and the extent of oxygenation impairment with intermediate FiO_2.[5] Therefore, the Alveolar-arterial oxygen difference ($AaDO_2$) is best assessed when breathing room air or 100% oxygen.[1, 4, 23] Second, it is not the most accessible parameter to determine as it prerequisites the calculation of the alveolar partial pressure first, making it somewhat tedious to use in clinical routine. To compensate for these variations in the $AaDO_2$ displayed with different FiO_2 and to simplify daily utility, other oxygen indices to evaluate oxygenation and pulmonary function have been examined.[4, 23-25] Examples include the ratio of PaO_2/FiO_2, P_AO_2/P_aO_2 and $AaDO_2/P_aO_2$. Of these parameters, the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (P_aO_2/FiO_2) is the only parameter that is simpler and quicker to calculate than the alveolar-arterial difference. Additionally, it is relatively stable with increasing oxygen concentrations above 50% making it a valuable alternative for monitoring patients receiving oxygen supplementation.[26]

1.3.4 Ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (P_aO_2/FiO_2)

The ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (P_aO2/FiO_2) has been established as a convenient and quick method to assess oxygenation.[23] It is simple to calculate as it only requires the arterial PO_2 and the FiO_2 at the time of analysis. Due to its

simplicity, it is routinely used to monitor patients' response to oxygen therapy, and this parameter is one vital criterion for establishing the diagnosis of ALI and ARDS. [4, 20]

The ratio of P_aO_2/FiO_2 is calculated by dividing the measured arterial partial pressure of oxygen by the fraction of inspired oxygen, expressed as a decimal, at the time of measurement:

$$P_aO_2/FiO_{2\,t}\,(mmHg) = \frac{P_aO_2}{FiO_2}$$

In healthy patients without oxygenation inefficiency, the normal value of P_aO_2/FiO_2 is between 400 and 500 mmHg, no matter if a patient is breathing ambient air or oxygen-enriched air. For example:

$$P_aO_2/FiO_2\ (mmHg) = \frac{110\ mmHg}{0.21} = 523\ mmHg$$

$$P_aO_2/FiO_2\ (mmHg) = \frac{90\ mmHg}{0.21} = 429\ mmHg$$

$$P_aO_2/FiO_2\ (mmHg) = \frac{500\ mmHg}{1.0} = 500\ mmHg$$

P_aO_2/FiO_2 values between 300 and 400 reflect mild oxygenation inefficiency.[5] The 2012 Berlin Definition for Acute Respiratory Distress Syndrom (ARDS) defines values between 200 and 300 mmHg as mild oxygenation impairment and values between 100 and 200 mmHg as moderate ARDS. A P_aO_2/FiO_2 value below 100 mmHg represents severe respiratory failure. [22] Despite its simplicity in use, the ratio can be difficult to interpret with variations in FiO_2.[12, 23] Studies have shown a complex, neither constant nor linear relationship between P_aO_2/FiO_2 and FiO_2.[12, 26, 27] In addition, results obtained with ambient air can be misleading in the presence of hypoventilation with increased P_aCO_2. Additionally, P_aO_2/FiO_2 is influenced by other extrapulmonary factors such as cardiac output, haemoglobin content and oxygen demand.[4]

However, the ratio of P_aO_2/FiO_2 is still a useful parameter, especially when continuous measurements are obtained in contrast to just a single one. Therefore, regular assessment of P_aO_2/FiO_2 can be helpful in monitoring patients' progress to oxygen supplementation.

2. Oxygen Supplementation

Oxygen therapy can assume a life-saving function in patients experiencing acute or chronic respiratory failure. Oxygen supplementation aims to increase the partial pressure of arterial oxygen by providing the patient with higher than normal levels of inspired oxygen.[28, 29] Consequently, by increasing P_aO_2, oxygen delivery to the tissues will improve. By improving oxygenation, oxygen supplementation can alleviate a patient's feeling of anxiety or panic caused by the sensation of asphyxiation and thus serves as one of the most important treatment options for respiratory emergencies. Providing oxygen can help stabilise the patient and allow for initial assessment without risking further respiratory deterioration.[30, 31]

2.1 Indications for oxygen therapy

The clinical presentation is the first and foremost indication that a patient requires oxygen therapy.[28] Anxiety, tachypnoea or dyspnoea with open mouth breathing, stridor or enforced abdominal breathing are clear signs a patient is in respiratory distress and in need of oxygen supplementation. Oxygen should be administered without delay to improve breathing, alleviate anxiety and stabilise the patient before further diagnostics, such as arterial blood gas analysis or thoracic imaging, can be performed.[28]

The main indication for commencing or continuing oxygen therapy is the presence of hypoxaemia, evaluated with arterial blood gas analysis. In general, oxygen therapy should be considered in all patients with a P_aO_2 of less than 70 mmHg.[28] Additional parameters such as $AaDO_2$, P_aO_2/FiO_2, S_aO_2 or S_pO_2 can help assess the severity of hypoxaemia and decide which oxygen supplementation method is ideal for the patient.

In addition to hypoxaemia, patients displaying signs of hypoxia benefit from oxygen therapy.[31] Hypoxia can result from increased oxygen demand in the tissues, for example, in sepsis or heatstroke, or from insufficient oxygen supply to the tissues caused by hypoxaemia, perfusion disturbances or limited oxygen-carrying abilities of the blood, for example, in anaemia.

Another application for oxygen therapy is anaesthesia and perioperative support.[30] Patients undergoing surgery or invasive diagnostic procedures require either sedation or general

anaesthesia. Therefore, oxygen therapy is imperative, especially if assisted manual or mechanical ventilation is performed. Furthermore, oxygen therapy can be used for perioperative support and preoxygenation, i.e. the supply of high oxygen levels before induction of anaesthesia.[32] Preoxygenation causes denitrogenation: alveolar nitrogen is washed out and replaced with oxygen leading to an increase in the alveolar partial pressure of oxygen.[32] Therefore, pre-oxygenation will ensure high enough alveolar oxygen concentrations to maintain ongoing gas exchange if induction of anaesthesia causes respiratory depression or even apnoea. This effect of continuous arterial oxygenation in the absence of active ventilation is termed apnoeic oxygenation.[33, 34] It helps to gain valuable time until a patient's airways are secured without risk of developing hypoxaemia.

2.2 Complications associated with oxygen therapy

Although oxygen is essential for sustaining all aerobic life, it can also have a toxic and potentially lethal effect.[28, 35, 36] Like any drug, this toxicity is dose-dependent, and complications are especially encountered with prolonged oxygen therapy at high FiO_2 levels.[28, 37, 38]

Possible complications resulting from oxygen therapy are hyperoxic acute lung injury (HALI)[37], absorption atelectasis[28, 39] and damage to the respiratory mucous membranes from prolonged exposure to dry and cold air.[40-42]

2.2.1 Hyperoxic acute lung injury (HALI)

While hypoxaemia refers to an abnormally low amount of P_aO_2, hyperoxia, in contrast, refers to higher than normal values of P_aO_2 as a result of administering FiO_2 above 21%.[43] Oxygen can have a toxic effect on the organism, particularly the lungs, and the risk of related damages increases with prolonged exposure to supranormal FiO_2 concentrations above 50%.[28, 37, 38]

Prolonged exposure to hyperoxic conditions causes an increase in reactive oxygen species (ROS).[37] ROS are regular products of metabolic oxidation processes and consist of free radicals and other oxygen species resembling the latter. ROS can lead to cell injury via lipid peroxidase and cause damage to DNA, proteins, and lipid membranes. Since the respiratory tract is directly exposed to toxic oxygen concentrations, the respiratory cells, especially alveolar epithelium and alveolar-capillary endothelium, are the primary targets displaying the first

signs of damage.[37] First signs of oxygen toxicity are already seen after four hours of receiving oxygen concentrations above 95%.[44]

Changes caused by oxygen toxicity in the lung are well described and consist of different phases; initiation, inflammation, proliferation and finally, fibrosis.[28, 37] A vicious cycle develops as inflammation causes even more ROS formation. The pathological damages to the lungs caused by oxygen toxicity resemble those seen in patients suffering from ALI/ARDS and are thus termed HALI: hyperoxic acute lung injury.[37]

The impact of oxygen toxicity depends on the duration of oxygen supplementation and the FiO_2 administered. Several studies showed a correlation between increasing FiO_2 values above 50% and the extent of the damages.[39, 45, 46] Thus oxygen concentrations during therapy should best be kept below 50% if tolerated by the patient.[28, 37, 43] With patients in need of higher FiO_2 levels, attempts should be made to wean the patient gradually to settings below 50%.

2.2.2 Absorption Atelectasis

Another risk of prolonged hyperoxic oxygen therapy is the formation of absorption atelectasis. Atelectasis generally refers to the partial or complete collapse of airways.[47] In the case of absorption atelectasis caused by hyperoxic conditions, the underlying mechanisms are denitrogenation and obstruction.[47, 48] Administering high oxygen concentrations will deplete the alveolar space of nitrogen and lead to high alveolar PO_2 values. Hyperoxic therapy also impacts the mucous viscosity and mucociliary clearance rate leading to mucous build-up, which might cause airway obstruction. As a result, alveolar collapse will occur once all the entrapped gas is eventually reabsorbed.[43, 47] When breathing ambient air consisting mainly of nitrogen, atelectasis formation would be a slow process as nitrogen has poor solubility and, therefore, barely any diffusion into the blood takes place.[1, 39] Oxygen, on the other hand, has a much higher solubility and will diffuse quickly, thus speeding up atelectasis formation when high alveolar oxygen concentrations are achieved by O_2 supplementation.[39] Additionally, prolonged high FiO_2 exposure impairs surfactant production causing alterations of surface tension, further assisting alveolar collapse.[37, 38] Maintaining FiO_2 values below 50% and keeping exposure duration short can help reduce the occurrence of absorption atelectasis.

2.2.3 Effects of inhaling dry and cold air

As air enters the body, it will be humidified and heated to body temperature as it moves through the upper respiratory tract.[1] Inhaled pollutants and pathogens will be filtered out and expelled via mucociliary clearance to protect the lungs.[42]

As most oxygen supplementation methods either administer cold air or bypass the upper airways entirely, damage to the respiratory epithelial cells can occur unless oxygen is adequately humidified before it reaches the patient. Without humidification and heating of inhaled air, exposure to dry and cold air will cause mucosal dehydration and, in turn, increase the viscosity of secretions, causing mucus build up in the airways.[42, 49] Additionally, breathing dry air will cause damage to the respiratory epithelium, thus further impairing mucociliary transport. Overall, by hindering these natural defence mechanisms, the risk of respiratory infections increases.[42, 49]

Humidification of medical oxygen is thus necessary, especially in long term oxygen therapy and is most commonly achieved by using a bubble humidifier.[28, 49] This device transfers oxygen through a water reservoir, increasing the water vapour before it reaches the patient. Other devices that can be used to achieve humidification are humidity exchange filters or nebulisers.[49] However, the ability to achieve sufficient humidification with such devices remains questionable as studies showed only a 40% saturation with bubble humidifiers.[41, 50] Furthermore, even with a humidifier, the gas reaching the patient will remain cold or warmed to room air at best, especially if the nasopharynx is bypassed. Administering cold and dry air was shown to cause discomfort in humans and dogs, particularly when using high flow rates.[40, 51]

2.3 Traditional oxygen therapy (TOT) in veterinary medicine

Different methods of oxygen supplementation exist, ranging from non-invasive to invasive techniques. The decision of which type is best suited for the patients depends, among others, on each patient's individual needs, underlying condition and overall clinical presentation, and equipment at hand.

2.3.1 Non-invasive methods

Flow-by oxygen

Flow-by oxygen is the easiest and fastest method to supply a patient with oxygen. One end of an oxygen tube is connected to an oxygen source, while the other open end is placed in close vicinity, about 2–4 cm, in front of the patient's face.[31] Ideally, a bubble humidifier should be connected to allow for humidification of the gas. Due to its simplicity, this method allows for immediate oxygen administration after a patient's admission or during the initial examination, providing immediate relief to respiratory distress. Furthermore, this method requires little equipment and is generally well tolerated by the patients. However, the flow-by method's disadvantages are high oxygen waste and related costs.[28] Due to the mixture of oxygen with ambient air, only a small percentage of oxygen reaches the patient, achieving only low FiO_2 values ranging from 25 to 45% compared to other oxygen supplementation methods.[28, 31] Although this method is generally well tolerated, some animals, particularly cats, do not tolerate high flow rates due to jet effects in the facial area and the related sound of oxygen escaping the open tube. In patients already experiencing respiratory distress, such additional stress can cause further deterioration of the patients' condition. Another disadvantage is that one staff member must constantly hold the oxygen tube near the patient, making it labour-intensive.[28]

Oxygen hood via Elizabethan collar

The use of an oxygen hood is another quick and easy implemented method of oxygen supplementation. An oxygen hood can easily be constructed by covering 75–90% of the opening of an Elizabethan Collar with clear plastic wrap and securing an oxygen tube inside the hood. The collar is then placed tightly over the patient's head and secured around the neck. After initial flooding of the hood with oxygen, the flow rate can be reduced to 0,5–1 L/min, which will deliver a FiO_2 of 30–40%.[28, 31]

Like the flow-by method, the advantages are easy and quick administration while the patient remains accessible for examinations or procedures while receiving oxygen. Additionally, it does not require extra staff to hold the oxygen line, and a collar is generally well tolerated. Disadvantages are the risk of carbon dioxide, temperature, and condensation accumulation

under the plastic wrap causing hypercapnia and hyperthermia.[28] Therefore, care must be taken to leave a big enough opening to allow carbon dioxide, humidity, and warmth to escape.

Oxygen cage

An oxygen cage is a closed environment flooded with oxygen in which the patient is placed. By flooding a confined enclosure with oxygen, high ambient oxygen levels of up to 60% can be achieved with this method.[28, 31] In addition, as the animal is not restrained, it can choose its preferred positioning, adding to the relief of respiratory distress. The enclosed environment often provides a sense of security for animals in distress, and the patient can be observed from outside the cage without having to discontinue the therapy. Various oxygen cages exist, ranging from repurposed and reconstructed transport cages to professional commercial oxygen cages. Commercial cages allow for manual setting and regulation of FiO_2 and control humidity, temperature, and carbon dioxide levels. Depending on the manufacturer FiO_2 up to 90% can be achieved with commercial cages. The main disadvantage of this method is that any manipulation or examination of the patient can only be achieved by opening the cage, causing a sudden and quick drop in oxygen concentration with a high risk of patient decompensation.[28, 31]

Face mask

Face masks are easy to use and provide a quick increase in FiO_2. A tight-fitting mask connected to an oxygen source is placed on the patient's face, covering the nose and mouth. The use of face masks is a standard routine in human emergency settings, and special masks can even be used to provide non-invasive ventilation (NIV) or continuous positive airway pressure (CPAP).[52, 53] While this oxygen supplementation method is easily applied to human patients, it can be challenging to implement in the veterinary setting.[53-55] Since face masks, especially NIV masks, are designed for human patients, they do not provide an adequate fit for the facial conformations of veterinary patients. Thus, a snug fit as needed for delivery of CPAP often cannot be achieved, especially in awake patients. Alternatively, cone-shaped masks placed over the snout can work well with dolichocephalic or mesocephalic dogs but can be problematic with brachycephalic breeds due to their facial deformations.[28] Thus, a lack of patient tolerance of the mask due to an ill fit is often the limiting factor for using this method

in veterinary medicine.[31] Depending on the flow rate and how tight the mask fits, a FiO_2 between 35–60% can be achieved with this method.[28, 31] Like other flow-by methods, it also allows simultaneous access to the patient for examination or diagnostics to be performed.

2.3.2 Invasive methods

Oxygen helmet

The oxygen helmet is a relatively novel method of oxygen supplementation. A specially prepared and sealed helmet is placed over the patient's head, similar in appearance to a diver's or astronaut's helmet. This method has been primarily used in neonatal medicine but has been successfully applied to dogs and even cats.[54, 56, 57]

The helmet is made of transparent plastic material and equipped with gas ports for in- and expiratory gas flow. Different valves and ports exist to adjust CPAP levels, prevent asphyxia, measure internal pressure, and allow access to the patient. The helmet is sealed around the patient's neck, providing a closed and controlled compartment. This method is generally well tolerated by the patients, even without sedation.[54] Further advantages compared to other methods are the provision of CPAP, the reduced waste of oxygen, and a high FiO_2 of 30 – 40% inside the helmet.[56] As with all sealed gas compartments, there is a risk of carbon dioxide retention and an increase in temperature inside the helmet, which can be avoided by increasing the oxygen flow, thus providing a carbon dioxide washout.[54] Since the helmet is designed for human patients, it can be difficult to achieve a proper seal around the neck of veterinary patients.

Nasal oxygen therapy

An alternative for nasal catheter placement is the use of nasal prongs connected to a humidified oxygen source.[28] Nasal prongs are quick and easy to place and are generally well-tolerated, although they can easily be removed by the patients with their paws or by rubbing the snout. Care should be taken to select the appropriate prong size for each patient, allowing enough space for carbon dioxide to be exhaled. So far, no studies exist regarding the FiO_2 achieved with nasal prongs in veterinary patients.

A more invasive method of oxygen supplementation is via nasal or nasopharyngeal catheters. For this method, a multi-fenestrated silicon or rubber catheter is placed directly into the nasal

or nasopharyngeal cavity and connected to a humidified oxygen source. Catheters are sutured to the side of the nares to avoid displacement. They can be placed unilateral or bilateral, depending on the patient's condition and oxygen requirements.[28, 51]

Since this method has the advantage of providing high levels of FiO_2 without waste of oxygen compared to other methods, it is primarily indicated if oxygen therapy for a more extended period is suspected.[28] According to a study by Dunphy et al.[51], flow rates of 100 ml/kg/min per catheter are recommended and can provide a FiO_2 of 60% when bilateral catheters are used. Furthermore, the patient remains accessible while receiving oxygen therapy, and the method is generally well-tolerated and technically easy and inexpensive.

However, nasal oxygen administration should be avoided in patients suffering from nasal obstruction, chronic rhinitis, facial trauma, or increased intracranial pressure.[28, 31] Disadvantages of this method are the risk of damage to the respiratory mucous membranes due to the dry and cold air and consequently discomfort for the patient.[41, 51] These adverse effects are especially pronounced if high flow rates are used. In addition, the catheter placement requires restraining of the patient, which can be difficult or even contraindicated in severely respiratory compromised patients. In this case, other methods should be used to stabilise the patient before the placement of nasal catheters is attempted.

Tracheal oxygen therapy

Oxygen can also be administered directly into the trachea via a nasotracheal catheter, a transcutaneous tracheal catheter (TTC), or a tracheal tube.[28, 58, 59] This method of oxygen supplementation bypasses the upper airways and is therefore indicated in patients with upper airway obstruction. High FiO_2 values with lower flow rates can be achieved by applying oxygen directly into the trachea by avoiding admixture from dead space or ambient air. Flow rates of 50-150 ml/kg/min should be used and can result in a FiO_2 between 60 and 80%.[31, 58] Disadvantages of this method can be kinking or displacement of the catheter, irritation and increased coughing, subcutaneous emphysema, and sedation required for catheter or tube placement.[28, 58, 59]

Mechanical ventilation (MV)

Endotracheal or tracheal tube placement with manual or mechanical ventilation is indicated in patients with severe hypoxaemia, severe hypercapnia, or if other non-invasive oxygen therapies fail to show signs of improvement.[28] Assisted ventilation provides secured airways and the most control over respiratory functions as pressure, FiO_2, PEEP, and respiratory rate can be adjusted to the patient's need.

However, the risk of iatrogenic airway infections, atelectasis formation, and ventilator-induced lung injury (VILI) exists and increases with time spent on the ventilator.[60]

2.4 Oxygen Therapy during Bronchoscopy in veterinary medicine

Although bronchoscopy is an essential diagnostic tool for patients suffering from respiratory diseases, it is also associated with an increased risk for the patient, with the development of hypoxaemia being the most commonly encountered complication.[9-11, 61]

The mere presence of the bronchoscope causes a partial occlusion of the airways and has been shown to cause a reduction of P_aO_2 of approximately 20 mmHg, which is even further exacerbated during bronchoalveolar lavage (BAL) sampling.[10, 11, 62] Additionally, bronchoscopy in animals requires general anaesthesia with the potential for further worsening respiratory depressive effects.[17, 18]

In human medicine, various oxygen delivery methods exist to avoid episodes of hypoxaemia during bronchoscopy, for example, utilising high-flow interfaces such as Venturi masks.[61, 63-65] However, as such masks are designed for humans, they do not provide the necessary tight fit in veterinary patients due to the differences in facial structures and are generally not well tolerated by the animals.

The placement of an endotracheal tube offers by far the safest airway management method.[18, 66] The bronchoscope can be inserted through a T- or Y-shaped connector into the tube down the airway while still allowing controlled assisted ventilation.[18, 66, 67] However, this method requires a sufficiently large enough tube size in relation to the diameter of the bronchoscope. Therefore, this method is limited to patient size and not applicable in small dogs or cats.

As an alternative in smaller patients, oxygen can be applied through the biopsy channel of the bronchoscope.[17, 18] However, short episodes of hypoxaemia, for example, during induction of anaesthesia or BAL sampling, have to be anticipated and accepted with this method. [17, 18] In

case of hypoxaemic events, the procedure needs to be stopped until the patient has stabilised before bronchoscopy can proceed.

In addition to the obvious disadvantages such as irregular oxygen supply and danger of hypoxaemia, oxygen application through the biopsy channel restricts oxygen supply to the lung area where the bronchoscope is placed. If the bronchoscope is wedged in a small bronchus, oxygen administration to a sealed restricted area can cause rupture of the present alveoli.[17] Furthermore, with this method, cold and dry medicinal oxygen is applied directly to the lower airways causing potential damage to respiratory mucous membranes, mainly when high flow rates are used.[51] Nasopharyngeal, nasotracheal or tracheal catheters can be used as alternative oxygen supplementation methods.[68] However, as catheter placement is quite invasive, they often require sedatives or anaesthetics, and patients need to be restrained during placement. In addition, drying of the mucous membranes also applies to these techniques, and so far, no study evaluating the effects of these different oxygen supplementation methods during bronchoscopy in veterinary patients exists.

Thus, the possibilities of adequate airway management during bronchoscopy in small animals are currently limited and overall unsatisfactory, putting patients at an increased risk for hypoxaemia when undergoing the procedure

3. High Flow Oxygen Therapy

High Flow Oxygen Therapy (HFOT) emerged in the 2000s as an alternative oxygen supplementation method in paediatric patients.[69-72] Compared to other methods, the main difference and advantage are that HFOT delivers heated and humidified medical gas to the patient via nasal cannulas. This preconditioning of the gas allows for much higher flow rates of up to 60 L/min without causing discomfort as no drying or causative damage to the respiratory mucosa occurs compared with other oxygen therapy methods.[69] Discomfort and respiratory functional changes due to dry and cold air are the flow-rate-limiting factors in TOT.[51, 71, 73]

Furthermore, HFOT devices contain an air-oxygen blender which allows the delivered oxygen concentration to be adjusted between 21 and 100%, independent of the flow rate.[69, 73]

Compared to other oxygen supplementation methods such as helmets or masks, the patient only needs a soft and slender silicone nasal cannula as an interface. This way, the patient does not experience discomfort or even claustrophobia due to, for example, a tight or ill-fitting

mask.[74, 75] In addition, HFOT even allows the patients to speak and consume food and water while continuing oxygen therapy, adding to much higher patient comfort and thus tolerance.[74, 76] The nasal cannulas are quick and easy to apply to the patient, and no special skills or technical knowledge for its setup is needed.

Besides its simplicity in use and good patient tolerance, HFOT has been shown to have several beneficial effects, such as improving oxygenation[70, 77, 78], decreasing dead space through carbon dioxide washout[79, 80], improving mucociliary clearance[41, 75], decreasing work of breathing (WOB)[71, 81], and even providing low levels of positive airway pressure (PAP)[82-84]. These beneficial mechanisms have led to an increasing application of HFOT beyond paediatric care. For example, HFOT is now used in patients from neonates to adults suffering from various respiratory diseases such as acute hypoxaemic respiratory failure (AHRF)[85-89] or infectious pulmonary diseases[90-92], in patients undergoing procedures such as endoscopy[93-97] and even in palliative care[98, 99]. Moreover, in recent years this method of oxygen supplementation experienced a further rapid surge due to the SARS-CoV-2/COVID-19 pandemic.[90, 100] In COVID-19 patients, HFOT is used to provide superior oxygen support in hypoxaemic patients, thus attempting to avoid escalating therapy to intubation and mechanical ventilation.

However, despite the increasing use as a valuable respiratory support method, it is important to know that HFOT functions as an open system, meaning sufficient gas leak is essential. Hence, it does not provide ventilatory support. While it can serve as an intermediate step between TOT and MV in an attempt to avoid escalation to the latter[78], it cannot replace assisted ventilation. Therefore spontaneous and sufficient breathing must be ensured in patients receiving HFOT.

3.1. Technical Details

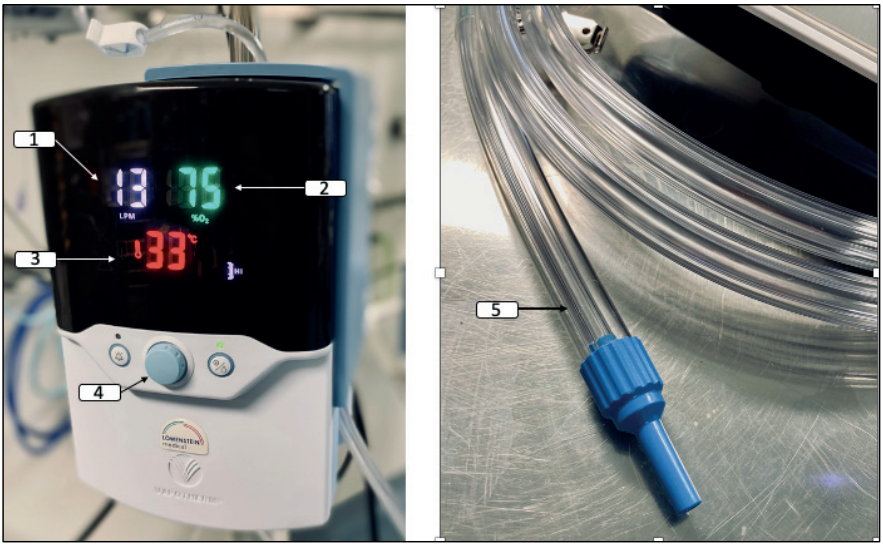
3.1.1 HFOT Device

Special commercially available High Flow devices and accompanying nasal cannulas are available to administer HFOT. Generally speaking, High Flow Oxygen devices mix medical air and oxygen using an air-oxygen blender before heating and humidifying the gas, which is then delivered through a heated tube system connected to a specifically designed nasal prong to the patient. This way, heated and humidified medical gas with adjustable FiO_2 concentrations reaches the patient.[101]

The two most common commercially available HFOT devices are the Vapotherm Precision Flow® and the Optiflow™ by Fisher & Paykel Healthcare Ltd., which differ slightly in their technical setup. As the present study uses the Vapotherm Precision Flow®, further technical details will focus on this device solely. The Vapotherm Precision Flow® consists of two major parts: the main unit incorporating the air-oxygen blender, flowmeter, sensors, and electronic components and the disposable patient circuit consisting of a vapour transfer cartridge, patient delivery tube and water reservoir.[101] The main unit is connected to a pressurised oxygen and air source, and the integrated air-oxygen blender mixes the gases and allows the user to adjust settings for both flow rate and oxygen concentration. Sterile water from a disposable reservoir is pumped through a process-controlled heater before flowing through the patient delivery tube and the vapour transfer cartridge. The transfer cartridge contains a membrane made of tiny hollow special polymer tubes that allow water vapour to diffuse through and enter the gas stream. The gas mixture thus becomes fully saturated with water vapour and heated to the set temperature.[102]

Once heated and humidified, it needs to be ensured that the gas reaches the patient in this condition, and no vapour or heat is lost as condensation. For this purpose, HFOT devices use different heated delivery tubes, most often containing a heating wire.[101] The Vapotherm Precision Flow®, however, uses a specifically designed triple-lumen heated delivery tube.[102] The heated and humidified gas mixture leaving the transfer cartridge flows through an inner tube inside the patient delivery tube. This tube is surrounded by another divided lumen through which warm water is constantly pumped. This way, the internal gas tube is insulated and its temperature maintained by surrounding it with a warm water 'jacket', ensuring that the gas mixture reaches the patient at the set temperature.[102]

High flow devices allow the user to adjust and set the flow rate, temperature, and oxygen content to be delivered to the patient. Specifically designed patient interfaces are needed for each HFOT device depending on the manufacturer



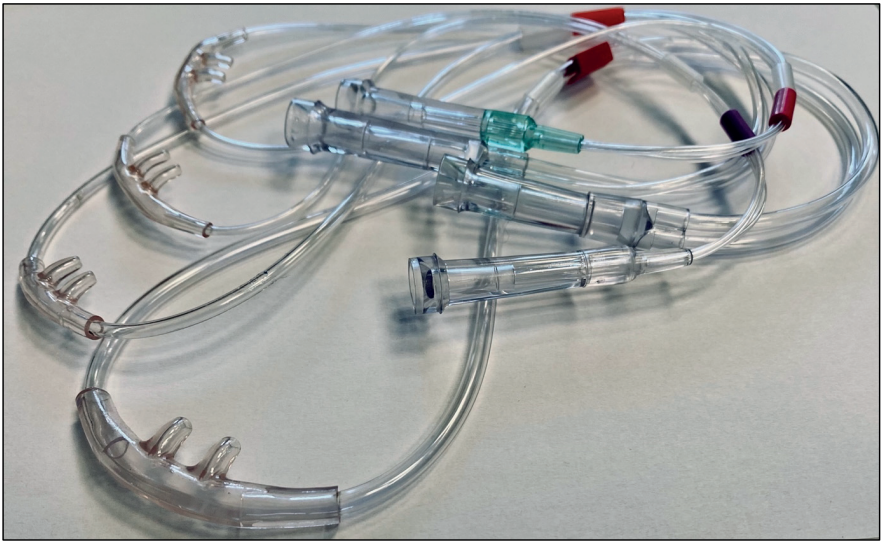
Picture 3 and 4: Vapotherm Precision Flow® High Flow Device and heated delivery tube. Device display showing settings for 1 = flow rate (LPM), 2 = FiO_2 (%) and 3 = Temperature (°C). 4 = Control push button for adjustment of the settings. 5 = triple-lumen delivery tube depicting the inner tube and outer 'jacket'. (Vapotherm, Precision Flow®, Vapotherm Inc., Exeter, USA).

3.1.2 Interface

A distinctive feature of HFOT is its patient interface. Soft silicone nasal cannulas are used to deliver medical gas to the patient. The nasal cannulas for HFOT differ slightly depending on the manufacturer and associated device.[101] The overall design is similar to standard nasal cannulas with two short nasal silicone prongs that can be inserted in each nare. The prongs are connected to a tubing system running along both sides of the patient's face, tucked behind the ears, merging at the back of the head. Here the tubes can be tightened with an adjustable clasp to ensure a tight fit without dislocating the prongs in the nares. The allocated High Flow delivery tube can then be connected to the nasal cannula system.

The Vapotherm Precision Flow® uses specifically designed cannulas called High-velocity nasal insufflation system® (Hi-VNI®, Vapotherm).[101] These cannulas are slightly thinner than standard prongs, both in outer and internal tube lumen diameter, thus creating higher flow velocity.[103] Additionally, the device delivers an equal flow from either side of the cannula

system to the tip of the prongs.[101] Hi-VNIs are available in eight different sizes for use from neonates to adults, covering a wide range of nares diameters.



Picture 5: Vapotherm Hi-VNI® nasal cannulas. (Vapotherm, Precision Flow®, Vapotherm Inc., Exeter, USA).

High Flow oxygen therapy is designed as an open system. Thus care must be taken to ensure enough space around the prongs in the nares for sufficient carbon dioxide washout. It is recommended that the prongs should not occlude more than 50% of the nares to achieve optimal results.[104]

The soft and slender silicone cannulas significantly relate to better tolerance and comfort of the system in patients. Unlike, for example, NIV masks that obstruct almost the entire face causing discomfort and possibly pressure lesions, HFOT nasal cannulas do not obstruct the patient and even allow the patient to speak and consume fluids and food without interrupting the oxygen therapy.[74, 75]

3.1.3 Settings

By incorporating an air-oxygen blender and an oxygen cell to continuously measure the achieved oxygen concentrations, HFOT allows the user to set the flow rate and the desired FiO_2 concentration of the supplied gas mixture. HFOT devices can achieve precise fractions of

inspired oxygen ranging from 21 to 100%, thus achieving much higher FiO_2 concentrations than any traditional oxygen therapy method.[74, 105, 106] The user is able to set precise FiO_2 concentrations depending on the patient's need and response to treatment. FiO_2 can be increased, or the patient weaned from high settings without switching to a different oxygen delivery method. This way, HFOT allows for an individualised approach to oxygen therapy.

FiO_2 setting should be chosen according to the patient's initial presentation, the severity of hypoxaemia and response to therapy. As with all oxygen delivery methods, a potential risk for oxygen toxicity related injuries exists, especially regarding the high oxygen concentrations High flow devices can deliver. Thus ideally, FiO_2 should not exceed 40–50%, especially for extended periods or otherwise be reduced to these concentrations as quickly as the patient's condition allows it.

Generally speaking, flow rates should equal or exceed the peak inspiratory flow to avoid entrainment of ambient air.[41, 106, 107] In healthy humans at rest, peak inspiratory flow is approximately 30 L/min [108]. However, this inspiratory need can increase up to 120 L/min in people experiencing respiratory distress [69, 108]. Therefore, a flow rate below the peak inspiratory flow will lead to additional room air recruitment to fulfil the inspiratory need, thus diluting the pre-set oxygen concentration, and the anticipated FiO_2 concentration will not be achieved.

Depending on the HFOT device used, flows up to 60 L/min are possible. The Vapotherm Precision Flow® provides two cartridge systems for flows of 1 to 8 L/min or 8 to 40 L/min. So far, no official guidelines on flow settings exist in human medicine. However, based on a study by Mauri et al.[86], it is recommended to start with flow rates of 60 L/min if tolerated by the patient and then titrate according to the patient's response. In paediatric settings, flow rates of 2–8 L/min are recommended.[109]

Although it would seem logical that a temperature setting of 37°C would be more comfortable for the patient as it closer resembles physiological core body temperature, a study by Mauri et al.[110] showed higher comfort levels at a lower temperature of 31°C compared to 37°C, regardless of the flow rates used.

As HFOT is used in a variety of respiratory conditions with differences in severity, it remains challenging to establish a generalised setting fitting all patients. However, the ease of making adjustments to flow, FiO_2 and temperature can be seen as an advantage, enabling an individualised approach to oxygen treatment.

3.2 Mechanisms of action

HFOT has been shown to improve oxygenation in various respiratory diseases and settings.[70, 77, 78] Several physiological mechanisms produced by HFOT are associated with this improvement of oxygenation.

First, improved oxygenation can be explained by the much higher fractions of inspired oxygen HFOT provides compared to TOT. One study using a manikin model evaluated FiO_2 concentrations achieved by different oxygen devices.[111] Although the HF device showed a discrepancy between set FiO_2 at 100% and an effective, inspired oxygen concentration of 76.67% to 78.67%, these values are still much higher than those achievable with conventional oxygen methods.[111] This study tested only two tidal volumes, and increasing flow rate improved oxygen delivery. Several other studies showed that delivered FiO_2 shows a closer correlation with set FiO_2 when higher flow rates are used.[105, 106, 112, 113] This is most likely due to less entrainment of ambient air and thus less dilution of the pre-set oxygen concentrations when high flows are used. The continuous delivery of high flow rates also maintains constant FiO_2 levels and further benefits oxygenation via a washout effect of carbon dioxide.[114]

By administering high flow rates, the nasopharyngeal space gets flushed with the oxygen-rich gas mixture, and the open leak system allows for carbon dioxide to be washed out of the upper airways. This CO_2 washout leads to a decrease of anatomic dead space by creating a large oxygen reservoir; thus, rebreathing of carbon dioxide is avoided. Several studies showed that sufficient leak around the nasal prongs combined with high flow rates is necessary to achieve an adequate CO_2 washout effect. For example, Moller et al.[80] showed that a flow increase from 15 to 45 L/min resulted in three times higher decrease of anatomic dead space.[80] Studies by Siveri et al.[104] and Frizzola et al.[115] showed a correlation between CO_2 washout, improved oxygenation and high or low nasal leak systems. These studies not only showed the effects of different prong sizes on carbon dioxide washout but also a relationship between high flow and achievable positive pharyngeal pressure. Positive airway pressure (PAP) therapy is commonly used in hypoxaemic patients with respiratory failure. By providing positive airway pressure, either continuous or end-expiratory, alveolar collapse can be prevented, and alveolar recruitment in already atelectatic areas facilitated. Although HFOT is not intended as a positive airway pressure delivery method, low levels of PAP have been

shown to occur.[82, 84, 116] Achievable pressures depend on several factors such as open or closed-mouth breathing, flow rate, patient size and prong-nares-ratio.[72, 82, 116-119]

High flow rates and a PAP effect also contribute to decreasing the resistance of the upper airways, thus reducing inspiratory effort and work of breathing (WOB).[71, 81] Work of breathing refers to the energy required to ventilate the lungs. While decreasing inspiratory resistance, the continuous delivery of high flow rates will increase expiratory resistance. This results in higher end-expiratory pressure, which can aid alveolar recruitment and increase end-expiratory lung volume.

In general, the pressure created by HFOT is relatively low, around 2–5 cmH20.[106] However, studies show wide variability in measured PAP and without using invasive measurement methods, it is difficult to precisely determine what airway pressure to expect. Studies using electrical impedance tomography showed a correlation between end-expiratory lung volume and airway pressure.[70, 120] How much of the positive airway pressure created by HFOT is really translated to the lungs is usually neither measured nor known during therapy, so a potential risk of barotrauma to the lungs exists.

Another main beneficial factor of HFOT is the application of heated and humidified oxygen, which sets this method apart from traditional oxygen supplementation methods. By preconditioning the gas mixture, HFOT avoids the negative impact cold and dry air has on the respiratory system. Respiratory mucosa serves to heat and moisten inhaled air and protect the airways as mucus production and ciliated cells provide essential defence mechanisms.[42] Inhaled particles, contaminants or microorganisms are trapped, transported and removed from the body by mucociliary clearance. The respiratory membranes are very susceptible to changes in humidity and temperature, and alterations from physiological conditions lead to changes in mucus viscosity, mucociliary transport mechanisms and bronchoconstriction.[121] Mucus accumulation and viscosity changes can lead to mucus plugging causing increased airway resistance and work of breathing while adding to the risk of airway infections.[122, 123]

Studies showed that cold and dry air also impacts nasal receptors, causing bronchoconstriction, which can be detrimental in patients suffering from asthma.[121] Providing warm and humidified air with HFOT has the opposite positive effects liquidising mucus, improving ciliary function and decreasing bronchoconstriction.[40, 75, 124, 125] In addition, studies in infants also showed improved weight gain when receiving HFOT compared to conventional oxygen methods.[126] Normal metabolic energy requirements are reduced by

heating and humidifying the administered air as the body does not need to take on this additional task.

3.3 Risks and Adverse effects

HFOT is a generally well-tolerated method, and only a few reports of adverse effects exist.[127-129] Mild adverse effects in humans usually relate to localised skin damage around the nasal philtrum after prolonged use.[130, 131] The two main concerns with the application of high flow oxygen are air leak syndrome and the risk of delayed escalation to mechanical ventilation.

Air leak syndrome can occur when overdistension of the airways due to excessively high pressures or volumes causes ruptures allowing air to escape to structures outside the respiratory system. Such an air leak can cause, for example, pneumothorax or pneumomediastinum and is also a reported adverse event in CPAP therapy and mechanical ventilation.[132] Positive pressure provided by HFOT is usually low due to the open system, with measured pharyngeal pressures of approximately 2–5 cmH_2O depending on open-mouth or closed-mouth breathing.[82, 106] However, increases in pressure of 0.7–0.8 cmH_20 for every 10 L/min increase in flow rate have been observed.[82, 116] In clinical settings, no measurement and regulation of actually achieved pressures occur during HFOT. Hence increased and potentially dangerous airway pressures can occur in small patients or if the prongs selected are too big, creating an insufficient nasal leak.[104]

One Case report discussed three incidents of air leak syndrome after using HFOT in children.[127] It was argued that the possible cause of air leakage was excessively high flow rates exceeding peak inspiratory flow, thus causing overdistension of the airways. Flow rates were retrospectively determined to have exceeded peak inspiratory flow.[127] In a more extensive retrospective study determining the risk of HFOT in 145 neonates, only two occurrences of new pneumothoraces were recorded, thus associating air leak syndrome due to HFOT with only a mild risk of 1%.[128]

Whenever traditional oxygen therapy fails to improve a patient's condition, further escalation to more superior methods such as NIV or CPAP support is necessary. Once NIV methods fail, the necessary step is an escalation to invasive procedures, i.e., intubation and assisted ventilation. HFOT has been successfully used to delay and even prevent escalation to invasive ventilation providing almost an intermediate step between non-invasive and invasive methods.[71, 78] The challenge with the use of HFOT is not to overlook signs of deterioration and

miss the point at which escalation to invasive measures is unavoidable. Several studies have tried to determine parameters to predict HFOT failure and not delay intubation and mechanical ventilation. Failure to improve oxygenation, worsening after initial improvement, persisting tachypnoea and thoraco-abdominal asynchrony have been discussed as possible markers for therapy failure.[133-136] However, given the high comfort and tolerance HFOT provides in patients experiencing respiratory distress, early recognition of therapy failure while receiving HFOT requires a high degree of observational skills and clinical judgement.
Although no absolute contraindications exist so far, it is recommended to avoid HFOT in patients suffering from nasal or head trauma or surgery, airway obstruction or severe epistaxis, and in patients failing to sustain sufficient spontaneous breathing.[52, 137]

3.4 Indications

The beneficial physiological effects of HFOT have led to an increasing application in various clinical settings in human medicine.[73, 75] Since its first usage in paediatric care, HFOT utilisation has expanded to intensive care and emergency medicine[52, 92, 138, 139], anaesthesia and perioperative care[52, 74, 137, 140] and even palliative care.[98, 99, 141] Most successfully, HFOT has been used in patients with acute hypoxaemic respiratory failure (AHRF).[85, 89, 142-144] So far, two GRADE (Grading of Recommendation, Assessment, Development, and Evaluations) based practice guidelines exist for HFOT in patients with AHRF.[89, 144] Rochwerg and colleagues[144] developed four recommendations for using HFOT, with strong recommendations to favour the use of HFOT over conventional therapy in hypoxaemic respiratory failure. A Task Force panel of the European Respiratory Society also used GRADE methods to establish eight recommendations for using HFOT in ARF along with TOT and NIV.[89] Use of HFOT in hypoxaemic ARF, postoperative setting, patients with risk of extubation failure and patients with chronic obstructive pulmonary disease (COPD) and hypercapnic acute respiratory failure were evaluated.[89] Besides AHRF, HFOT has found beneficial use in the perioperative setting during recovery from anaesthesia[74] or preoxygenation[33, 140, 145]. The high patient comfort and ability to continue talking and eating during therapy[74] while providing superior oxygenation to conventional methods have also led to the application of HFOT in do not intubate patients and palliative care.[98, 141] Here, HFOT can alleviate respiratory distress in end of life settings. Furthermore, HFOT use in patients undergoing invasive procedures such as bronchoscopies has increasingly been studied with promising outcomes.[93, 94, 96, 97]

3.5 HFOT during bronchoscopy

Bronchoscopy serves as an essential diagnostic and therapeutic tool in pulmonary medicine. Although the overall complication rate is low, patients undergoing bronchoscopy are exposed to an increased risk of developing hypoxaemia due to several factors.[9-11, 61] First, many patients in need of bronchoscopy already suffer from an underlying respiratory disease with impaired gas exchange and consequent hypoxaemia beforehand. Sedation or anaesthesia necessary for the procedure can cause desaturation or exacerbate pre-existing hypoxaemia due to respiratory depression.[11] Second, the insertion of the bronchoscope into the airways causes a certain degree of airway obstruction.[10, 11, 61] Depending on the patient size and correlated diameter of the tracheal lumen in relation to the bronchoscope, occlusion can take up to 20% of the tracheal cross-sectional area.[10, 11] Third, bronchoscopy is usually combined with additional diagnostic sampling techniques, for example, bronchoalveolar lavage (BAL). Instillation of lavage solution will cause an increasing V/Q mismatch, while excessive suctioning to retrieve the fluid can cause alveolar collapse and a decrease in local alveolar oxygen concentration. Although the effects of BAL sampling are only temporary, they lead to a considerable drop in arterial PO_2.[13, 14]

Hypoxaemia is thus a common occurrence, and arterial partial pressure of oxygen has been shown to drop up to 20 mmHg during bronchoscopy, with the most severe decline occurring during BAL.[10, 11, 138] Maintaining adequate oxygenation is thus essential to avoid or minimise the occurrence of hypoxaemic events. Different methods for oxygen supplementation can be used during bronchoscopy.[65] Conventional oxygen therapy via nasal cannulas can achieve FiO_2 of 35 – 40% depending on flow rate and minute ventilation.[146] Alternatively, the bronchoscope's working channel can be used to supply oxygen to the patient.[68] While this technique has been shown to increase oxygenation rapidly, it can only be used as long as the working channel of the bronchoscope is not needed otherwise. Additionally, oxygen administration occurs only in the regions of the lungs in which the bronchoscope is placed, leaving other sections without adequate supplementation.[17]

NIV masks can be used as they provide not only high FiO_2 but also additional ventilatory and pressure support.[147] However, using NIV requires experienced personnel, is time-consuming and manoeuvring the bronchoscope through the mask can be challenging, especially in small paediatric patients.[14, 148]

As the airways need to be shared between the anaesthetist, patient and bronchoscopist, it can remain challenging to provide adequate oxygenation, especially in patients with pre-existing respiratory dysfunction. It is not uncommon for bronchoscopic procedures to be paused until the patient's saturation levels are stabilised or even forgo additional diagnostics such as BAL in patients deemed too respiratory unstable.[96, 147, 149]

Since HFOT has been successfully used in patients with AHRF, its application during bronchoscopy to avoid hypoxaemia has been increasingly studied. The beneficial physiological mechanism of HFOT combined with the increased patient comfort, quick setup and ease of use make it an interesting alternative to explore. Lucangelo et al.[93] evaluated the use of HFOT with two different flow settings in 45 patients undergoing bronchoscopy, comparing it to oxygen delivery via Venturi mask. The study demonstrated that HFOT with a flow of 60 L/min was superior in providing oxygenation to High Flow at 40 L/min and oxygen supplementation via Venturi mask.[93]

However, a follow-up study by Simon et al.[150] raised doubts about the effectiveness of HFOT during bronchoscopy compared to NIV, as HFOT did not provide the expected improvements. However, the patient group in this study consisted of patients suffering from moderate to severe AHRF and two patients were even deemed too sick for HFOT before bronchoscopy could be initiated. Additionally, one patient transitioned to NIV as s/he experienced apnoea during induction. Since HFOT cannot provide ventilatory support, this escalation was a necessary choice. However, the study did show that HFOT was well tolerated in patients with stable oxygenation during bronchoscopy. [150]

Another prospective study comparing HFOT versus NIV during bronchoscopy in hypoxaemic patients showed that overall, both methods provided similar effectiveness in avoiding hypoxaemia, while NIV provided greater stability in severely hypoxaemic patients. [147]

The superiority of NIV in both studies is easily explained. This method supplies high FiO_2, ventilatory support, and even CPAP, thus improving oxygenation in patients with hypoxaemia due to hypoventilation. In the study by Simon et al., [150] NIV was set to a PEEP of 3–10 cmH_20 and pressure support of 15–20 cmH_20, creating an obvious advantage over HFOT. The follow-up study by Saksitthichok et al.[147] adjusted NIV settings to reflect expected values achievable with HFOT, thus showing a closer correlation between both methods.

Several studies exist comparing the effectiveness of HFOT compared to TOT in order to avoid hypoxaemia during bronchoscopy.[13, 14, 95, 148, 151-153] A prospective trial in 812 patients by Wang

et al.[14] showed that the occurrence of single hypoxaemic events was significantly lower in patients receiving HFOT than in the group with traditional oxygen supplementation. Similar positive results have been shown in other studies proving that HFOT can be superior to TOT during bronchoscopy and provide at least equal support compared to NIV in patients with mild to moderate respiratory failure[96, 150]. Although HFOT can temporarily bridge short periods of hypoxia during apnoea via apnoeic oxygenation[149], it is expectingly inferior to NIV in patients experiencing hypoxaemia due to hypoventilation as HFOT cannot provide ventilatory support.[96]

As NIV is of limited use in veterinary medicine due to intolerance and often ill-fit of the masks[154, 155], HFOT represents an interesting alternative to avoid hypoxaemia in veterinary patients undergoing bronchoscopy.

3.6 High Flow in Veterinary Medicine

Increasing utilisation of HFOT in human medicine has also opened the doors for its application in veterinary medicine. Its use in paediatric care makes it especially interesting for small animal veterinary medicine due to the similarities in patient size.

Besides the physiological benefits of HFOT, the adjustable FiO_2 settings, quick and easy setup, and no special training requirements make it additionally attractive. Furthermore, whenever traditional oxygen therapy methods fail, patients need to be escalated to more advanced methods. As NIV is not a viable option in veterinary medicine, intubation and mechanical ventilation are the consequent steps. However, in veterinary medicine, escalation to mechanical ventilation correlates with high mortality.[60] The possibility of using HFOT as a tool to escalate from TOT by providing superior oxygenation while also potentially avoiding mechanical ventilation is thus of particular interest in veterinary medicine.

So far, HFOT in veterinary medicine is still in its infancy and only a couple of studies evaluating the use of HFOT in dogs exist.[154-160] Daly et al.[155] evaluated the general tolerance and safety of HFOT in healthy dogs compared to TOT. HFOT was well-tolerated and safe to use, and the increase in PaO_2 was nearly two times higher than with traditional oxygen therapy. A retrospective study by Keir et al.[154] evaluated the use of HFOT in moderate to severe hypoxaemic dogs failing TOT. Although all dogs showed initial improvement with a significant increase in PaO_2, two dogs died due to the severity of their condition. A third dog died due to fatal arrhythmias; however, hypoxaemia was resolved before its death.[154] A recent

prospective study showed similar results in dyspnoeic dogs failing TOT.[160] HFOT was safe to use and well-tolerated in this patient population, and all dogs showed initial improvement with a significant increase in PaO_2 and SpO_2. However, 5/11 (45%) dogs still needed to be escalated to mechanical ventilation within 24 hours.

A prospective trial by Jagodich et al.[158] also showed that HFOT is safe to use and well-tolerated in dogs suffering from AHRF. 22 dogs with hypoxaemia from various causes were transitioned to HFOT after failing to improve with traditional oxygen supplementation methods. All dogs showed improvements in oxygenation, dyspnea scores and respiratory rates. While three dogs died and nine were euthanised ten dogs survived. Out of the surviving dogs, eight managed to avoid intubation and mechanical ventilation while the remaining two survived following temporary tracheostomy and mechanical ventilation respectively.

The same author evaluated the utility of HFOT in brachycephalic dogs during recovery from general surgery with promising outcomes for future applications.[157] All dogs showed clinical improvement in dyspnoea scores, including respiratory rate and severity of stridor over time.[157] The use of HFOT in brachycephalic dogs is of particular interest due to the high prevalence of respiratory decompensation due to the anatomic abnormalities in these breeds. As these breeds suffer from enlarged soft tissue compressed into shortened anatomical head structures, it is believed that pressure created by HFOT will distend the nasopharynx, stenting it open and thus alleviating inspiratory resistance and reducing work of breathing.[157]

A third prospective study by Jagodich et al.[156] evaluated different flow settings of HFOT on tolerance and safety in awake and sedated healthy dogs. Flow settings of 0.4, 1, 2 and 2.5 L/min/kg were used based on calculated minute ventilation using 6–8 L/kg tidal volume. While all flow settings increased P_aO_2, tolerance declined with flow rates above 2 L/kg/min. Additionally, no further beneficial effects in relation to P_aO_2, FiO_2 or airway pressure were noted with flow rates above 2 L/kg/min. On the lower end, flow rates of 0.4 L/kg/min showed no significant differences in the evaluated parameters compared to TOT via nasal cannula at the same flow rate. Based on their findings, the author recommends flow rates between 0.4 and 2 L/kg/min for HFOT in dogs.[156]

Harduin et al. [159] evaluated the effects of two temperature settings on tolerance in non-dyspnoeic dogs. Settings of 31°C and 37 °C at flow rates of two and four times the estimated minute volume were used based on a previous study protocol in humans[110]. While all dogs

showed good tolerance to all applied settings, no significant difference between both temperature and flow settings was shown.[159] Thus, no recommendations for flow or temperature settings in dogs receiving HFOT could be made. Just as in human patients, it is advisable to titrate all settings after initiating HFOT to match the individual patient's response.

Complications of HFOT in veterinary patients seem to be equally rare as in humans, as air leak syndrome directly related to HFOT has not been reported in the veterinary literature. Only one study encountered one dog with a persisting pre-existent pneumothorax which only resolved once HFOT was discontinued[154], attributing air leak encounters an equally low risk as in human medicine. However, the current literature regarding air leak syndrome in human and veterinary medicine is minimal and not all existing studies used thoracic radiographs to confirm or exclude air leaks.

So far, the most common event reported in three veterinary studies was the occurrence of aerophagia.[155-157] In the study by Jagodich et al.[156], all eight dogs enrolled suffered from aerophagia after receiving HFOT. However, none of the dogs showed clinical signs or required medical intervention. Unfortunately, radiographs were not performed after receiving different HFOT flow rates or after TOT, so assessing the true prevalence of aerophagia remains difficult. In the other study by the same author, one out of five brachycephalic dogs required intervention to relieve severe gastric distension, though no further episodes occurred afterwards despite continuing the HFOT.[157]

Currently, no veterinary studies exist regarding the use and efficacy of HFOT in dogs undergoing bronchoscopy. The present study tries to fill this gap, hypothesising that HFOT will be a safe and superior means to improve oxygenation and avoid hypoxaemic events in dogs undergoing bronchoscopy, thus improving patient safety.

III. Study objectives

The study's main aim was to evaluate and compare the effects of High Flow Oxygen Therapy on oxygenation during fibreoptic bronchoscopy and BAL sampling in dogs compared to oxygen supplementation with a traditional method.

The secondary objectives were to assess the safety of High Flow Therapy in relation to adverse events and evaluate achievable tracheal oxygen concentrations with both methods.

It was hypothesised that the theoretical advantages of HFOT would translate to the present patient population and improve oxygenation in dogs during bronchoscopy, thus lowering the amount of hypoxaemic events. Based on previous studies in dogs and people, it was argued that HFOT would be a safe method to use without any detrimental side effects and that higher FiO_2 concentrations would be achieved with this method due to higher applicable flow rates.

IV. Material and Methods

1. Study design

The study was conducted as a prospective randomised trial, comparing High Flow oxygen therapy with a traditional oxygenation method during flexible bronchoscopy in dogs.

The study protocol was approved by the Regierungspräsidium Gießen and registered under the trial number (No V 54 – 19 c 20 15 h 02 GI 18/17 kTV 12/2020).

2. Subjects

All client-owned dogs presented to the Small Animal University Hospital Gießen requiring fibreoptic bronchoscopy and bronchoalveolar lavage (BAL) fluid collection were eligible for study inclusion.

The decision to perform fibreoptic bronchoscopy and sample collection was left to the discretion of the primary treating veterinarian and was not part of the study itself.

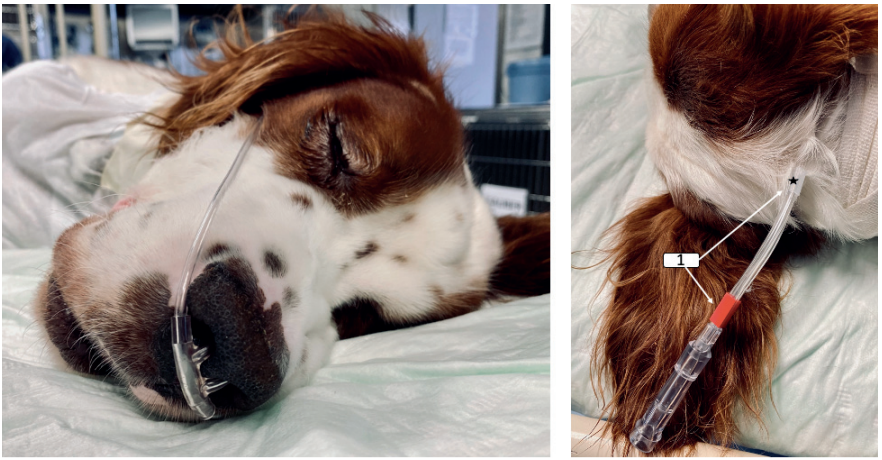
Inclusion criteria for the study were a bodyweight of at least three kilograms, the presence of an indwelling arterial catheter, a baseline arterial blood gas analysis on ambient air, and initial thoracic radiographs. The initial arterial blood gas analysis and thoracic radiographs were both part of the routine workup. Furthermore, all patients were required to breathe spontaneously throughout the endoscopic procedure for inclusion in the study.

Thus, exclusion criteria were failure to breathe spontaneously throughout, requiring intubation and or escalation to manual or mechanical ventilation. Additionally, patients were excluded if no arterial catheter could be placed or if the catheter dislocated and further arterial blood gas analyses could not be obtained.

3. Study groups

After enrolment, patients were randomly assigned to two groups. Randomisation was achieved using computer-generated block randomisation to receive either High Flow Oxygen Therapy (HFOT) or traditional oxygen supplementation (TOT).

In both groups, soft silicon nasal cannulas with double prongs were used as a patient interface for oxygen supplementation. The prongs were inserted into the nostrils and the tubing was secured behind the patient's heads. The cannula size was selected, ensuring that not more than 50% of the nares would be occluded.



Picture 6: Placement of nasal cannulas occluding approximately 50% of the nares. Front view of nares and view of the back of the head showing how to secure the nasal cannulas using adjustable clasps (1).

3.1 High Flow Oxygen Therapy (HFOT) Group

High Flow Oxygen was administered using the Vapotherm Precision Flow® device[1] with the matching nasal cannulas[2] as patient interface. High Flow parameters were set at a flow of 1 L/kg/min, a temperature of 35°C and a FiO_2 of 100%. Flow settings were based on the results of a previous study evaluating the effect of HFOT in dogs.[156] The high flow device was turned on at least 10 minutes before connecting to the patient to ensure that the air was sufficiently warmed and humidified.

3.2 Traditional Oxygen Therapy (TOT) Group

Patients enrolled in the control group received oxygen supplementation following current procedures used in our clinic. Pure oxygen was humidified using a standard bubble humidifier[3] and delivered to the patients via an oxygen line attached to a nasal cannula. If the standard nasal cannula[4] did not fit the patient's size, the same nasal cannulas as in the High

[1] Precision Flow®, Vapotherm Inc., Exeter, USA
[2] High Velocity Nasal Insufflation (HI-VN®) Cannula (for use with Precision Flow), Intermediate Infant/Infant/Pediatric-Small/Pediatric-Adult-Small, Vapotherm Inc., Exeter, USA
[3] Kendall™, Sterile Water for Inhalation, Covidien, Mansfield, USA
[4] Sauerstoff-Nasenbrille mit Sicherheitsschlauch, Centramed, Koblenz, Germany

Flow Group were used. Oxygen flow was set at 200 ml/kg/min[51] using a standard flow meter[5] to adjust the flow.

4. Study Procedure

4.1. Premedication and Preoxygenation

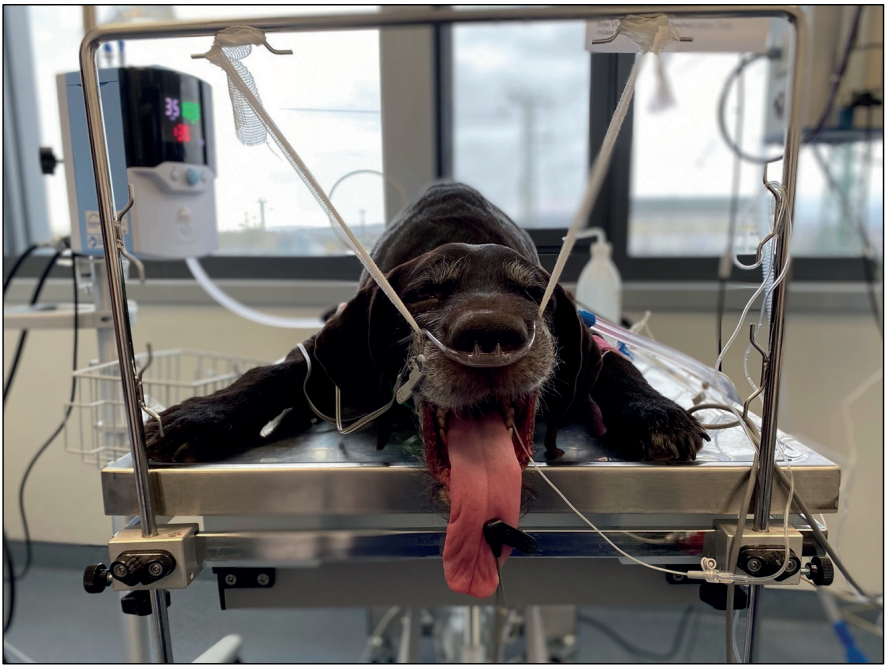
All patients received a venous catheter before the commencement of the study. Approximately 15 minutes before induction, the dogs were placed on the bronchoscopy table, and 0.2 mg/kg butorphanol was administered intravenously as sedative premedication. Afterwards, the dogs were allowed to rest in sternal recumbency until the medication took effect.

A suitable nasal cannula size was chosen and fitted to the patient. Patients in both groups received preoxygenation for 5 minutes using the allocated oxygen delivery method before induction of anaesthesia.

4.2 Anaesthesia induction

All patients received 0.5 mg/kg diazepam and 2–4 mg/kg propofol titrated to effect for induction of anaesthesia. After induction, the patients were placed in sternal recumbency. The patients' upper jaws were suspended from a specific suspension device using a gauze bandage to ensure the mouth was kept ajar throughout the bronchoscopy. The allocated oxygen delivery method remained attached to the patients the entire time to ensure a continuous oxygen supply for the duration of the entire procedure.

[5] MediFlow®Ultra II, GCE Mediline, Chotebor, Czech Republic



Picture 7: Patient placement: the patient is placed in sternal recumbency and the upper jaw is suspended using a gauze bandage to ensure oral access of the bronchoscope.

4.3. Fibreoptic bronchoscopy and bronchoalveolar lavage (BAL)

After the patients were positioned correctly, a flexible fibreoptic bronchoscope was inserted through the oral cavity into the trachea. First, the airways were endoscopically examined by the primary treating veterinarian. After visual examination, the bronchoscope was wedged into a suitable bronchial segment for fluid sample collection. Next, bronchoalveolar lavage was performed by administering approximately 0.5 ml/kg sterile saline solution, which was immediately aspirated. During the bronchoscopic procedure, anaesthesia was maintained by administering propofol as a constant rate infusion with 0.1 mg/kg/min. With the completion of the fibreoptic bronchoscopy, the constant rate infusion was discontinued. The time from insertion of the bronchoscope until its removal after BAL sampling was defined as the duration of bronchoscopy and recorded for each patient.

4.4. Recovery

After completion of the bronchoscopy, oxygen supplementation was continued in all patients until they were awake and able to lift their heads. This period was defined as the recovery phase, and its duration was recorded for each patient. In addition, the total duration of anaesthesia, from induction until recovery, was also recorded.

As soon as the patients could lift their heads, oxygen supplementation was stopped, and the nasal cannulas were removed. Subsequently, repeat thoracic radiographic images were taken to assess the extent of any adverse effects, such as gastric distension or pneumothorax. Afterwards, patients were transferred to the appropriate ward or ICU for further monitoring and care.

5. Data collection

5.1. Baseline characteristics

Baseline characteristics for all patients included breed, age, weight, sex, indication for bronchoscopy and vital signs (HR, RR, Temp). In addition, baseline arterial blood gas analyses while breathing ambient air were performed in all patients. All parameters were collected and recorded as part of the initial diagnostic workup.

5.2. Vital signs during anaesthesia

During the entire anaesthesia, vital signs including heart rate, ECG, respiratory rate, and body temperature were continuously monitored and recorded every minute using a CARESCAPE B650 monitor[6].

5.3. Tracheal Gas Measurement

Before insertion of the bronchoscope, a tracheal catheter was placed for continuous tracheal FiO_2 monitoring. For this purpose, a 4.5 F multi-fenestrated catheter[7] was inserted through the oral cavity into the trachea and placed proximal to the tracheal bifurcation. Correct placement was visually controlled via the bronchoscope, and depending on its position, the catheter was either advanced or withdrawn accordingly. The catheter was then connected to

[6] CARESCAPE B650 Monitor, General Electric Healthcare, Chicago, USA
[7] Braun Ernährungssonde CH 4,5, Braun, Melsungen, Germany

the monitor via a gas sampling line, and tracheal FiO_2 values were continuously displayed and recorded every minute. During the recovery phase, the catheter remained in position for as long as tolerated by the patients.

5.4. Pulse Oximetry (SpO_2)

Pulse oximetry was continuously monitored and recorded every minute during the entire anaesthesia. Two pulse oximetry sensor clips[8] were attached at different anatomic locations. Possible placement sites included the tongue, lips, pinnas or on the digits of the front or rear paws. In addition, the locations and potential problems such as dislocation of the sensor or poor probe signal were noted. One or both clips were already attached during the preoxygenation phase if tolerated by the dogs. Otherwise, probes were placed immediately after induction. During the recovery phase, the sensors remained attached for as long as tolerated by the patients.

5.5 Arterial Blood Gas Analyses

Since arterial blood gas analysis is considered the gold standard for assessing oxygenation, several arterial blood gas analyses were performed at predetermined time points (t0 – t6) during the procedure.

An indwelling arterial catheter was placed in either the left or right dorsal pedal artery under sterile conditions during the initial workup. For blood sampling, 1 ml heparinised arterial collection syringes[9] were used, and at least 0.3 ml of blood was drawn, depending on the patients' size. Samples were analysed immediately after blood collection using the COBAS blood gas analyser[10]. Heart rate, respiratory rate, rectal temperature and tracheal FiO_2 at the time of each blood collection were noted.

The first arterial measurement (t0) was performed on ambient air as part of the diagnostic workup. Subsequent measurements were taken 5 minutes after the start of preoxygenation (t1), immediately after anaesthesia induction (t2), both immediately before (t3) and directly after BAL collection (t4), and immediately before the discontinuation of oxygen

[8] Nellcor SpO2 Multisite Sensor, Covidien, Mansfield, USA
[9] BD A-Line, Arterial Blood Collection Syringe, Becton,Dickinson and Company, Plymouth, United Kingdom
[10] Cobas® b 123 System, Roche Diagnostics Deutschland GmbH, Mannheim, Germany

supplementation (t5). One final arterial blood gas measurement was taken 1 hour after the last measurement while breathing room air (t6).

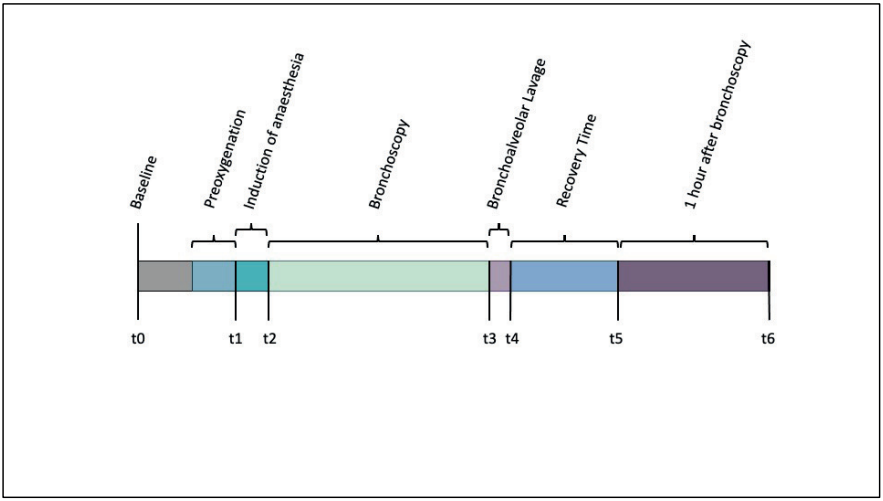


Figure 1: Timeline depicting the bronchoscopic procedure and the time points of arterial blood gas sampling.

5.6 Oxygen Indices

The arterial P_aO_2 values obtained were used to calculate the alveolar-arterial oxygen difference (AaO_2) and the ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (P_aO_2/FiO_2)

5.6.1. Alveolar-arterial oxygen difference ($AaDO_2$)

The Alveolar-arterial oxygen difference ($AaDO_2$) is best assessed when breathing room air. Thus, it was calculated for each patient at times t0 and t6 using the P_aO_2 values obtained by arterial blood gas analysis.

$AaDO_2$ was calculated using the following formula:

$$AaDO_2(mmHg) = P_AO_2 - P_aO_2$$

The Alveolar partial pressure P_AO_2 was calculated using the alveolar gas equation:

$$P_AO_2 = FiO_2\left(P_{atm} - P_{H_2O}\right) - \frac{P_aCO_2}{R}$$

Where:

P_{atm} = Atmospheric Pressure at place of measurement (Gießen/sea level = 760 mmHg)

P_{H20} = Water Vapour Pressure (47 mmHg)

R = respiratory quotient, with a standard value of 0.8

Furthermore, it was assumed that $P_aCO_2 = P_ACO_2$

As calculations were only made at t0 and t6 with the patients breathing room air, FiO2 = 21%

5.6.2 Ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2)

The ratio of partial pressure of arterial oxygen/fraction of inspired oxygen (P_aO_2/FiO_2) was calculated whenever tracheal oxygen concentration values could be obtained. It was calculated by dividing the arterial partial pressure of oxygen by the fraction of inspired oxygen, expressed as a decimal, at the time of analysis.

$$P_aO_2/FiO_{2\,t(0..6)}\,(mmHg) = \frac{P_aO_{2(t0..6)}}{FiO_{2\,(t0..6)}}$$

5.7 Complications and Adverse Effects of Oxygen Therapy

Previously described adverse effects of High Flow Oxygen Therapy in dogs include gastric distension and pneumothorax.[154-157] Thoracic radiographs were performed before and immediately after the fibreoptic bronchoscopy to evaluate the occurrence of such adverse effects. The initial radiographs were then compared with the subsequent radiographs to detect changes resulting from oxygen supplementation. Any occurrence of oesophageal and gastric distension, pneumothorax or pneumomediastinum was recorded for each patient. In addition, localisation of the distension (oesophageal, gastric or both) and severity were also recorded whenever air accumulation occurred. Since no official grading system exists, severity of aerophagia was graded as mild if only slight signs of aerophagia were visible, as moderate if distension of the stomach reached the caudal rib and/or if air was present in one

third of the oesophagus, and as severe if gastric distension was visible beyond the contour of the caudal rib and/or if air was present in more than one third of the oesophagus.

Any severe complications such as apnoea, cyanosis or cardiac arrest were recorded for each patient. These complications would be considered discontinuation criteria, and the patient withdrawn from the study.

6. Statistical analysis

Statistical analysis was performed using a commercially available statistical software (GraphPad Prism 9, GraphPad Software LLC., San Diego, California, USA).

Data distribution was assessed for normality using the Shapiro-Wilk normality test. Normally distributed data were expressed as mean and standard deviation, and non-normal variables were expressed as median and range.

Unpaired student's t-tests were used to compare normally distributed data between the groups, while paired t-tests were used for comparison within the groups. Non-parametric data were assessed using the Mann-Whitney-U-test, and a Chi-square test was performed to evaluate the relationship between categorical variables. For all comparisons, P-values < 0.05 were considered statistically significant. All data are shown as box-and-whisker plots, in which the box represents the interquartile range (IQR), and the central line marks the median value. The whiskers indicate the furthest data point within 1.5 times the IQR, and outliers beyond that distance are plotted with a dot or triangle depending on the group.

V. Results

1. Subjects

Between May 2020 and June 2022, a total of 23 dogs met the inclusion criteria for participation in the study. Three dogs had to be excluded because arterial blood sampling could not be obtained at all specified time points due to dislocation of the indwelling arterial catheter shortly after the start of the procedure in all cases.

Eventually, a total of 20 dogs were included in the study, with ten dogs represented in each of the groups.

1.1 Patient characteristics in the traditional oxygen therapy group (TOT)

The TOT group consisted of eight purebred dogs and two dogs of mixed breed. Breeds included one of each of the following: Jack Russel Terrier, Akita Inu, Magyar Vizsla, Wirehaired Dachshund, German Longhaired Pointer, Chihuahua, Pyrenes Mountain dog and one Golden Retriever.

Median age was 10 years (range from 1–12 years), and the median weight was 19.75 kilograms (range from 4.4–47.8 kg). Three of the ten dogs were female, two female spayed, two male, and three dogs were male neutered.

No	Breed	Age (years)	Weight (kg)	Sex
1	Mix	12	12.5	fs
2	Jack Russel Terrier	9	7.3	f
3	Akita Inu	1	35.0	m
4	Magyar Vizsla	10	27.0	mn
5	Wirehaired Dachshund	12	4.4	fs
6	German Longhaired pointer	10	30.3	m
7	Chihuahua	11	6.5	mn
8	Pyrenes Mountain Dog	5	47.8	f
9	Mix	10	9.7	mn
10	Golden Retriever	12	35.8	f

Table 3: Patient characteristics for the traditional oxygen therapy group (TOT). F= female, fs = female spayed, m = male, mn = male neutered.

1.2 High Flow Oxygen Therapy (HFOT) group

The HFOT group included three mixed breed dogs and seven purebred dogs. Breeds presented were one each of the following: Husky, Rhodesian Ridgeback, Cocker Spaniel, Airedale Terrier, Wirehaired Dachshund, White Shepherd and one German Wirehaired Pointer.

The median age of patients within the HFOT group was 7.5 years (range from 2–13 years), and the median weight was 22.85 kilograms (range from 6.4–45.0 kg). Three dogs were female, two female spayed, three male and two male neutered.

No	Breed	Age (years)	Weight (kg)	Sex
1	Husky	11	31.4	m
2	Rhodesian Ridgeback	4	45.0	m
3	Cocker Spaniel	11	11.5	f
4	Mix	2	6.4	fs
5	Airedale Terrier	9	18.0	f
6	Wirehaired dachshund	7	10.7	mn
7	Mix	13	8.1	mn
8	Mix	8	27.7	fs
9	White Shepherd	5	32.7	f
10	German Wirehaired pointer	7	34.8	m

Table 4: Patient characteristics for the High Flow Oxygen group (HFOT). F = female, fs = female spayed, m = male, mn = male neutered.

2. Baseline parameters

Physiological baseline parameters recorded for each patient in each group included respiratory rate, heart rate, core temperature, arterial partial pressure of oxygen (P_aO_2) on ambient air, partial pressure of carbon dioxide (P_aCO_2), and pH. In addition, the Alveolar-arterial Oxygen difference ($AaDO_2$) and the ratio of partial pressure of oxygen to fraction of inspired oxygen (P_aO_2/FiO_2) were also calculated for each patient at baseline.

There were no significant differences between both groups regarding patient characteristics or baseline physiological parameters. P-Values for individual parameters are listed in Table 5. Five dogs in the TOT group and five dogs in the HFOT group showed hypoxaemia, defined as P_aO_2 < 80 mmHg, at baseline. Out of these dogs, one in each group showed severe hypoxaemia with a P_aO_2 < 60 mmHg at baseline. The final diagnosis for the dog in the TOT group was tracheobronchomalacia, and for the dog in the HFOT group diagnosis was pulmonary fibrosis with bronchial collapse. Surprisingly, both dogs were presented as outpatients on the day of bronchoscopy, and both showed no distinct clinical signs indicating the severity of hypoxaemia.

The main indication for bronchoscopy was persistent chronic coughing, and the final diagnosis varied between all patients. Indications and final diagnoses are listed in Table 5.

Parameter	**TOT**	**HFOT**	**P-Value**
Number of patients	10	10	
Gender			
Female	3 (30%)	3 (30%)	
Female neutered	2 (20%)	2 (20%)	
Male	2 (20%)	3 (30%)	
Male neutered	3 (30%)	2 (20%)	
Age (years)	10 (1 – 12)	7.5 (2 – 13)	0.2698
Weight (kg)	19.75 (4.4 – 47.8)	22.85 (6.4 – 45)	0.8784
Heart Rate (beats/min)	99 ± 19	111 ± 17	0.1642
Respiratory Rate (breaths/min)	34 ± 17	33 ± 6	0.4953
Core Temperature (°C)	38.4 ± 0.8	38.8 ± 0.4	0.1302
P_aO_2 (mmHg)	76.5 ± 13	79.4 ± 15.6	0.6635
P_aCO_2 (mmHg)	36.1 ± 3.7	34.3 ± 4.7	0.3586
pH	7.397 ± 0,03	7.396 ± 0.03	0.9758
P_aO_2/FiO_2 (mmHg)	364.4 ± 61.8	377.9 ± 74.4	0.6636
$AaDO_2$	28 ± 12	28 ± 18	0.9725
Main indication for bronchoscopy: Chronic coughing	n = 4	n = 6	

Chronic progressive tachypnoea with acute coughing	n = 2	n = 1	
Chronic coughing with exercise intolerance	n = 1	n = 1	
Chronic coughing with intermittent fever	n = 1	n = 2	
Exercise-induced dyspnea and cyanosis with acute coughing	n = 1		
Chronic coughing with exercise intolerance and chronic tachypnoea	n = 1		
Final diagnosis:			
Chronic bronchitis	n = 1	n = 2	
Chronic bronchitis with bacterial pneumonia	n = 1		
Chronic bronchitis with bronchial collapse	n = 1		
Bronchopneumonia	n = 1	n = 3	
Bacterial pneumonia (Strept. equi sub. zooepidemicus)	n = 1		
Bronchial collapse with secondary pneumonia	n = 1		
Tracheobronchomalacia	n = 1		
Eosinophilic bronchopneumopathy		n = 1	
Allergic pneumonitis		n = 1	
Multicentric high-grade lymphoma		n = 1	
Pulmonary fibrosis with bronchial collapse		n = 1	
Immune-related pneumonitis	n = 1		
Fever-of-unknown-origin (FUO)		n = 1	
Laryngeal paralysis unilateral bilateral	n = 2 n = 1 n = 1		

Table 5: Patient Characteristics and physiological parameters at baseline. Data shown are listed as mean ± standard deviation, median and range or as numbers and percentages. P-Values are shown for evaluated comparison between both groups. P_aO_2 = partial pressure of arterial oxygen, P_aCO_2 = partial pressure of

arterial carbon dioxide, P_aO_2/FiO_2 = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, $AaDO_2$ = alveolar-arterial oxygen difference.

3. Outcome of arterial partial pressure of oxygen (P_aO_2) at specified time points

3.1 P_aO_2 after preoxygenation (t1)

Preoxygenation with nasal cannula was well tolerated by all patients in both groups. Three dogs, two in the HFOT group and one in the TOT group, showed initial pawing at the nasal cannula, which subsided after a few minutes.

P_aO_2 within the TOT group showed an increase from 76.52 $\pm$ 12.97 mmHg at baseline (t0) to 200.3 $\pm$ 96.5 mmHg after preoxygenation (t1). Within the HFOT group, P_aO_2 increased from 79.36 $\pm$ 15.61 mmHg at baseline (t0) 375.6 $\pm$ 95.3 mmHg after preoxygenation (t1). While there was no significant difference in P_aO_2 between both groups at baseline, after preoxygenation, patients achieved significantly higher values of P_aO_2 in the HFOT group compared to patients receiving TOT (P = 0.0007).

Differences in P_aO_2 values between both groups at baseline and after preoxygenation are shown in Figures 2 and 3.

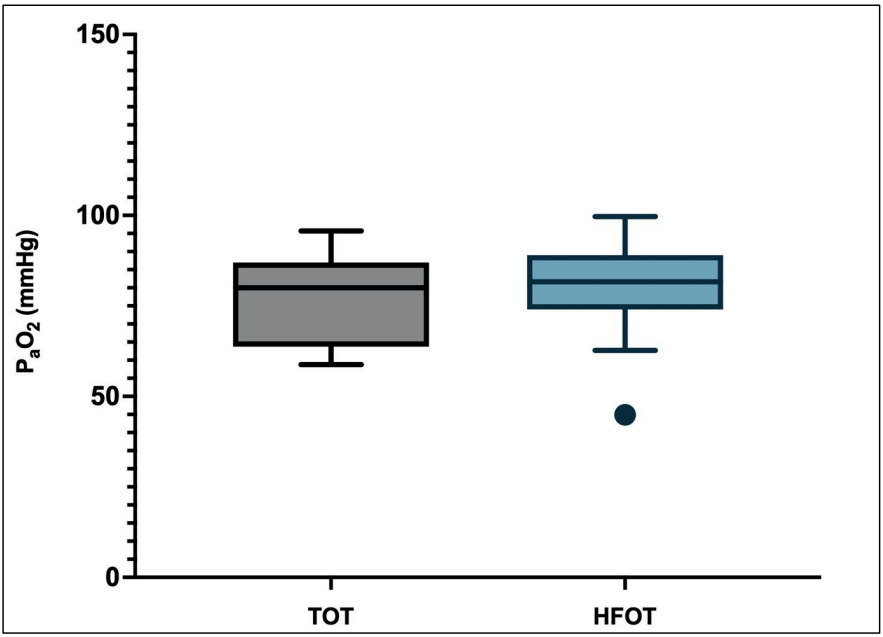


Figure 2: Difference in P_aO_2 in mmHg at baseline (t0) between the traditional oxygen therapy group and the High Flow Oxygen Therapy group. P-value = 0.6635.
P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

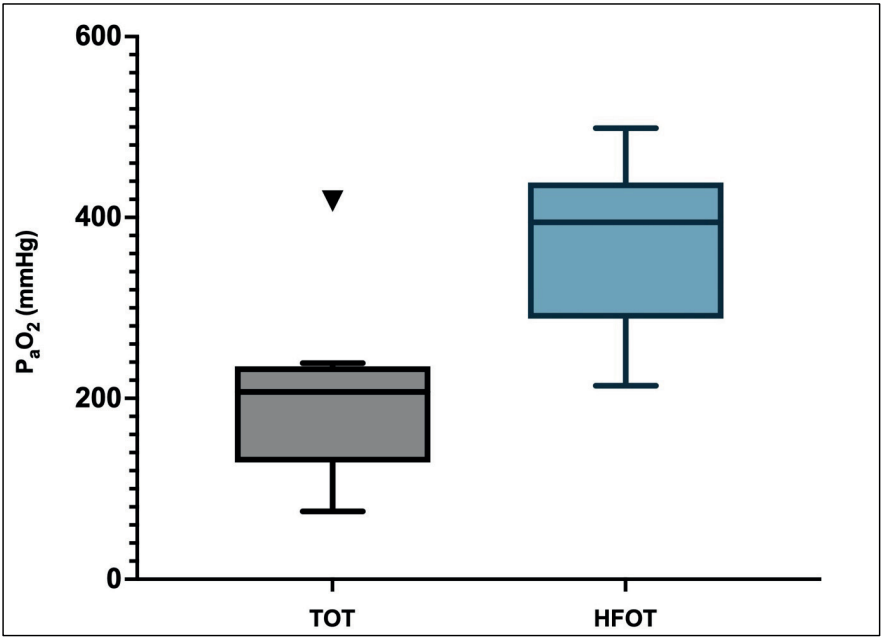


Figure 3: Differences in P_aO_2 after 5 min of preoxygenation (t1) between the TOT and the HFOT group. P-value = 0.0007. P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

3.2 P_aO_2 after induction of anaesthesia (t2)

Nearly all patients showed a decrease in P_aO_2 after induction of anaesthesia, except for two dogs in the TOT group which showed an increase in P_aO_2 after induction. Both dogs were tachypnoeic or panting before induction which might have affected the inspiratory volume and thus the amount of oxygen-enriched air reaching the alveoli. No dog showed apnoea after induction, and spontaneous breathing was maintained in all patients. Mean P_aO_2 after induction of anaesthesia (t2) was 189.3 $\pm$ 103.4 mmHg in the TOT group and 241 ± 115 mmHg in the HFOT group. One dog in the HFOT group showed a drastic drop from 413.1 mmHg after preoxygenation to only 82.9 mmHg after induction of anaesthesia. The same dog was

classified as severely hypoxaemic at baseline. There was, however, no statistically significant difference in P_aO_2 after induction between both groups (P = 0.3037).

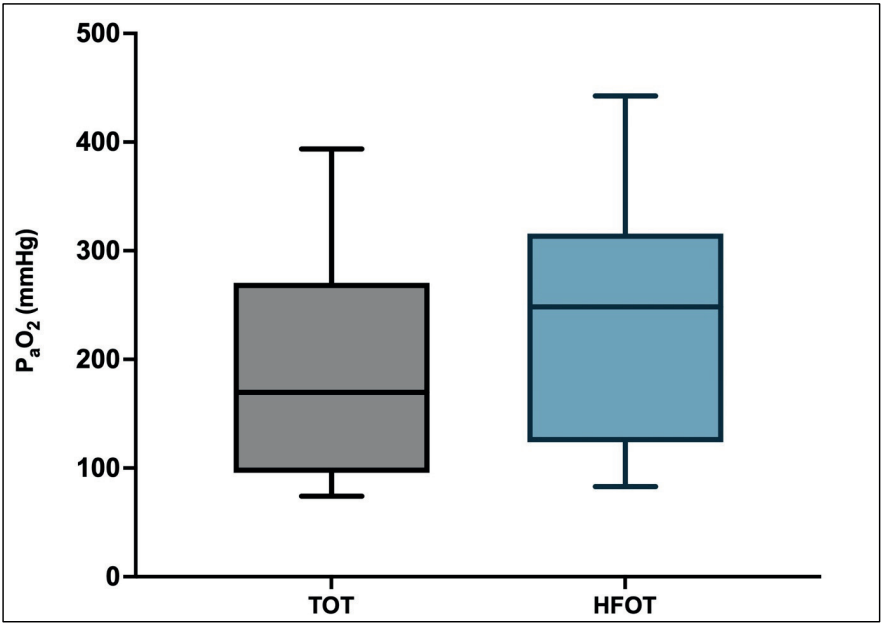


Figure 4: Differences in P_aO_2 after induction of anaesthesia (t2) between both groups.
P = 0.3037. P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow oxygen therapy.

3.3 P_aO_2 before BAL sampling (t3)

There was no statistically significant difference in arterial partial pressure of oxygen immediately before bronchoalveolar lavage (BAL) between both groups (P = 0.1094). Mean P_aO_2 in the TOT group was 218.3 $\pm$ 133.6 mmHg and 317.2 $\pm$ 128.8 mmHg in the HFOT group. Although no statistical difference could be established, the visual graphic analysis shows a trend toward higher P_aO_2 values within the HFOT group, as shown in Figure 5.

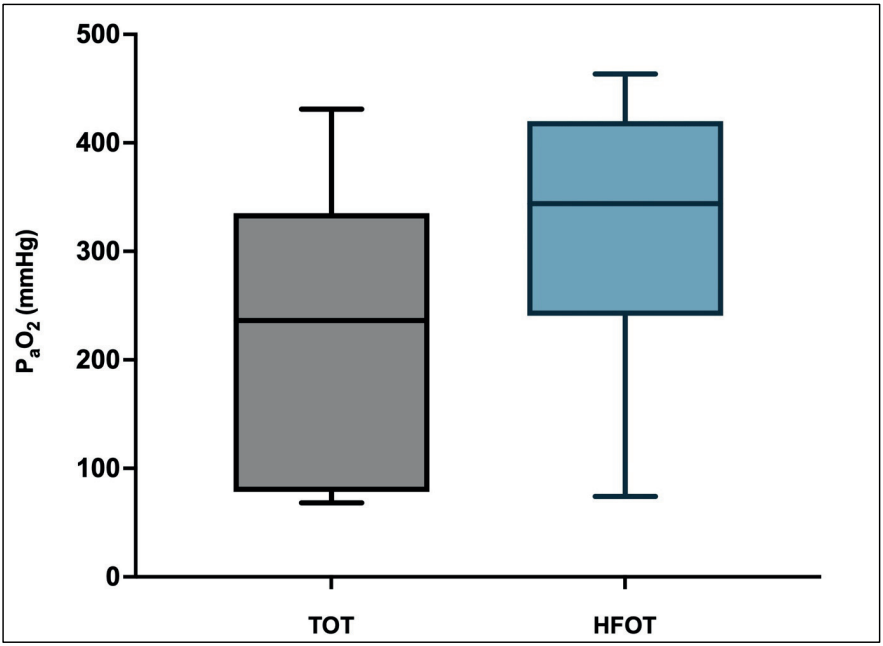


Figure 5: Comparison of P_aO_2 before BAL (t3) between both groups. P = 0.1094.
P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy, BAL = bronchoalveolar lavage.

Four dogs in the TOT group and one in the HFOT group showed a decrease in P_aO_2 below 100 mmHg at t3. However, the dog in the HFOT group was the same dog experiencing hypoxaemia in previous measurements. Out of the four dogs in the TOT group, three experienced hypoxaemia below 80 mmHg and all were hypoxaemic at baseline. All remaining dogs showed an increase in P_aO_2 from the previous measurement within both groups.

3.4 P_aO_2 after BAL sampling (t4)

Five dogs in the TOT group experienced a decrease in P_aO_2 after BAL sampling, with one patient decreasing below 60 mmHg. This dog also showed a decrease in P_aO_2 before lavage sampling yet achieved values above 200 mmHg at time points t1, t2 and t5. The remaining dogs showed a slight increase in P_aO_2 compared to values before BAL sampling. Mean P_aO_2 in the TOT group after BAL sampling was 192.4 $\pm$ 117,5 mmHg.

One dog within the HFOT group experienced severe hypoxaemia immediately after BAL sampling, decreasing from a previous P_aO_2 of 74.1 mmHg at t3 to 46.7 mmHg. Again, this was the same dog showing inadequate oxygenation after induction and before BAL and severe hypoxaemia at baseline. Out of the remaining dogs in the HFOT group, six showed a slight decrease and three a slight increase in P_aO_2 after bronchoalveolar lavage, yet none decreased below 140 mmHg and mean P_aO_2 within the HFOT group was 305.0 $\pm$ 128.0 mmHg.
Although a clear visual trend towards higher P_aO_2 values within the HFOT group can be seen in Figure 6, statistical analysis barely failed to show a significant difference (P = 0.0553).

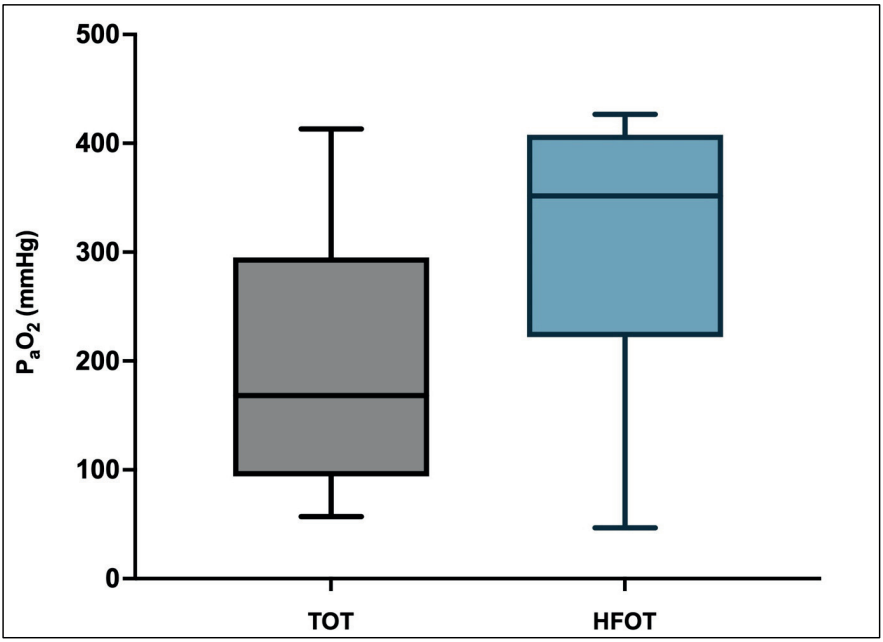


Figure 6: Difference in P_aO_2 between the TOT and the HFOT group after bronchoalveolar lavage (t4). P = 0.0553. P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy, BAL = bronchoalveolar lavage.

3.5 P_aO_2 at the end of the procedure (t5)

There was a significant difference in P_aO_2 at the end of the procedure between the TOT group and the HFOT group (P= 0.0131).

Mean P_aO_2 in the TOT group was 204.2 ± 103.4 mmHg and mean P_aO_2 in the HFOT group was 330.8 ± 102.3 mmHg. No dogs in either group experienced P_aO_2 below 90 mmHg. The lowest value in the TOT group was 91.7 mmHg, and in the HFOT group 119.1 mmHg.

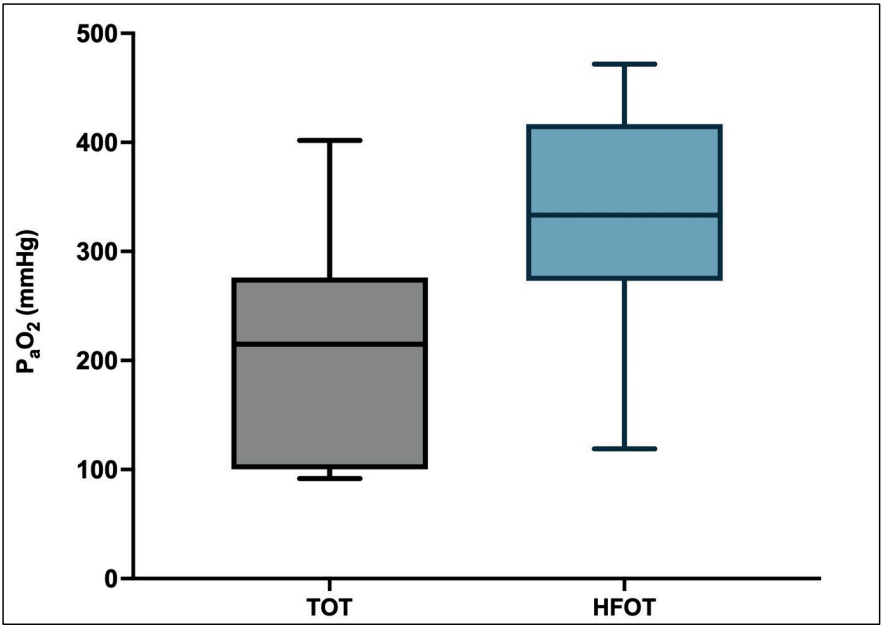


Figure 7: Difference in P_aO_2 at the end of the procedure (t5) between the TOT and the HFOT group. P = 0.0131. P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

3.6 P_aO_2 one hour post procedure (t6)

A comparison of P_aO_2 values obtained one hour post procedure showed no significant difference between the two groups (P = 0.9754). Mean P_aO_2 in the TOT group was 86.75 ± 18.7 mmHg and 87.0 ± 17.0 mmHg in the HFOT group. Although six dogs in the TOT group and nine dogs in the HFOT group showed an increase in P_aO_2 compared to baseline values, there was no significant difference between t0 and t6 for either group (TOT: P = 0.1723, HFOT: P = 0.3091).

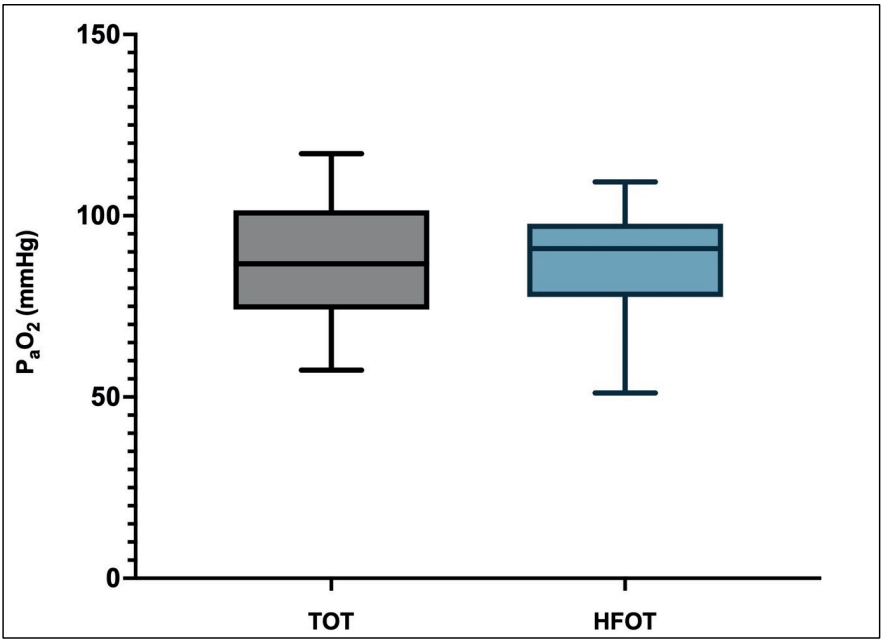


Figure 8: Comparison of P_aO_2 values obtained one hour after discontinuation of oxygen therapy (t6) between both groups. P = 0.9754.
P_aO_2 = partial pressure of oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

3.7 Comparison of P_aO_2 at all specified time points

Figure 9 shows the changes in P_aO_2 across all time points, from baseline to one hour after the procedure. The steep drop from t1 to t2 in the HFOT group is the result of one single patient suffering from pulmonary fibrosis. However, visual graphical analysis shows again a clear trend toward higher P_aO_2 values in patients receiving HFOT.

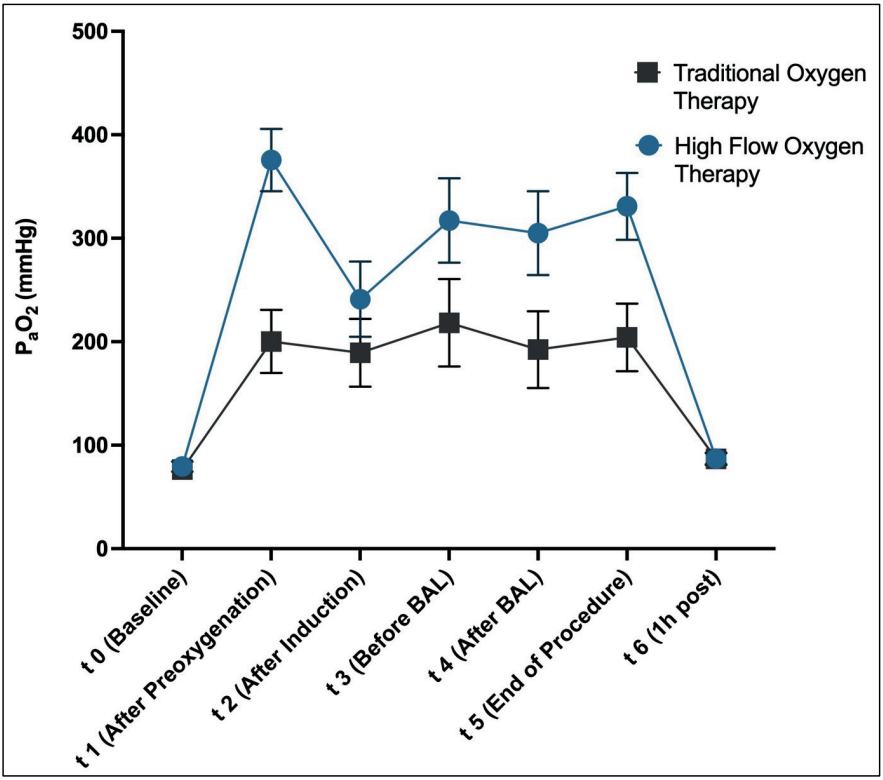


Figure 9: Changes in P_aO_2 from baseline to one hour after the procedure. Values are given as mean and standard deviation. P_aO_2 = partial pressure of arterial oxygen, BAL = bronchoalveolar lavage.

This trend is further emphasised when comparing the mean P_aO_2 values of each patient obtained during oxygen supplementation (t1–t5), as shown in Figure 10. The difference in P_aO_2 between patients receiving TOT or HFOT is statistically significant, with P = 0.0114.

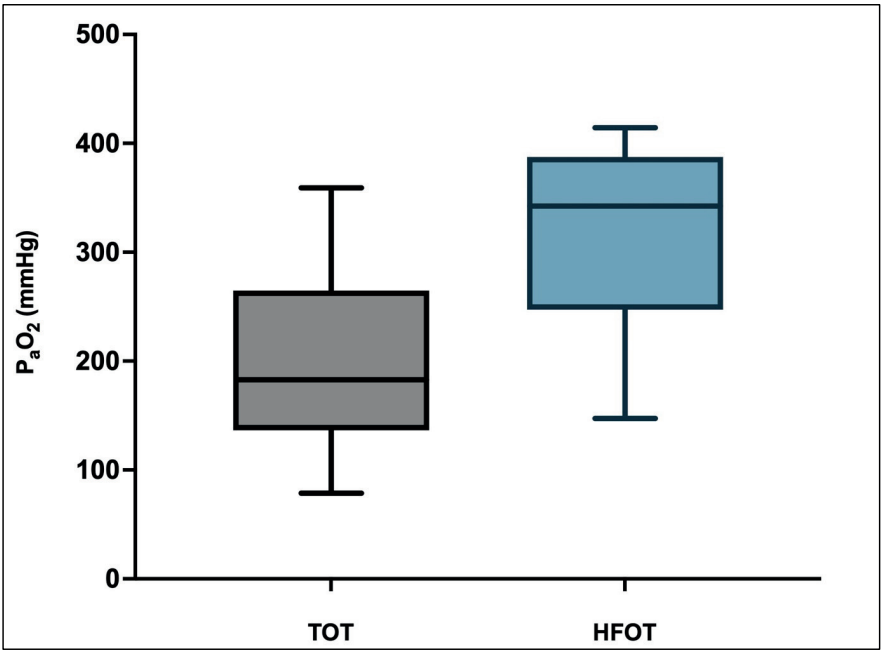


Figure 10: Difference in mean P_aO_2 values between TOT and HFOT group from timepoints t1 to t5. P = 0.0114. P_aO_2 = partial pressure of arterial oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

Individual values of partial pressure of arterial oxygen for each patient at each time point are listed in Table 6 for those receiving traditional oxygen therapy and Table 7 for patients receiving High Flow Oxygen therapy.

Patient	T0	T1	T2	T3	T4	T5	T6	Mean t1 - t5
1	66.4	227.7	102.8	68.2	114.2	103.0	78.8	108.7
2	61.0	418.0	308.9	340.6	326.3	401.7	57.4	273.4
3	95.7	163.2	393.6	431.0	413.2	271.5	90.5	265.5
4	82.3	234.1	170.5	272.2	284.8	245.9	96.4	198.0
5	82.3	75.1	74.1	74.8	77.4	91.7	81.1	79.5
6	90.5	201.3	164.8	200.3	214.9	204.9	101.4	168.3
7	58.8	239.0	168.9	79.6	99.6	116.7	117.1	125.7
8	64.7	88.7	74.3	292.2	191.6	92.0	60.1	123.4
9	77.7	142.7	178.0	333.3	144.9	289.9	83.0	178.5
10	85.8	213.0	257.5	90.7	57.0	224.8	101.7	147.2

Table 6: Individual P_aO_2 values in mmHg at time points t0 – t6 for patients receiving traditional oxygen therapy (TOT). Mean values include measurements from timepoints t1 – t5 during bronchoscopy.

Patient	T0	T1	T2	T3	T4	T5	T6	Mean t1 - t5
1	91.7	392.6	376.6	425.1	406.0	471.8	95.6	322.8
2	78.2	303.6	295.5	463.5	426.6	385.1	104.4	293.8
3	44.9	413.1	82.9	74.1	46.7	412.3	51.1	160.7
4	77.8	421.1	275.4	321.8	248.2	328.3	92.3	252.1
5	62.7	214.0	126.2	133.6	143.4	119.1	86.1	126.4
6	84.0	491.0	442.5	366.2	371.0	286.0	68.7	301.3
7	87.2	382.6	116.8	276.5	332.3	259.5	92.1	221.0
8	79.3	396.7	262.9	418.2	413.5	338.4	80.6	284.2
9	88.1	242.3	233.9	284.7	267.1	277.6	109.3	214.7
10	99.7	498.7	198.5	407.9	395.5	430.1	89.8	302.9

Table 7: Individual P_aO_2 values in mmHg at time points t0 – t6 for patients receiving High Flow Oxygen Therapy (HFOT). Mean values include measurements from timepoints t1 – t5 during bronchoscopy.

4. Tracheal FiO_2 and oxygen indices

4.1 Tracheal fraction of inspired oxygen (FiO_2) before and after BAL (t3 and t4)

Tracheal FiO_2 could only be measured after induction (t3) up until the end of the procedure while the patients were under anaesthesia. This is because measurements were not possible while the patients were awake, and it was logistically impossible to place the sampling line after induction and before arterial blood sampling at t2. However, tracheal FiO_2 values at t3 and t4 could be obtained for seven dogs in the TOT group and all dogs in the HFOT group. The missing values in the TOT group were due to repeated blocking of the sampling line with mucus and secretions.

Patients in the HFOT group achieved higher tracheal FiO_2, ranging from 76.5% to 96% (Mean: 89 ± 6%) compared to patients receiving traditional oxygen supplementation (Mean: 72 ± 18%). This difference achieved statistical significance (P = 0.0109), as seen in Figure 11.

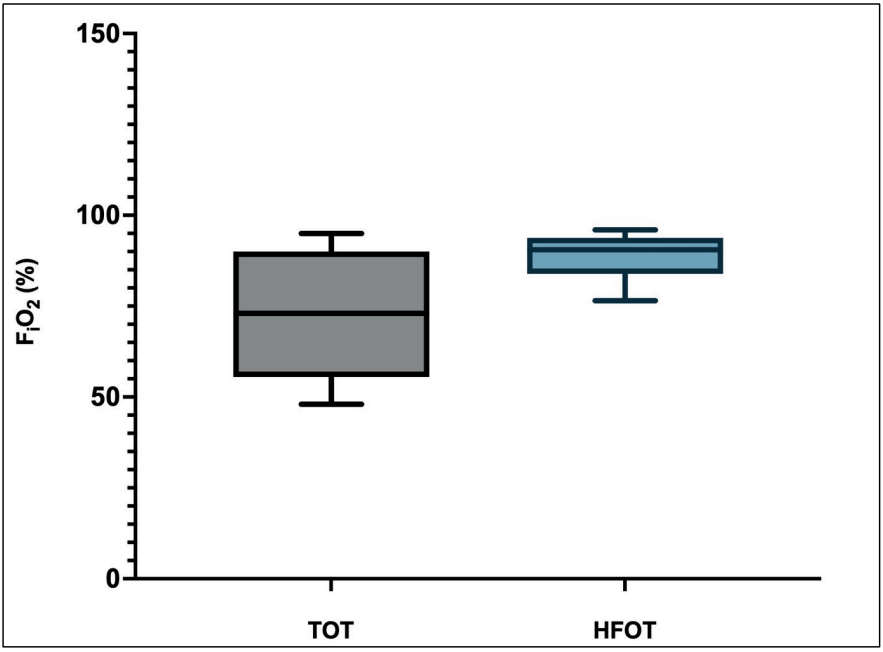


Figure 11: Differences in FiO_2 at t3 and t4 between both groups. P = 0.0109.
FiO_2 = fraction of inspired oxygen, TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

4.2 P_aO_2/FiO_2 at baseline, t3 and t4.

Due to the missing tracheal FiO_2 values, P_aO_2/FiO_2 could only be calculated for 17 dogs (TOT: n = 7 and HFOT: n= 10) at time points t3 and t4. There was no statistically significant difference in P_aO_2/FiO_2 values between the two groups at the mentioned time points (t3: P = 0.6160, t4: P = 0.5170).At both time points, two dogs in each group had a P_aO_2/FiO_2 ratio below 200 mmHg, defined as moderate oxygenation impairment. Both dogs also experienced hypoxaemia after BAL sampling. None of the patients in either group showed a P_aO_2/FiO_2 ratio below 200 mmHg at baseline.

4.3 $AaDO_2$ at baseline (t0) and one hour after the procedure (t6)

The alveolar-arterial difference was calculated for each patient while breathing room air at t0 and t6. There was no significant difference in $AaDO_2$ values between the groups at baseline (P = 0.9725) or one hour after the procedure (P = 0.8143).

Eight dogs in the TOT group and seven in the HFOT group had an elevated $AaDO_2$ difference at baseline. The highest value of 66.3 mmHg was in the HFOT group in the same patient experiencing severe hypoxaemia during the entire procedure diagnosed with pulmonary fibrosis and bronchial collapse. However, all dogs in both groups showed a slight decrease in $AaDO_2$ values obtained one hour after the procedure compared to baseline.

5. Partial pressure of carbon dioxide (P_aCO_2) at all time points

There were no significant differences in P_aCO_2 between the two groups at all specified time points. Seven patients in the TOT group and six in the HFOT group showed increased levels of P_aCO_2 between induction of anaesthesia and the end of the procedure. None of the patients showed remaining elevated levels of P_aCO_2 one hour post-procedure.

6. Duration of bronchoscopy and recovery time

The average recovery time was 14.8 ± 4.9 mins in the TOT group and 12.4 ± 3.8 mins in the HFOT group. The average duration of bronchoscopy was 23 ± 11 mins in the TOT group and 19 ± 7 mins in the HFOT group. There was no significant difference in the duration of bronchoscopy (P = 0.3787) or recovery time between the TOT group and the HFOT group. (P = 0.2393).

Subjectively, recovery from anaesthesia appeared to be smoother for the patient in the HFOT group as animals seemed to show less disorientation than patients in the TOT group. However, no standardised evaluation scale was used, and observations remain highly subjective.

7. Complications and adverse events

Both oxygen delivery methods were well tolerated by all patients. Three dogs, one in the TOT group and two in the HFOT group, showed initial pawing at the cannula, which might have been a sign of discomfort. However, pawing subsided in all these dogs after a few minutes of acclimatisation to their designated oxygen delivery method.

None of the patients experienced complications during anaesthesia, although several dogs in both groups showed hypoxaemia on blood gas analysis. None of the patients showed signs of atelectasis, pneumothorax or pneumomediastinum in the thoracic follow-up radiographs at the end of the procedure.

The only adverse event recorded was aerophagia in a total of 14 patients. A total of six patients in the TOT and eight in the HFOT group showed some degree of aerophagia when comparing radiographs from before and after the procedure. In the TOT group, two dogs had mild and moderate gas distension of the oesophagus, one dog had mild gastric dilation, and three dogs showed gas distension of both the oesophagus and stomach, with one each having mild, moderate and severe signs of gas insufflation.

In the HFOT group, four dogs showed oesophageal gas distension, two dogs had gastric dilation, and two dogs had dilation of both the oesophagus and stomach. Five dogs showed only mild radiographic signs of aerophagia, three of the oesophagus, one of the stomach and one in both locations. The two other dogs experiencing gastric distension, and one of the dogs with signs of gastric and oesophageal insufflation had severe signs of aerophagia on radiographs.

Overall, none of the patients experiencing aerophagia had clinical signs at the time of radiographic imaging, nor one hour after the procedure. Therefore, there was no need for intervention in any of the patients. The distribution of aerophagia between both groups is depicted in Figure 12.

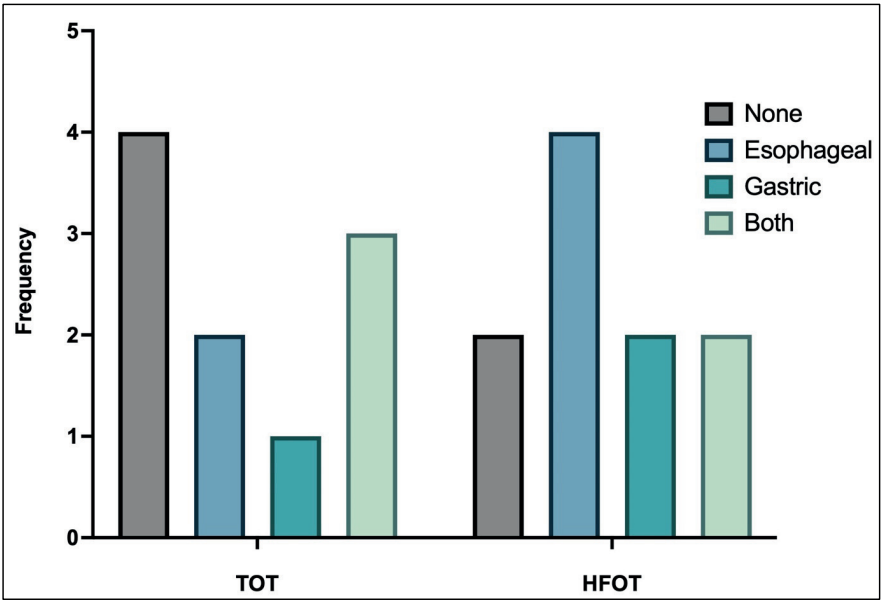


Figure 12: Frequency and distribution of aerophagia compared between the TOT and HFOT groups. TOT = traditional oxygen therapy, HFOT = High Flow Oxygen Therapy.

VI. Discussion

To the author's knowledge, this is the first veterinary study to evaluate the use of High Flow Oxygen Therapy and its effects on oxygenation during bronchoscopy in dogs.

While bronchoscopy is a valuable diagnostic and therapeutic tool for patients with respiratory diseases, it is not without risks. The development of hypoxaemia is the most commonly encountered complication, especially during bronchoalveolar lavage.[10, 11, 62, 161] In small animals, the risk of hypoxaemia is further increased as general anaesthesia is required for the procedure. Induction of anaesthesia and obstruction of the airways with the bronchoscope can lead to further respiratory compromise.[66, 162-164] Adequate oxygen supplementation during the procedure is thus essential, but patient size can be a limiting factor in the available options for oxygen supplementation.

HFOT has several beneficial effects and has been shown to improve oxygenation in people during bronchoscopy, especially compared to traditional oxygen supplementation methods.[13, 14, 93, 95, 148, 151] Therefore, it was argued that High Flow Oxygen Therapy could also constitute a suitable alternative oxygen supplementation method for dogs undergoing bronchoscopy. The aim of the study was to evaluate the safety of HFOT and its effect on oxygenation in dogs during bronchoscopy and BAL sampling. It was hypothesised that HFOT would be safe to use and that dogs receiving High Flow Oxygen Therapy would achieve higher P_aO_2 values during bronchoscopy than those receiving oxygen via TOT. Thus, HFOT could reduce the risk of hypoxaemia and become a valuable alternative to maintaining adequate oxygenation during bronchoscopic procedures in dogs.

The study data reflected previous results from studies in people that High Flow Oxygen Therapy improves oxygenation during bronchoscopy.[14, 93, 96, 147-149] Dogs in the HFOT group showed overall higher arterial partial pressure of oxygen and fewer incidents of hypoxaemia, with only one dog experiencing desaturation below 80 mmHg during the procedure. Although a comparison of both oxygen supplementation methods did not achieve statistical significance at all time points, a clear trend towards improved oxygenation in the HFOT group can be observed at all times.

1. Subjects and baseline parameters

A total of 20 dogs were included in the study. There was no significant difference in weight, age or gender between both groups and no specific breed was distinctly present in the study population. (See Table 5)

Final diagnoses varied among patients, with bronchopneumonia being the most common. Since bronchoscopy was part of the diagnostic workup, final diagnoses could not be established before study inclusion. Therefore, the arterial partial pressure of oxygen was measured, and $AaDO_2$ was calculated for each patient at baseline, which allowed evaluation and comparison of pulmonary function between the patients. There was no significant difference between baseline P_aO_2, $AaDO_2$ or any other physiological parameter between both groups, creating an ideal basis for the following comparison of responses to the different oxygen supplementation methods.

Half the dogs in each group were hypoxaemic at baseline, and two dogs in each group showed P_aO_2 values below 60 mmHg, classifying them as severely hypoxaemic.[5] The dog in the TOT group was diagnosed with tracheobronchomalacia. Airway collapse causes airway obstruction with subsequent hypoventilation of affected lung areas resulting in an increased ventilation-perfusion imbalance, thus explaining hypoxaemic episodes. The severely hypoxaemic dog in the HFOT group was later diagnosed with pulmonary fibrosis and bronchial collapse. Reasons for hypoxaemia in patients suffering from pulmonary fibrosis are impaired gas exchange due to abnormal collagen accumulation resulting in structural changes of the lung parenchyma. Thickening of the alveolar wall causes diffusion impairment, although depending on the severity of the disease, hypoxaemia is usually only pronounced in exercise conditions. Additionally, pulmonary fibrosis causes increasing areas of ventilation-perfusion mismatch, exacerbating hypoxaemia.[165, 166] The dog also showed a markedly increased $AaDO_2$ gradient at baseline, making a ventilation-perfusion imbalance and diffusion impairment the most likely explanation why this particular patient was the only dog in the HFOT group who failed to show sufficient oxygenation from induction until the time of removal of the bronchoscope.

None of the remaining four dogs with hypoxaemia at baseline in the HFOT group experienced hypoxaemia during bronchoscopy, with P_aO_2 ranging between 119 and 468 mmHg. In comparison, in the TOT group, three of the five initially hypoxaemic dogs and two dogs with

normal baseline values developed hypoxaemia with a P_aO_2 below 80 mmHg at least once during the following bronchoscopic procedure.

2. Oxygen therapy methods

During preoxygenation, while dogs were still awake, all showed good tolerance to the nasal cannulas and their designated oxygen delivery method. Initial pawing at the cannulas in a few cases subsided shortly. This correlates with studies in people showing occasionally brief moments of discomfort during acclimatisation to HFOT[77, 167] and studies in dogs receiving HFOT, which showed overall good tolerance of the method [155-160]. However, the sedative effect of the administered butorphanol might have also affected the tolerance during preoxygenation.

Flow settings in the HFOT group were based on recommendations of a previous study evaluating HFOT use in healthy dogs.[156] The study showed that flow rates between 1 and 2 L/kg/min achieved the best result without causing discomfort to the patients. However, one dog in the HFOT group of the present study had a body weight above 40 kg and thus received a lower flow rate than previously planned (approx. 0.9 L/kg/min instead of 1 L/kg/min), as the Vapotherm Precision Flow has a maximum flow limit of 40 L/min. Although this dog showed initial hypoxaemia, P_aO_2 values increased after administration of HFOT and ranged from 295 to 470 mmHg throughout the procedure. Due to the improved oxygenation and the otherwise even smaller patient population size, this patient was not excluded from the study despite receiving a lower flow rate.

Oxygen settings of 100% were chosen for the HFOT group to achieve the maximum effect on oxygenation and allow for better comparison with the TOT group. The study showed a significant difference in tracheal FiO_2 concentration between both groups. Since higher achievable FiO_2 levels are one of the main beneficial factors of HFOT, this finding was somewhat expected. Previous studies in people showed that HFOT could achieve oxygen concentrations of about 76% [111], although most studies were measured either in the oropharynx[105] or using airway models.[111-113] The present study measured FiO_2 at the tracheal bifurcation, and probe placement was visually confirmed in all dogs during bronchoscopy. Dogs in the HFOT group achieved higher FiO_2 concentrations with a mean of 89%, ranging from 76 to 96%. Although high concentrations were expected, tracheal measurement showed

higher values than anticipated from previous study results, and all patients reached 90% or above at some point during the continuous measurement.

Surprisingly, dogs in the TOT group also achieved higher values than expected, with a mean of 73%, ranging from 43 to 95%. One study in dogs comparing oxygen administration via unilateral and bilateral nasal catheters showed that bilateral oxygen administration with a flow rate of 100 ml/kg/min per catheter produces mean tracheal FiO_2 of approximately 60%.[51] Although comparable, oxygen concentrations achieved with nasal cannulas were not evaluated in the study by Dunphy et al., and to the author's knowledge, no other studies exist assessing achievable FiO_2 with oxygen supplementation via nasal cannulas.

It is most likely that patient positioning resulted in the high FiO_2 values in both groups. Dogs were placed with an open mouth to allow oropharyngeal access for the bronchoscope resulting in an enlarged oropharyngeal area serving as an oxygen reservoir. By creating a large oxygen reservoir, anatomic dead space will decrease, and FiO_2 will increase as less entrainment of ambient air will occur. This effect has been shown to occur in people receiving HFOT, especially when breathing with their mouths open.[105, 114] An enlarged oxygen reservoir by open-mouth breathing reducing air entrainment may also be responsible for the higher FiO_2 measurements obtained in the TOT group compared to the ones in the study by Dunphy et al.[51]

3. Oxygenation during bronchoscopy

As previously mentioned, hypoxaemia is a common complication of bronchoscopy, and proper oxygen supplementation is thus essential during the procedure. However, adequate oxygenation can be difficult to achieve during bronchoscopy, especially in small or already compromised patients.

Several studies in people showed promising results using HFOT during bronchoscopy to avoid hypoxaemic events, especially when compared to TOT.[14, 95, 96, 147-150] Although in people HFOT did not always prove superior to NIV methods [147, 150], NIV methods using masks often do not constitute a feasible option in veterinary small animal medicine due to the differences in facial structures and consequently ill fit of masks. In people, HFOT during bronchoscopy proved superior to TOT methods[13, 14, 148] in terms of improving oxygenation and preventing desaturation and at least equal to NIV methods[147], thus making it a possible alternative to maintain oxygenation during bronchoscopy in small animals.

3.1 Preoxygenation and Induction

Induction of general anaesthesia always carries an increased risk of developing hypoxaemia as it leads to respiratory depression, decreased cardiac output and ventilation-perfusion mismatch caused by hypoventilation or apnoea.[162, 163] This risk is further exacerbated in patients with pre-existing respiratory diseases affecting pulmonary functions. To prolong the time before desaturation between induction of anaesthesia and securing of the airways, preoxygenation with high FiO_2 concentrations is generally performed.[32] Preoxygenation aims to increase alveolar PO_2 by flushing out and replacing alveolar nitrogen with oxygen, creating a reservoir effect to prolong the safe apnoea time before the airways can be secured.

In people, preoxygenation is usually performed using a NIV mask; however, several studies showed a beneficial effect of using HFOT for preoxygenation.[33, 168, 169] High FiO_2, a CO_2 washout effect, increased PAP, good tolerance and patient comfort, and quick set up, combined with the main advantage that oxygen administration can be continued without interruption while the airways are being secured, all make HFOT an interesting alternative to mask preoxygenation. This applies especially to veterinary patients in which the use of masks is not always a feasible option.

The findings in the present study reflect results from previous studies in people as dogs preoxygenated with HFOT showed significantly higher P_aO_2 after five minutes of preoxygenation than patients in the TOT group. In addition, none of the dogs within the HFOT group experienced a P_aO_2 value below 214 mmHg, while four dogs each reached values above 300 and 400 mmHg. Although TOT was also effective in most patients, two dogs failed to show an increase in P_aO_2 above 90 mmHg after preoxygenation. Additionally, only one dog reached P_aO_2 above 400 mmHg, with the remaining patients ranging from 75 to 239 mmHg.

Differences in flow rates and achievable FiO_2 are the most likely explanation for the improved oxygenation achieved within the HFOT group. Although no tracheal FiO_2 could be measured as dogs were still awake, all patients in the HFOT group had tracheal oxygen concentrations above 80% after induction. It can thus be assumed that tracheal FiO_2 reached similar high oxygen concentration levels at the time of preoxygenation. Therefore, the results of this study show that HFOT can be safely, easily and effectively used as a method of preoxygenation in dogs before anaesthesia. By improving oxygenation and increasing P_aO_2, the safe apnoea period and the time available to secure the airways before critical desaturation occurs can be prolonged.

Induction of anaesthesia causes central respiratory depression leading to hypoventilation or brief periods of apnoea.[2, 162, 163] Nearly all dogs in this study showed an anticipated drop in PaO_2 immediately after induction of anaesthesia combined with an increase in P_aCO_2 in each patient, confirming hypoventilation as the main reason for desaturation after induction.

Although HFOT managed to prevent desaturation below 116 mmHg in nine out of 10 dogs after induction, the difference in P_aO_2 between both groups did not reach statistical significance. This could be due to the fact that two dogs in the TOT group showed an actual increase in P_aO_2 after induction from the previously obtained measurement after preoxygenation. One possible explanation for this increase is a difference in induction time, allowing for a prolonged preoxygenating effect. Induction was performed slowly and titrated to effect to maintain spontaneous breathing in all patients. Therefore, both dogs in the TOT groups might have experienced a more prolonged onset of action and an associated extended period of less depressive ventilatory effects. As oxygen supplementation continued without interruption, the preoxygenation time would have been prolonged, or a lighter anaesthetic depth might have been achieved, thus causing the higher P_aO_2 values after induction. However, the duration of induction was not measured to confirm a prolonged preoxygenation period.

Despite not achieving statistical significance, there is a clear visual and numerical trend towards improved oxygenation by HFOT after induction of anaesthesia. However, the small patient numbers make it difficult to predict outcomes in a larger patient population.

3.2 Before bronchoalveolar lavage (BAL)

Arterial blood gas samples were again obtained after visual evaluation of the bronchial tree and immediately before BAL sampling. The bronchoscope was already placed in the designated bronchial segment at the time the blood sample was drawn; thus, a partial bronchial occlusion occurred in all patients.

Although there was no statistically significant difference in P_aO_2 before BAL sampling between both groups, P_aO_2 values were again higher in the HFOT group, with a mean of 317 mmHg compared to 218 mmHg in the TOT group. Additionally, three dogs in the TOT group had a P_aO_2 below 80 mmHg and one below 100 mmHg. Two were the smallest patients in the group, and one dog was even the smallest in the entire patient population.

Body size likely played a role in these findings, with a higher degree of airway obstruction by the bronchoscope occurring in smaller patients, hindering sufficient oxygen administration. Since desaturation did not occur in the smallest patients in the HFOT group, the differences in flow rate and FiO_2 between both methods might have played a key role. Lower flow rates applied with TOT might simply not have been sufficient to create high enough FiO_2 to overcome the desaturation caused by the airway obstruction with the bronchoscope. However, one dog in the TOT group not only failed to show improved oxygenation after preoxygenation but also in all subsequent measurements. This dog was the smallest in the entire patient population, and failure to improve after preoxygenation and after the removal of the bronchoscope might have also been the result of an underlying pulmonary shunt. A pulmonary shunt is the most extreme form of V/Q mismatch, and a characteristic occurrence is a failure to show an adequate response to oxygen therapy.

Additionally, it was also not possible to obtain FiO_2 measurements in this dog due to excessive mucus production repeatedly blocking the sampling line. Therefore, alveolar collapse and a V/Q mismatch due to obstruction with mucus or secretions might be another possible explanation for the failure to improve despite oxygen therapy. Excessive mucus might have simply acted as a mechanical barrier creating a further obstruction of the already narrowed tracheal lumen due to the presence of the bronchoscope. Interestingly, in the present study, FiO_2 measurements could only be obtained in seven patients in the TOT group in all cases due to the increased presence of mucus. While small amounts of mucus and secretions were also observed in dogs in the HFOT group, none showed such severe build-up that FiO_2 measurement was affected or not possible. Although this could be due to differences in underlying respiratory pathologies and severity of secondary infections, the use of humidified and warm air in the HFOT group could easily explain the difference between both groups. Cold and dry air has been shown to affect mucociliary clearance and mucus consistency, and the application of dry and cold air in the TOT group might have worsened already compromised clearance mechanisms.[42, 49]

In the HFOT group, the dog diagnosed with pulmonary fibrosis and bronchial collapse was the only patient with a P_aO_2 below 100 mmHg at this point of the procedure. Respiratory compromise caused by the underlying pulmonary fibrosis might have been further pronounced due to the bronchial collapse, which might have been exacerbated due to local irritation from the bronchoscope. None of the remaining dogs in the HFOT group experienced

P_aO_2 below 133 mmHg, with two dogs achieving values above 300 and four above 400 mmHg. Again, a clear trend towards improved oxygenation achieved with HFOT can be seen, suggesting superiority of the HFOT method compared to TOT.

3.3 After bronchoalveolar lavage (BAL)

BAL sampling has been shown to cause worsening of hypoxaemia during bronchoscopy in people.[15, 62] Installation of sample fluid obstructs the affected bronchi while suctioning to retrieve fluid can cause alveolar and bronchial collapse leading to atelectasis formation. A subsequent decrease or absence of ventilation in the affected areas leads to an increased V/Q mismatch. Furthermore, for proper sampling, the bronchoscope needs to be wedged in the lower airway segment, consequently blocking the affected lung area, further hindering gas from reaching the alveoli, eventually resulting in alveolar collapse. Failure to retrieve all fluid results in remnants left in the airways, although saline will slowly either be expelled via coughing or absorbed and hypoxaemic events during bronchoscopy are usually only temporary.[9-11, 62, 161]

Because of these pathomechanisms, a decrease in P_aO_2 after BAL was expected to occur. The main question was if HFOT could prevent desaturation to critical levels during this phase of bronchoscopy. While five dogs in the TOT group experienced desaturation, with two dogs below 80 mmHg and one below 60 mmHg, only one dog in the HFOT group experienced a decrease in P_aO_2 below 100 mmHg after BAL. This patient was once again the dog suffering from pulmonary fibrosis. After BAL sampling, this particular dog experienced severe hypoxaemia with a P_aO_2 below 50 mmHg. In retrospect, this value would have called for intervention and escalation to advanced oxygen therapy in the form of assisted ventilation. However, continuous monitoring showed only a brief few-second drop of S_pO_2 to a value below 88%, and the patient had no visible cyanosis or other clinical signs suggesting the need for escalation at the time. Due to the delay caused by the duration of the blood gas analyser, these low values were also not immediately recognised at the time of BAL sampling. By the time sample analysis was completed, the bronchoscope was already removed from the airways. Additionally, the patient showed a S_pO_2 of 94%, and the choice to no longer intervene was further confirmed by the following BGA sample, showing an elevation of the P_aO_2 above 400 mmHg.

While HFOT improved oxygenation in nine out of 10 patients after BAL sampling, nearly reaching statistical significance, it remains questionable if HFOT is suitable for patients with severe hypoxaemia or if other oxygenation methods should be employed in these patients. Similar concerns were also raised by the authors of two studies in people evaluating HFOT compared to NIV during bronchoscopy.[147, 150] Both studies concluded that HFOT should not be used in people with severe hypoxaemia as it cannot provide assisted ventilation or positive pressure support. It is possible that simply increasing the flow rate would have been sufficient to improve oxygenation in this particular dog, as hypoxaemia most likely resulted from an altered gas exchange due to pulmonary fibrosis and airway collapse. Higher flow rates might have been able to create a PEEP effect, hindering the collapse of smaller airways and increasing FiO_2.

Despite this one severely hypoxaemic patient, it is important to note that none of the other dogs in the HFOT group experienced a desaturation below 140 mmHg with a mean P_aO_2 of 305 mmHg compared to a mean of 192 mmHg in the TOT group with three dogs showing values below 100 mmHg. A possible explanation for this observation can be the combination of high FiO_2 and high flow rates creating high enough airway pressure to prevent alveolar collapse during BAL sampling.

Although differences in P_aO_2 between both groups barely missed statistical significance, visual and numerical data analyses show that HFOT improves oxygenation during bronchoscopy and prevents desaturation during BAL in most patients. Care should be taken, however, in patients with severe hypoxaemia at baseline, and alternative oxygenation methods should be considered in these patients.

3.4 At the End of the Procedure

Since the bronchoscope was removed from the airways immediately after obtaining the BAL sample, all dogs had received uninterrupted oxygen supplementation for a prolonged time by the time this measurement was obtained. Therefore, a similar condition existed as to the measurement after preoxygenation. Once again, all the advantages of HFOT come to play, resulting in statistically significant improved oxygenation at the end of the procedure.

Besides showing the beneficial effects HFOT has on oxygenation in anaesthetised patients, this measurement also confirms that alterations in pulmonary function and the occurrence of hypoxaemia during bronchoscopy and BAL sampling are only temporary. However, short

periods of hypoxaemia can still have detrimental effects, especially in already compromised patients and should never be considered a benign event as even short periods can result in further deterioration with pulmonary, cardiac, vascular, and neurological consequences.[161, 170]

3.5 One hour post procedure

Values obtained one hour after the procedure without continued oxygen therapy showed that the effects of oxygen supplementation are only short-lived and diminish once oxygen administration is discontinued. However, all patients showed slightly higher P_aO_2 values and lower $AaDO_2$ ratios compared to values obtained at baseline.

Although the reason for this observation is unknown, it is possible that either sufficient PAP to cause alveolar recruitment during the procedure occurred or that suctioning of BAL fluid also removed build-up mucus in lower airways resulting in clearance of the airways with subsequent improved ventilation/perfusion. Brach et al.[161] also observed an improvement in regional V/Q immediately after bronchoscopy in people using scintiphotography. Removal of mucus plugs and thick secretions were noted in all affected patients and is likely the reason for the observed improvement. Longhini et al.[171] evaluated the use of HFOT and TOT in people during bronchoscopy using additional electric impedance tomography (EIT). The results also showed an increase in P_aO_2 by the end of the procedure in the patients receiving HFOT. EIT assessment suggested prevention of alveolar collapse due to positive airway pressures achieved with the HFOT as the underlying mechanism for this observation. It is thus likely that this effect also occurred in the dogs of the present study, improving P_aO_2 by alveolar recruitment. However, it is unclear how long this effect would last, and therefore it can only be speculated as a possible explanation for the improved arterial partial pressure one hour after the procedure.

3.6 Overall outcome

Overall, HFOT showed improved oxygenation at all points, and patients experienced fewer periods of desaturation. Besides one patient who suffered from a severe respiratory compromising disease, none of the remaining dogs in the HFOT group experienced hypoxaemia during bronchoscopy, including during BAL sampling. HFOT can thus be seen as superior in improving oxygenation compared to TOT, although care should be taken in

severely hypoxaemic patients at baseline and possibly alternative oxygen methods allowing for CPAP ventilation might be the preferred choice in these patients. Since this present study only evaluated one flow rate setting for the HFOT group, it remains unknown if higher flow rates might have prevented desaturation even in the severely hypoxaemic dog and if it would have led to statistically significant differences compared to TOT at all time points. Future studies evaluating different flow rates in larger patient populations might prove helpful in answering still-open questions.

4. Complications and adverse events

Although HFOT is generally safe to use, a few adverse effects can occur.[72, 127-129] Air leak syndrome and a delay in advancing the patient to mechanical ventilation are of primary concern. However, air leak syndrome seems to be a rare occurrence in people, with one study in neonates showing a risk of approximately 1% [128], and so far, no events of air leak syndrome caused directly by HFOT have been reported in the veterinary literature. The results of the present study reflect these findings, as none of the dogs had clinical or radiographic signs of pneumothorax or pneumomediastinum at the end of the procedure.

Failure to identify HFOT non-responders and thus delaying mechanical ventilation is a main concern with patients receiving HFOT. Although only one of the ten dogs in the HFOT group experienced P_aO_2 values below 100 mmHg, with a severe drop below 50 mmHg after BAL sampling, the patient was not escalated to advanced oxygen therapy. In retrospect, given the already low P_aO_2 values before BAL sampling and the severe drop after, interference and escalation of the oxygen therapy would have been called for and probably been beneficial to the patient. However, continuous monitoring did not indicate a prolonged safety concern for the patient, and it remains questionable if intubation and assisted ventilation would have been quicker than relying on continuous oxygen therapy to stabilise the patient, as desaturation during bronchoscopy is usually only a temporary occurrence. Furthermore, even assisted ventilation might not have prevented desaturation, given this patient's severe underlying respiratory disease.

As this is also the first known study to evaluate serial arterial blood gas analyses during bronchoscopy in dogs, what can be gathered from the data is that despite all preparations and initial improvements of oxygenation, bronchoscopy and, in particular, bronchoalveolar lavage can cause severe deterioration of oxygenation, especially in already compromised

patients. Ideally, a patient's pulmonary function should be evaluated before the procedure, as all patients that deteriorated during bronchoscopy showed hypoxaemia at baseline, regardless of their group allocation.

This study's main adverse event was the occurrence of aerophagia in a total of 14 dogs. Aerophagia was also the most common adverse event reported in three other veterinary studies.[155-157] In the study by Jagodich et al.[156], the entire patient population of eight dogs experienced aerophagia after receiving HFOT. However, radiographic images were not performed after each flow rate or after using conventional oxygen therapy methods. Since the possibility of aerophagia was expected, radiographic images before and after the procedure for both groups were thus incorporated into the study design to establish the full extent of aerophagia and its correlation to HFOT.

Six dogs in the TOT group and eight in the HFOT group showed some degree of aerophagia at the end of the bronchoscopic procedure. Although most cases showed only mild signs, three dogs in the HFOT group and one in the TOT group had severe signs of gaseous distension. The precise cause of aerophagia in these patients is unknown but can be explained by several factors.

For one, aerophagia is a common occurrence in people receiving CPAP ventilation.[172-175] One study in neonates developing a so-called 'CPAP belly' postulated a correlation between body weight and the occurrence of gastrointestinal distension.[175] One might similarly expect that aerophagia would have occurred mainly in smaller dogs, especially as their airways experienced a higher degree of obstruction by the bronchoscope, thus possibly redirecting high gas flows to alternative routes. However, all the dogs with signs of severe aerophagia had a body weight above 27 kg. Jaile et al.[175] suggested functional immaturity of the gastrointestinal tract might be an underlying factor in smaller neonatal patients, making it an unlikely cause for the present population as all dogs were between seven and twelve years of age. Correlations with gastroesophageal reflux disease or decreased lower oesophageal sphincter tonus have also been suggested as possible cofactors in people experiencing aerophagia after CPAP ventilation[173, 176, 177], yet in all cases, CPAP itself seems to be the main significant factor. It is possible that in the present study population, HFOT created high enough pharyngeal airway pressures to dilate the oesophagus, inadvertently insufflating the gastrointestinal tract. A case report on gastric distension in a paediatric patient after using HFOT[178] argued that too deeply inserted nasal airways likely caused high enough pharyngeal

airway pressure to distend the oesophageal sphincter resulting in gastric distension. Different studies showed a linear relationship between flow rate and pharyngeal pressures in patients receiving HFOT.[84, 106, 116] Therefore, larger dogs with correspondingly higher flow rates might have experienced higher pharyngeal airway pressures opening the oesophageal sphincter. However, most studies reported high pressures only for closed mouth conditions[82, 106, 116, 119], and as all dogs in the present study were positioned with their mouths ajar, it is unlikely, albeit not impossible, that such high airway pressures could have been achieved that would have made splinting and insufflation of the oesophagus possible. Unfortunately, pharyngeal airway pressure was not measured in the present study. Future studies evaluating the correlation of airway pressures with occurrences and severity of aerophagia in dogs might thus be beneficial to gain a better understanding of the reasons behind aerophagia in dogs receiving High Flow Oxygen Therapy.

Second, physiological alterations due the general anaesthesia might have also been responsible for aerophagia in some patients. On the one hand, as spontaneous breathing had to be maintained throughout the procedure, some patients might have shown increased swallowing due to insufficient anaesthetic depth. However, insufficient anaesthetic depth was not clinically detected in any patient throughout the procedure. On the other hand, possible anaesthesia-related reduced oesophageal sphincter tone might have also played a role.[179-181] Low doses of propofol have been shown to cause a reduction in upper oesophagus sphincter tone[180], while a large group of anaesthetic drugs can affect the lower oesophageal sphincter[179, 181]. However, since aerophagia also occurred in studies using HFOT in awake dogs, it is more likely that aerophagia is related to the high flow rates per se and the resulting high airway pressures. Therefore, aerophagia might have already occurred during the phase of preoxygenation. During this period, most patients either had their mouths closed, thus higher airway pressures would have been possible, and a few patients showed panting, which would have caused increased swallowing of air.

Although radiographs showed severe gastric and or oesophageal distension in four dogs, none of the patients showed clinical signs such as abdominal pain, regurgitation or discomfort, thus, an intervention was not deemed necessary in any patient. In addition, all patients were clinically reassessed at the time of the following arterial blood gas sampling, one hour after the procedure. Still, none of the dogs showed clinical signs or the need for intervention.

The current data reflects the results of previous studies in people and dogs alike that HFOT is a safe method to improve oxygenation, and air leak syndrome, although possible, remains a rare occurrence.[72, 128, 129] However, in accordance with previous studies in dogs, aerophagia is a relatively common side effect of HFOT and should be closely monitored, although none of the patients needed intervention. As aerophagia also occurred in patients receiving TOT, monitoring is warranted for all patients receiving oxygen supplementation and further studies in dogs evaluating the occurrence of aerophagia in relation to oxygen therapy are needed.

For the present study, FiO_2 settings of 100% were chosen for patients receiving HFOT to gain the maximum effect on oxygenation. Since all dogs in the HFOT group achieved tracheal FiO_2 concentrations above 75%, with five dogs showing concentrations above 90%, care should be taken with regard to oxygen toxicity. Although no signs of oxygen toxicity, such as absorption atelectasis, were detectable on thoracic radiographs, mild pulmonary changes caused by these high oxygen concentrations might not have been detectable with radiographic imaging and thus cannot be excluded. Studies in people showed that early signs of atelectasis were already present on computer tomographic images within five to seven minutes after preoxygenation with 100% oxygen.[39] CT imaging was not performed so as not to prolong anaesthesia unnecessarily and because the main focus of the study was on the assessment of HFOT under normal conditions for bronchoscopic procedures. Due to the high achievable tracheal oxygen concentrations with HFOT, it is advisable to reduce the FiO_2 setting to concentrations below 40% as soon as possible and if tolerated by the patient, especially in prolonged use of HFOT to avoid potential negative implications of oxygen.

5. Limitations of the study

The present study has some limitations. First, the patient population is heterogenous in terms of underlying diseases. Differences in severity and pathomechanisms of the underlying conditions might have affected oxygenation and response to oxygen therapy. However, choosing a patient population with a similar diagnosis would have been impossible in a prospective study, as bronchoscopy was part of the diagnostic workup, and final diagnoses were not yet made. A retrospective analysis of patients' responses to oxygen supplementation suffering from the same underlying respiratory condition might prove useful in the future.

However, to create an equal basis for comparison despite differences in underlying diseases, arterial blood gas analysis was performed for each patient at baseline as the gold standard for evaluating pulmonary function[5]. Here, an equal amount of patients in each group showed hypoxaemia, and there was no significant difference in P_aO_2 values or calculated oxygen indices at baseline between both groups despite differences in the final diagnosis. However, differences in response to oxygen supplementation due to underlying pathomechanisms should be kept in mind and might have had an impact on some of the values obtained.

Second, the main limitation of the study is the small sample size. The initial target was 25 dogs per group. This target was deemed achievable based on a retrospective analysis of patient numbers presented for bronchoscopy in the previous three years before data collection commenced. Approximately 80 to 100 dogs were presented for diagnostic bronchoscopy during the previous three years. However, from Mai 2020 until August 2022, only 23 patients eligible for study inclusion were presented, of which three dogs had to be excluded. One possible explanation for the sudden drop in patient numbers could be the corona pandemic resulting in lockdown periods, travel restrictions and changes in our hospital admission procedures. However, the actual reasons for the decline in patient numbers remain unknown and are most likely due to a combination of multiple factors.

The small sample size might have also affected the outcome of occurring complications. As air leak syndrome is already a rare occurrence in people[128], the study might have simply been underpowered to detect such rare complications associated with HFOT.

VII. Conclusion

The present study shows that HFOT is a safe and easy method to improve oxygenation in dogs undergoing bronchoscopy. Although TOT via nasal cannulas managed to provide adequate oxygen supplementation in some patients, HFOT proved to be statistically superior for preoxygenation, and the data suggests fewer incidents of desaturation occur during bronchoscopy and BAL sampling. Improved oxygenation likely resulted from higher achievable oxygen concentrations, higher flow rates and resulting airway pressure, while the benefits of applying humidified and warmed air on mucociliary clearance prevented excessive mucus build-up. While HFOT showed improved oxygenation compared to TOT in patients experiencing mild to moderate hypoxaemia before the procedure, care should be taken in patients with severe hypoxaemia at baseline. Depending on the suspected underlying respiratory pathology, alternative oxygen supplementation methods incorporating CPAP or assisted ventilation should be considered for these patients, as HFOT remains an open system relying on the patient's spontaneous breathing.

VIII Summary

Hypoxaemia is a common complication in dogs undergoing bronchoscopy, and the options for adequate oxygen supplementation are often limited, particularly in small veterinary patients. High Flow Oxygen Therapy (HFOT) has been used successfully in human hypoxaemic patients to improve oxygenation in various settings, including during diagnostic and therapeutic bronchoscopy.

The aim of this study was to evaluate the effect of HFOT on oxygenation in dogs undergoing bronchoscopy compared to a traditional oxygen supplementation method. Additionally, the study aimed to assess if HFOT is a safe method to use during bronchoscopy and to determine if complications would occur.

Twenty privately owned dogs presented for diagnostic bronchoscopy were included in the study. Age and weight ranged from 1 to 13 years and 4.4 to 47.8 kg, respectively. All dogs were randomly assigned to receive either HFOT or traditional oxygen therapy (TOT) using nasal cannulas during the procedure. Arterial blood gas analyses were obtained for each patient at seven different predetermined time points: at baseline, after preoxygenation, after induction of anaesthesia, before and after bronchoalveolar lavage, at the end of the procedure, and one hour after the end of oxygen supplementation. In addition, thoracic radiographs were performed for each patient before and immediately after the bronchoscopy to assess the occurrence of complications such as air leak syndrome or aerophagia.

Parametric and non-parametric statistical tests were used depending on data distribution to compare the partial pressure of oxygen at all time points between the group. Additionally, tracheal FiO_2, calculated oxygen indices, and trend analysis of P_aO_2 over time were evaluated. Finally, the occurrence and frequency of adverse effects were assessed using a Chi-square test.

Overall, HFOT led to higher values of P_aO_2 in nearly all patients throughout the procedure, with fewer episodes of desaturation occurring compared to the TOT group. Statistical significance could be achieved for values obtained after preoxygenation and at the end of the procedure. Values obtained after BAL barely missed the statistically significant cut-off ($P< 0.05$). However, only one patient in the HFOT group experienced desaturation below 80 mmHg, and the lowest P_aO_2 experienced in the remaining dogs within the group was 117 mmHg. In comparison, five dogs in the TOT group experienced hypoxaemia at least once

during the procedure despite oxygen supplementation. Furthermore, a comparison of mean P_aO_2 values from preoxygenation to the end of the procedure showed a statistically significant difference between the groups. Visual graphical analysis also indicates an overall better performance of HFOT than TOT regarding oxygenation. Additionally, HFOT achieved statistically significantly higher tracheal FiO_2 values than TOT.

There were no serious adverse events related to HFOT, although several dogs in both groups experienced aerophagia to various degrees. However, none of the dogs required medical intervention to alleviate gaseous distension.

In conclusion, HFOT is a safe oxygen supplementation method and can improve oxygenation in dogs undergoing bronchoscopy compared to traditional oxygen supplementation methods. HFOT can thus reduce and even prevent occurrences of life-threatening periods of hypoxaemia even during bronchoalveolar lavage sampling compared to TOT.

VIII Zusammenfassung

Hypoxämie ist eine häufig auftretende Komplikation während Bronchoskopien, und die Möglichkeiten einer adäquaten Sauerstofftherapie sind in der Veterinärmedizin oftmals begrenzt, insbesondere bei kleinen Patienten. Die High Flow Sauerstofftherapie (HFOT) wurde bereits erfolgreich in der Humanmedizin eingesetzt, um die Oxygenierung bei Patienten in verschiedenen Situationen zu verbessern, unter anderem während diagnostischer und therapeutischer Bronchoskopien.

Ziel der Studie war es, die Auswirkung der High Flow Oxygen Therapie (HFOT) auf die Oxygenierung bei Hunden während diagnostischer Bronchoskopien im Vergleich zu einer herkömmlichen Methode der Sauerstoffsupplementation (Traditional Oxygen Therapy = TOT) zu evaluieren. Zusätzlich wurde evaluiert, ob die HFOT eine sichere Methode der Sauerstoffsupplementation während Bronchoskopien darstellt und ob Komplikationen auftreten.

Insgesamt 20 Hunde, vorgestellt zur diagnostischen Therapie, wurden in die Studie aufgenommen. Alle Hunde wurden randomisiert und entweder der HFOT-Gruppe oder der TOT-Gruppe zugeordnet. Die Sauerstoffapplikation erfolgte in jeder Gruppe mittels Nasenbrillen. Die Oxygenierung wurde mittels arteriellem Sauerstoffpartialdruck (PaO_2) bewertet. PaO_2 wurde für jeden Patienten zu 7 festgelegten Messzeitpunkten erhoben: vor Bronchoskopie (t0), nach Präoxygenierung (t1), nach Einleitung der Anästhesie (t2), vor und unmittelbar nach broncho-alveolären Lavage (t3 und t4), am Ende der Bronchoskopie (t5), sowie eine Stunde nach Beendigung (t6). Zusätzlich wurden bei jedem Patienten vor und unmittelbar nach der Bronchoskopie Röntgenaufnahmen des Thorax angefertigt, um das Auftreten von Komplikationen wie Air-Leak-Syndrom oder Aerophagie zu erfassen.

Je nach Datenverteilung wurden parametrische und nicht-parametrische statistische Tests verwendet, um PaO_2 zu allen Zeitpunkten zwischen den Gruppen zu vergleichen. Außerdem wurden die tracheale Sauerstoffkonzentration (FiO_2), die berechneten Sauerstoffindizes und die Trendanalyse des PaO_2 im Zeitverlauf ausgewertet. Das Auftreten und die Häufigkeit von unerwünschten Wirkungen wurden mittels Chi-Square-Test bewertet.

Insgesamt führte die HFOT bei fast allen Patienten während des gesamten Eingriffs zu höheren PaO_2 Werten und es traten insgesamt weniger Hypoxämie-Phasen auf als in der TOT-Gruppe. Statistische Signifikanz konnte für die nach der Präoxygenierung (t1) und am Ende der Bronchoskopie (t5) ermittelten PaO_2 Werte erreicht werden. PaO_2 Werte nach BAL verfehlten nur knapp den statistisch signifikanten Cut-off ($P < 0,05$). Allerdings kam es nur bei einem einzigen Patienten in der HFOT-Gruppe zu einer Hypoxämie mit einem PaO_2 unter 80 mmHg. Der niedrigste PaO_2-Wert bei den übrigen Hunden der HFOT-Gruppe lag bei 117 mmHg. Im Vergleich dazu trat bei fünf Hunden in der TOT-Gruppe trotz Sauerstoffsupplementierung mindestens einmal während des Eingriffs eine Hypoxämie-Phase auf. Darüber hinaus zeigte ein Vergleich der Mittelwert der PaO_2 Messungen während der gesamten Oxygenierungsphase (t1-t5) ebenfalls einen signifikanten Unterschied zwischen den Gruppen ($P = 0,0114$). Zusätzlich erreichten Patienten in der HFOT-Gruppe statistisch signifikant höhere tracheale FiO_2-Werte als in der TOT-Gruppe.

Es traten keine schwerwiegenden Komplikationen im Zusammenhang mit der HFOT auf. Mehrere Hunde in beiden Gruppen zeigten eine Aerophagie von unterschiedlichem Ausmaß, jedoch benötigte keiner der Hunde eine therapeutische Intervention, um die Aerophagie zu beheben.

Zusammenfassend stellt die HFOT eine sichere Methode der Sauerstoffsupplementation bei Hunden während diagnostischer Bronchoskopien dar. Im Vergleich zu herkömmlichen Methoden bewirkt die HFOT eine Verbesserung der Oxygenierung, auch während der broncho-alveolären Lavage. Die HFOT kann somit das Auftreten von lebensbedrohlichen Episoden der Hypoxämie während Bronchoskopien reduzieren oder gar verhindern.

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