Cardiopulmonary effects of three different ventilation treatments in healthy anaesthetised dogs

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Submitted in fulfilment of the requirements for the degree of Master of Science in the Department of Companion Animal Clinical Studies in the Faculty of Veterinary Science, University of Pretoria

Date Submitted: October 2020

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Acknowledgements

I would like to thank the following individuals:

Gareth Zeiler for giving me this opportunity, moulding me into the anaesthesiologist and researcher I am, showing me that nothing is unreachable and for inspiring me to always give my best.

Roxanne Buck for your all your time, patience and knowledge you have invested in me. For being the voice of reason during our residency.

Jessica Price, my beautiful wife, for providing me with all the love an emotional support over the last three years of the residency.

Tim Krafft for giving Gareth and myself the unhindered opportunity to practice anaesthesia to the level we can.

Wollies Animal Shelter, Stepahnie Rotherham and **Ellen Heydenrych** for your trust in me; allowing me to use your beautiful boys in the study.

Natalie Dumas and Marlize Vermaak for your endless help, support and friendship which extends far beyond this project.

Magda Kruger for your enthusiasm in my project and helping me with the data collection process.

Abdur Kadwa and Justin Grace for your friendship and always having my back over the last three years.

Jeffery Ngqungqa, Philip Mampane and **Themba Somo** for all the good laughs and making sure the project ran smoothly.

Katie Edmonds for the doing the castrations and providing good company.

My parents for your assistance in funding my education and patiently listening to all my work stories.

Abstract

Objective To compare the effect of invasive continuous positive airway pressure (CPAP), pressure-controlled ventilation with positive end expiratory pressure (PCV+PEEP) and spontaneous breathing (SB) on carbon dioxide removal, blood oxygenation and indicators of tissue perfusion in healthy anaesthetised dogs.

Study design Prospective randomised crossover study.

Animals Fifteen intact male dogs of various breeds of mean (± standard deviation) age and weight of 25 (± 19) months and 21.7 (± 9.9) kg, respectively.

Methods Dogs were anaesthetised (buprenorphine, medetomidine, propofol) and maintained with isoflurane in 50% oxygen-air mixture and kept in right lateral recumbency. Ventilation treatments (CPAP: 4 cmH_2O; PCV+PEEP: 10 cmH_2O peak inspiratory pressure, 4 cmH_2O positive end-expiratory pressure, respiratory rate of 10 breaths $minute^{-1}$ and inspiratory-to-expiratory ratio of 1:2; SB: standard circle circuit, no pressure applied) were administered to each dog consecutively in random order under the same anaesthetic period with 5-minute SB washout period between treatments. Arterial and central venous blood samples for gas analysis were collected at the start (0 minutes) and end (20 minutes) of each ventilation treatment. Arterial to venous content difference was calculated for each ventilatory treatment. Other physiological variables and spirometry measures were collected at 5-minute intervals from start to end for each ventilation treatment. Data was compared using a general linear mixed model ($p < 0.05$).

Results Arterial oxygen tension was significantly higher and carbon dioxide tension lower after PCV+PEEP than CPAP and SB (all: $p < 0.001$), but no different between CPAP and SB (p =

1.000 and $p = 0.697$ respectively). Central venous oxygen and carbon dioxide tensions were significantly lower after PCV+PEEP compared to SB and CPAP (all: $p < 0.001$). The tidal volume and minute volume were higher during PCV+PEEP than during SB and CPAP (both: $p < 0.001$). Arterial-venous oxygen content difference was higher with PCV+PEEP compared to SB and CPAP (both: $p < 0.001$).

Conclusion and clinical relevance. An increased tidal volume with PCV+PEEP resulted in improved arterial oxygenation and carbon dioxide elimination as compared to CPAP and SB. CPAP resulted in similar oxygenation and ventilation to SB. Increased oxygen extraction occurred with PCV+PEEP, probably associated with a reduced cardiac output. The clinical benefit of short-term invasive CPAP over SB in the healthy anaesthetised dog remains uncertain.

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Abbreviations

aHt	Arterial haematocrit
°C	Degrees Celsius
$CaCO_2$	Carbon dioxide content of arterial blood
CaO_2	Oxygen content of arterial blood
CaO_2-$CcvO_2$	Arterial to central venous oxygen content difference
CbO_2	Oxygen content of blood
CC	Closing capacity
CcO_2	Oxygen content of alveolar capillary blood
$CcvO_2$	Oxygen content of central venous blood
cmH_2O	Centimetres of water pressure above atmospheric pressure
CO_2	Carbon dioxide
$CvCO_2$	Carbon dioxide content of mixed venous blood
CvO_2	Oxygen content of mixed venous blood
CPAP	Continuous Positive Airway Pressure
CVC	Central venous catheter
cvHt	Central venous haematocrit
DAP	Diastolic arterial blood pressure
Est $\dot{Q}_s/\dot{Q}_t$	Estimated shunt fraction
F_E´Iso	End-tidal isoflurane concentration in percent
FiO_2	Fraction inspired oxygen
f_R	Respiratory rate
fr	French gauge
FRC	Functional residual capacity
Ga	Birmingham gauge
g dL^{-1}	Grams per decilitre
g L^{-1}	Grams per litre
HR	Heart rate
Hb	Haemoglobin concentration
ICU	Intensive Care Unit
I:E	Inspiratory to Expiratory ratio
IPPV	Intermittent Positive Pressure Ventilation
kg	Kilograms
L $minute^{-1}$	Litres per minute
MAP	Mean arterial blood pressure
mg kg^{-1}	Milligram per kilogram body mass
mL kg^{-1} $hour^{-1}$	Millilitre per kilogram body mass per hour
mm	Millimetre
mmHg	Millimetres mercury
mL	Millilitre
mL dL^{-1}	Millilitres per decilitre
mL L^{-1}	Millilitres per litre
mL $minute^{-1}$	Millilitres per minute
O_2	Oxygen
p	Statistical p-value

P_ACO_2	Partial pressure of carbon dioxide in alveolar gas
$PaCO_2$	Partial pressure of carbon dioxide in arterial blood
$PaCO_2$-$P_E'CO_2/PaCO_2$	Estimated alveolar dead space fraction
PAO_2	Alveolar partial pressure of oxygen
PaO_2	Partial pressure of oxygen in arterial blood
P(A-a) O_2	The alveolar to arterial oxygen partial pressure difference
Pbar	Atmospheric pressure
PbO_2	Partial pressure of oxygen in blood
PCO_2	Partial pressure of carbon dioxide
PCV	Pressure Controlled Ventilation
$PcvCO_2$	Partial pressure of carbon dioxide in central venous blood
$PcvO_2$	Partial pressure of oxygen in central venous blood
$P_E'CO_2$	End-tidal carbon dioxide partial pressure
$P\bar{E}CO_2$	Mean expired carbon dioxide partial pressure
PEEP	Positive End Expiratory Pressure
P:F	The ratio of arterial partial pressure of oxygen to the fraction inspired oxygen
P_{H2O}	Saturated vapour pressure of water at 37 degrees Celsius
P_{mean-A}	Mean alveolar pressure
$P_{mean-AW}$	Mean airway pressure
PO_2	Partial pressure of oxygen
PSV	Pressure support ventilation
P_{trans}	Trans-pulmonary pressure
$PvCO_2$	Partial pressure of carbon dioxide in mixed venous blood
PvO_2	Partial pressure of oxygen in mixed venous blood
$\dot{Q}$	Cardiac output
$\dot{Q}_s/\dot{Q}_t$	Venous admixture
RQ	Respiratory Quotient
SaO_2	Functional percent saturation of haemoglobin with oxygen in arterial blood measured with a blood gas analyser
SAP	Systolic arterial blood pressure
SB	Spontaneous breathing
SbO_2	Functional percent saturation of haemoglobin with oxygen in blood measured with a blood gas analyser
$ScvO_2$	Functional percent saturation of haemoglobin with oxygen in central venous blood measured with a blood gas analyser
SpO_2	Peripheral arterial haemoglobin oxygen saturation measured by pulse oximetry
T	Oesophageal temperature
T0, T5, T10, T15, T20	Study time points of five-minute intervals from start to end
umol L^{-1}	Micromoles per litre
$\dot{V}CO_2$	Carbon dioxide production
VCV	Volume controlled ventilation
V_D/V_T	Physiological dead space
$\dot{V}_E$	Expiratory minute volume
VILI	Ventilator induced lung injury
V_T	Tidal volume

V̇/Q̇	Ventilation to perfusion ratio of the lung
Δ	Change in value from T0 value
WOB	Work of breathing

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Chapter 1

1.1 Defining relevant physiological concepts

This dissertation investigated three different ventilation treatments in anaesthetised healthy dogs. There are physiological concepts that are technical and are important to define before the literature is reviewed. The relevant physiological concepts are defined with a discussion on their clinical importance provided.

Ventilation to perfusion ratio ($\dot{V}/\dot{Q}$): The $\dot{V}/\dot{Q}$ represents the relationship between gas delivered and blood flow to an alveolus. The relationship between ventilation and perfusion of an alveolus will influence the partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) in the blood leaving that alveolus (Petersson & Glenny 2014). For example, in an alveolus where no diffusion impairment exists, alveolar gas tension equilibrates with alveolar blood gas tensions when $\dot{V}/\dot{Q}$ is optimal. The $\dot{V}/\dot{Q}$ is optimal when ventilation (mL minute^{-1}) is equal to perfusion (mL minute^{-1}) (at a ratio of 1.0). The maximum achieved alveolar partial pressure of oxygen (P_AO_2) and subsequently the PO_2 in the blood leaving the alveolus will be less in an alveolus with a lower $\dot{V}/\dot{Q}$ than an alveolus with a greater $\dot{V}/\dot{Q}$ (Petersson & Glenny 2014). This is because in alveoli with lower $\dot{V}/\dot{Q}$, oxygen (O_2) is removed from the alveolar gas by the passing blood at a faster rate than ventilation can deliver O_2 to the alveoli (Figure 1-1). As ventilation is responsible for removing carbon dioxide (CO_2) from the alveolus while perfusion delivers CO_2 to the alveolus, alveoli with lower $\dot{V}/\dot{Q}$ ratios will result in a higher alveolar PCO_2 (P_ACO_2) and subsequently higher values of PCO_2 in the blood leaving that alveoli (Petersson & Glenny 2014).

Right-to-left intrapulmonary shunting represents blood flowing through alveoli with no ventilation ($\dot{V}/\dot{Q}$ of zero) (Figure 1-1). That is, PO_2 and PCO_2 of the blood leaving the alveolar capillary is equal to that of mixed venous blood. Alveolar dead space represents alveoli with $\dot{V}/\dot{Q}$ tending towards infinity (Figure 1-2). Thus, these alveoli are ventilated but not perfused. Ventilation to these units is completely wasted (they do not participate in gas exchange). In fact, alveoli with $\dot{V}/\dot{Q}$ greater than 1 will all have some degree of wasted ventilation (Petersson & Glenny 2014). If a large portion of minute volume ($\dot{V}_E$) is wasted and not compensated for, O_2 delivery and CO_2 removal to and from the pulmonary blood can be affected. Looking at the lung as a whole, a range of $\dot{V}/\dot{Q}$ ratios exists, decreasing from non-dependent to dependent lung lobes (Rahn et al. 1956). Thus, the overall combination of alveoli with different $\dot{V}/\dot{Q}$ will influence arterial blood gas tensions.

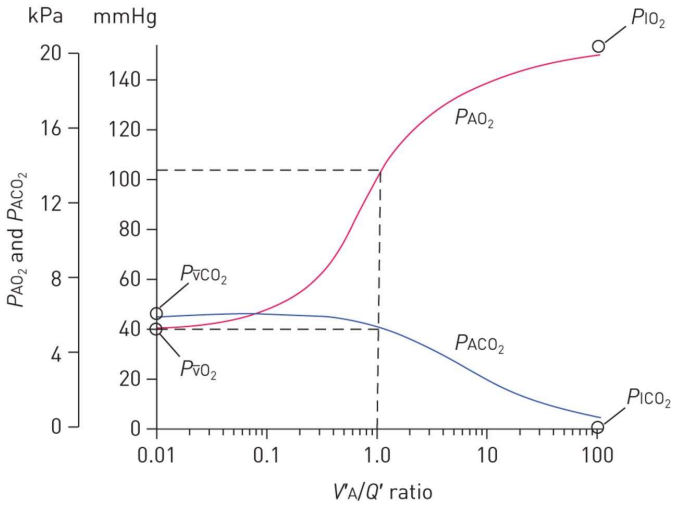

Figure 1-1 The change in alveolar oxygen (P_AO_2) and carbon dioxide partial pressures (P_ACO_2) with the change in $\dot{V}/\dot{Q}$ of a single alveolus. With high and low $\dot{V}/\dot{Q}$, P_AO_2 and P_ACO_2 tend towards the partial pressures of inspired values (P_IO_2 and P_ICO_2) and mixed venous values ($P\bar{v}O_2$ and $P\bar{v}CO_2$) respectively.

Figure taken from: Petersson J, Glenny RW (2014) Gas exchange and ventilation–perfusion relationships in the lung. European Respiratory Journal 44, 1023-1041.

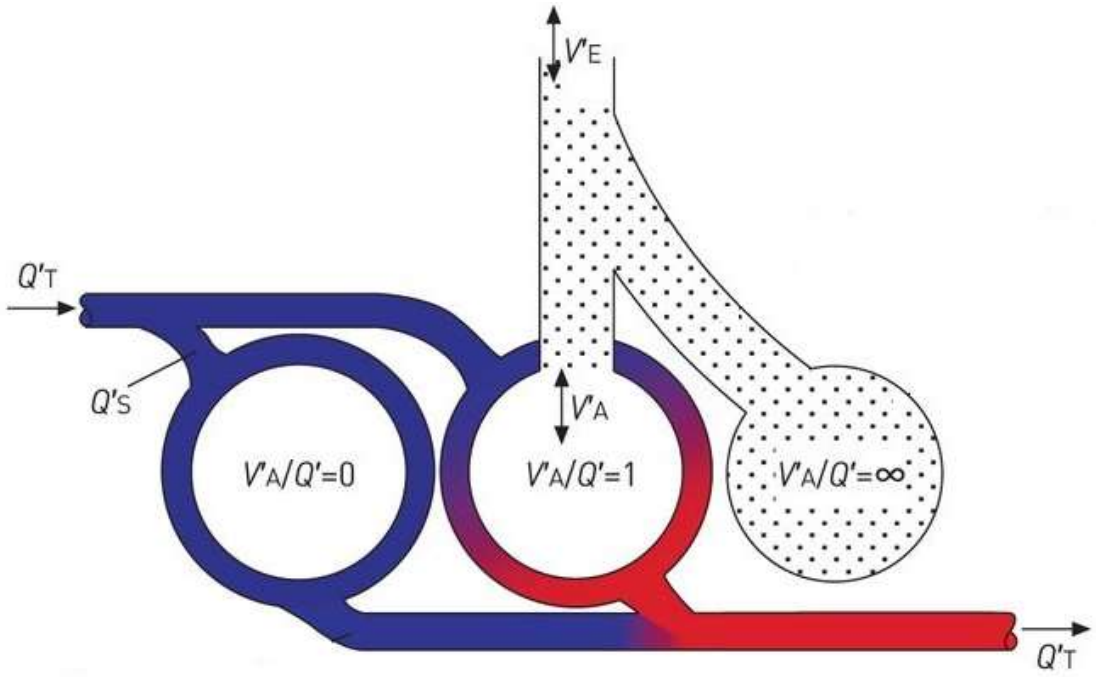

Figure 1-2 An illustration representing the extremes of $\dot{V}/\dot{Q}$ ratios amongst alveoli. Blood emerging from alveoli with $\dot{V}/\dot{Q}$ = 0 have O_2 and CO_2 partial pressures equivalent to mixed venous blood. This blood flow ($\dot{Q}s$) represents right to left intrapulmonary shunt. Alveoli with $\dot{V}/\dot{Q}$ equal to infinity do not participate in gas exchange. Thus, ventilation to these units is wasted. In alveoli with $\dot{V}/\dot{Q}$ = 1, optimal gas exchange takes place so that O_2 and CO_2 partial pressures in the alveoli and emerging capillary blood are equal. $\dot{V}_E$, is minute volume; $\dot{V}_A$ is alveolar ventilation; $\dot{Q}_T$, is total blood flow.

Figure taken from: Petersson J, Glenny RW (2014) Gas exchange and ventilation–perfusion relationships in the lung. European Respiratory Journal 44, 1023-1041.

Functional residual capacity (FRC) and closing capacity (CC): The volume left in the lungs at the end expiration during tidal breathing is the FRC (Wanger et al. 2005). The lung volume at which the dependent airways begin to close is the CC of the lung (Lumb 2017). If FRC

decreases below CC then dependent airways will close during tidal respiration. Both FRC and CC decrease with the induction of anaesthesia, however not to equal extent (Juno et al. 1978).

Compliance and resistance: Compliance of the respiratory system represents the ratio between change in thoracic volume and change in pressure required to produce the change in volume (Ball et al. 2018). Thus, compliance is the ease by which the elastic properties of the respiratory system can be overcome to generate a volume. Respiratory system compliance includes both the compliance of the thoracic wall and the lungs. Lung compliance has been shown to decrease with the induction of anaesthesia, most likely due to atelectasis formation, reducing the number of alveoli that can receive a given tidal volume (V_T) (Gold & Helrich 1965). The resistance of the respiratory system is the represented by the pressure required to generate a flow of gas into or out of the respiratory system and includes resistance of the airways, respiratory tissue, gas compression and inertance of tissues and gases (Mead 1956; R. H. Ingram & Schilder 1966; Milic-Emili et al. 1990). Measured compliance can be dynamic or static. Dynamic compliance (lung or respiratory system) refers to compliance derived from all pressures and volumes obtained during a normal respiratory cycle, thus it includes the pressure required to overcome resistance to gas flow within the airways. Static compliance (lung or respiratory system) refers to compliance derived from measured pressures and volumes obtained during multiple inspiratory pauses, thus eliminating resistance from gas flow within the airways. Unless otherwise stated, the term compliance in this text will refer to static compliance.

Trans-pulmonary pressure (P_{trans}): The P_{trans} is the difference between the pressure at the airway opening and intrapleural pressure (Henderson et al. 2017). Trans-pulmonary pressure represents the pressure required to expand the lungs and produce flow through the airways

(Henderson et al. 2017). Mean airway pressure ($P_{mean-AW}$) is the pressure at the airway opening averaged over the respiratory cycle (Marini & Ravenscraft 1992a). Mean alveolar pressure (P_{mean-A}) represents the average pressure in the alveoli throughout the respiratory cycle (Marini & Ravenscraft 1992a). As long as inspiratory and expiratory resistances to gas flow are equal, $P_{mean-AW}$ will equal P_{mean-A}, regardless of the ventilation being spontaneous or mechanical (Marini & Ravenscraft 1992a). Thus, in healthy patients $P_{mean-AW}$ will closely reflect P_{mean-A}. Trans-alveolar pressure is the pressure differences between the alveolus and the interpleural space. The relationship between P_{trans}, lung compliance and lung resistance can be demonstrated in the equation of motion:

$$P_{trans} = (V_T/C_L) + (R_L \times \dot{V})$$

Where P_{trans} is the trans-pulmonary pressure, V_T is the tidal volume entering the lungs, C_L is the compliance of the lungs, R_L is the resistance to gas flow into the lungs and $\dot{V}$ is the flow of gas into the lungs.

Work of breathing (WOB): Work of breathing, is the energy (Joules) expended by the respiratory musculature, ventilator or both in order to produce a breath (flow and volume). Work done must overcome both elastic and resistive components of the respiratory system. Mathematically, WOB is the integral of the dynamic pressure volume curve (Figure 1-3) (Huhle et al. 2018). Thus, as the compliance of the respiratory system decreases or resistance increases, more pressure is required to produce a given volume and flow and thus WOB increases. In spontaneously breathing animals an increase in WOB results in an increase in demand placed on the respiratory muscles with the potential to fatigue (Grinnan & Truwit 2005).

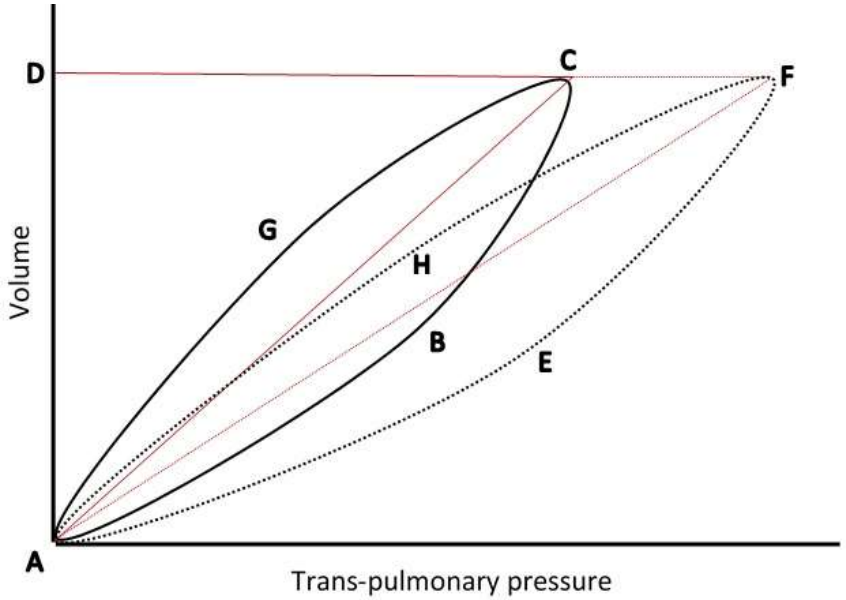

Figure 1-3 A theoretical dynamic pressure-volume curve during a ventilator-delivered breath in two patients with different lung compliances but equal respiratory resistance. Solid line pressure-volume curve: patient 1 with a higher lung compliance; dotted line pressure-volume curve: patient 2 with lower lung compliance. WOB in patient 1 is defined by the area ABCDA: area ABCA represents work required to overcome inspiratory resistance, area ACGA represents work required to overcome expiratory resistance, area ACDA represents the work required to overcome lung elastance. WOB in patient 2 is defined by area AEFDA: area AEFA represents work required to overcome inspiratory resistance, area AFHA represents work required to overcome expiratory resistance, area AFDA represents the work required to overcome lung elastance. It can be seen that area AEFDA is larger than area ABCD, thus more work is required to deliver a breath when lung compliance decreases. If patient 1 and 2 have equal respiratory resistance, it can be seen that the additional work required to produce a breath is due to area AFCA, which represent the work required to overcome additional lung elastance.

Physiological dead space: Physiological dead space is the combination of anatomical and alveolar dead space. Anatomical dead space represents conducting airways where no gas exchange takes place.

Minute volume ($\dot{V}_E$): Minute volume is the volume of gas moving in and out of the lungs per minute. It is calculated as the product of V_T and respiratory rate (f_R).

1.2 Introduction

The means by which a breath is generated during intermittent positive pressure ventilation (IPPV), continuous positive airway pressure (CPAP) and spontaneous breathing (SB) can be divided into two types. Namely, natural-type which requires thoracic muscle (costal and diaphragm) function to generate a breath (SB and CPAP) and artificial-type in which the breath is generated by a ventilator (IPPV). Continuous positive airway pressure differs from SB in that a constant pressure above atmospheric is applied at the airway opening throughout the respiratory cycle (Burrows 1975). Thus, CPAP can be thought of SB with an applied positive end expiratory pressure (PEEP) as well as a pressure equal to PEEP maintained at the airway during inspiration. Besides how a breath is generated, $P_{mean\text{-}A}$, and thus also intrathoracic pressures, vary among CPAP, SB and IPPV. This difference in $P_{mean\text{-}A}$ is due to variations in PEEP and driving pressure, with a higher PEEP and driving pressures generating a higher $P_{mean\text{-}A}$ (Marini & Ravenscraft 1992a). Thus, $P_{mean\text{-}A}$ is highest for IPPV followed by CPAP then SB. These differences in $P_{mean\text{-}A}$ and means by which breaths are generated are important as these two aspects account for the majority of varied cardiovascular and respiratory physiological responses amongst IPPV, CPAP and SB.

There are two basic control methods of delivering a breath during IPPV; they are volume controlled (VCV) or pressure controlled (PCV) ventilation (Hopper & Powell 2013). With VCV,

the ventilator delivers a pre-set V_T by means of a constant inspiratory flow applied over a set inspiratory time for each breath. Thus, with VCV the inspiratory pressure obtained depends on the compliance and resistance of the respiratory system. With PCV, a pre-set constant inspiratory pressure is applied and the V_T obtained depends on inspiratory time as well as respiratory system resistance and compliance. When comparing PCV and VCV in healthy anaesthetised dogs, with PCV set to target the same V_T administered with VCV, PCV resulted in an improved respiratory system compliance and thus a lower peak inspiratory pressure (Fantoni et al. 2016). However, there was no difference in cardiac output between VCV and PCV (Fantoni et al. 2016). In humans with respiratory failure, similar results were observed to those of Fantoni et al. (2016) (Al-Saady & Bennett 1985). In addition, improved arterial oxygenation and reduced physiological dead space were also observed with PCV as compared to VCV (Al-Saady & Bennett 1985). These effects indicate that PCV may be better at recruitment of atelectatic alveoli than VCV. The alveolar recruitment benefits obtained with PCV may be due to the fact that a constant inspiratory pressure is maintained at the airway during inspiration.

The most common indication for the use of a mechanical ventilator in human intensive care units (ICU) is acute respiratory failure (Esteban et al. 2000). Acute respiratory failure is likely also the most common indication for the use of a mechanical ventilator in dogs. Acute respiratory failure can be divided into failure of oxygenation or failure of ventilation (Tung 1997). Failure of oxygenation is considered as an arterial partial pressure of O_2 (PaO_2) of 60 mmHg or less while receiving an inspired fraction of O_2 (FiO_2) of 1.00 (Tung 1997; Hopper & Powell 2013). Acute ventilatory failure occurs when the arterial partial pressure of CO_2 ($PaCO_2$) rises above 55-60 mmHg (Tung 1997; Hopper & Powell 2013). Dogs presenting with acute respiratory failure often require general anaesthesia to tolerate invasive support of

ventilation whether with IPPV or CPAP. Anaesthesia creates physiological changes that may exacerbate acute respiratory failure in patients with underlying pulmonary pathology or induce acute respiratory failure in the healthy patient. Thus, this study was designed to compare the cardiopulmonary effects of CPAP, PCV+PEEP and SB in order to help establish the value of each ventilatory treatment in the anaesthetised dog both in an ICU or surgical theatre setting.

1.3 Literature review

1.3.1 Ventilation-perfusion disturbances and anaesthesia

Within five minutes of inducing general anaesthesia, atelectasis develops in the most dependent parts of the lungs in human patients (Brismar et al. 1985; Strandberg et al. 1986). Similarly, atelectasis has been shown to develop in anaesthetised dogs (Staffieri et al. 2007; Allison et al. 2017). In the awake animal, the negative intrapleural pressure creates a positive trans-alveolar pressure gradient that is large enough to prevent the formation of atelectasis. With the induction of anaesthesia, the diaphragm and thoracic musculature relaxes resulting in an increase in intrapleural pressure in the dependent thoracic regions (Froese & Bryan 1974; Brismar et al. 1985; Hedenstierna et al. 1985; Hedenstierna & Edmark 2010). This increase in intrapleural pressure in the dependent thorax, decreases the trans-alveolar pressures in the corresponding regions, with a subsequent decrease in alveolar volume. This reduction in alveolar volume decreases the functional FRC of the lung (Hedenstierna et al. 1981a; Hedenstierna et al. 1981b). When CC exceeds FRC, small airway closure occurs and atelectasis develops as gas is absorbed behind the closed airways (Hedenstierna et al. 1981a; Hedenstierna et al. 1981b; Hedenstierna & Edmark 2010). In addition to complete airway closure, a critical $\dot{V}/\dot{Q}$ of each alveolus exists, below which the rate of gas absorption exceeds

gas delivery resulting in alveolar collapse (termed absorption atelectasis) (Dantzker et al. 1975). Thus, factors increasing the critical $\dot{V}/\dot{Q}$ of alveoli promote atelectasis formation. The two important factors, affecting the critical $\dot{V}/\dot{Q}$ are the FiO_2 and the mixed venous partial pressure of O_2 (PvO_2) (Dantzker et al. 1975). An increase in FiO_2 raises the critical $\dot{V}/\dot{Q}$, by creating a greater gradient for O_2 diffusion from the alveoli to the blood as well as by removing the less blood-soluble nitrogen present in the alveoli which tends to lower the critical $\dot{V}/\dot{Q}$ (Dantzker et al. 1975). Similarly, a greater gradient for diffusion of O_2 occurs when PvO_2 decreases, as could occur with increased tissue O_2 extraction. Thus, the ratio of inspired O_2 to air (containing nitrogen) influences the development of atelectasis, with a higher FiO_2 resulting in greater and quicker atelectasis formation (Dantzker et al. 1975; Joyce et al. 1993; Staffieri et al. 2007). As anaesthesia increases the range of $\dot{V}/\dot{Q}$ present in the lung, it's possible that more alveoli reach critical $\dot{V}/\dot{Q}$ (Tokics et al. 1996; Putensen et al. 2002). As atelectatic alveoli are perfused but not ventilated, the degree of atelectasis that develops under general anaesthesia correlates with the magnitude of intrapulmonary right-to-left shunt (Hedenstierna et al. 1986).

In addition to the development of atelectasis during anaesthesia, changes in the distribution of ventilation also affect the overall ventilation to perfusion matching in the lung. During anaesthesia, ventilation shifts to the non-dependent lung regions where intrapleural pressures are more negative (Wagner et al. 1975; Rooney et al. 2009; Ambrisko et al. 2017; Ambrosio et al. 2017). As opposed to a decreased FRC in the dependent lung, this distribution of ventilation increases FRC in the non-dependent lung (Hedenstierna et al. 1981b). Alveoli that are ventilated and not perfused contribute to alveolar dead space. Thus, this shift in ventilation with the induction of anaesthesia has the potential to increase alveolar dead space. Significant alveolar dead space or regions with high $\dot{V}/\dot{Q}$ will interfere with CO_2 removal

potentially resulting in hypercarbia (Dueck et al. 1977). In summary, anaesthesia, whether ventilating spontaneously or mechanically, creates a lung with a greater range of $\dot{V}/\dot{Q}$ ratios than the awake patient, with potential to interfere with gas exchange (Tokics et al. 1996; Putensen et al. 2002).

1.3.2 Recruitment of atelectatic lung

The benefits of recruiting atelectatic alveoli are, a decrease in intrapulmonary right-to-left shunting, potentially limiting ventilator induced lung injury (VILI) and improving pulmonary compliance. The reduction in VILI occurs with alveolar recruitment by reducing the number of stress raisers (junction of normal and atelectatic alveoli), reducing atelectrauma, and reducing dynamic energy delivered with each breath (Muscedere et al. 1994; Hess 2015; Protti et al. 2015). Improving pulmonary compliance can decrease the WOB (Gherini et al. 1979; Katz & Marks 1985; Duncan et al. 1986). As anaesthesia is known to decrease respiratory drive, strategies that increase pulmonary compliance during spontaneous breathing (PEEP or CPAP) may theoretically have the potential to increase V_T and thus maintain a lower $PaCO_2$ (Gherini et al. 1979; Sollevi & Lindahl 1995).

The extent to which the atelectatic alveoli are recruited depends on the maximum trans-pulmonary pressure achieved during inspiration. Thus, supplementing spontaneously generated trans-pulmonary pressure with CPAP or elevating trans-pulmonary pressure with IPPV may help with recruitment of atelectatic alveoli (Gherini et al. 1979). However, if V_T and inspiratory flows are equal, SB and IPPV will produce the same P_{trans} (Bellani et al. 2016). In this scenario, where P_{trans} is equal between natural and artificial-types of ventilation, the extent of alveolar recruitment may still be different due to differing distributions of this pressure during inspiration among ventilation types. As the diaphragm functions best in the

most dependent parts of the thorax, were atelectasis is most prominent, natural-type ventilation (SB and CPAP) may help distribute trans-pulmonary pressure to the more dependent lung (Froese & Bryan 1974). This effect has been demonstrated where the addition of spontaneous breaths during IPPV was shown to improve $\dot{V}/\dot{Q}$ matching and reduce shunt fraction in comparison to IPPV alone (Putensen et al. 1994; Putensen et al. 1999).

Besides recruiting alveoli, alveoli must be kept open during the expiration phase of the respiratory cycle. Positive end expiratory pressure is commonly applied during anaesthesia to keep recruited alveoli open (Brismar et al. 1985; Allison et al. 2017). Pulmonary tissue displays hysteresis whereby less pressure is required to produce the same volume during deflation compared to inflation (Gattinoni et al. 2017). Due to this phenomenon, a low level of PEEP may be effective at keeping previously recruited alveoli open. Atelectatic alveoli differ from each other in that the pressure required to open them and keep them open is different. In the healthy lung this difference most likely depends on the position of the atelectatic alveoli within the lung, with the more dependent alveoli requiring higher pressures to open and keep open (Crotti et al. 2001). The level of PEEP needed to keep the majority of alveoli open in healthy anaesthetised subjects will likely depend on body position during anaesthesia and FiO_2 (Staffieri et al. 2007; le Roux et al. 2016). In anaesthetised dogs receiving a FiO_2 of 1.00 the application of 5-10 cmH_20 PEEP during SB and IPPV has been shown to significantly reduce pulmonary atelectasis (De Monte et al. 2013; Allison et al. 2017). A PEEP of 4 cmH_2O has been recommended as a starting point when applying IPPV to dogs (Hopper & Powell 2013).

1.3.3 Side effects of alveolar recruitment

As a vertical pressure gradient, increasing from non-dependent to dependent regions, exists within the thorax of an anesthetised patient, the effects of PEEP will be predominately distributed to the non-dependent lung zones (Froese & Bryan 1974). During inspiration with IPPV, where the diaphragm is not participating in ventilation, ventilation distribution to the non-dependent lung will be more significant than during SB or CPAP (Rooney et al. 2009; Ambrisko et al. 2017). Thus, the application of PEEP as well as IPPV has the potential to increase the number of alveoli with high $\dot{V}/\dot{Q}$ ratios and increase alveolar dead space (Froese & Bryan 1974). The extent by which IPPV with PEEP or CPAP will increase alveolar dead space will depend on the $P_{mean\text{-}A}$ generated and extent of atelectatic alveolar recruitment. For instance, there is an almost linear relationship with reduction in shunt fraction and increase in PEEP during IPPV. However, beyond a certain PEEP value, when no more alveoli are recruited, an increase in alveolar dead space will occur (Suter et al. 1975; Dueck et al. 1977).

Besides the development of alveolar dead space, the effects of the different ventilation types on cardiac function need to be evaluated. Although higher trans-pulmonary pressures associated with IPPV and CPAP can decrease shunt fraction and improve arterial oxygenation, they may not result in the best O_2 delivery (Suter et al. 1975). Oxygen delivery to tissue is not only dependent on arterial O_2 content (the volume of O_2 carried per unit volume of arterial blood) (CaO_2) but also cardiac output. It is well known that IPPV decreases cardiac output by decreasing venous return through increasing intrapleural pressure (Cournand & Motley 1948). The extent to which IPPV reduces venous return will depend on pulmonary compliance as this will affect how much pressure is transferred to the pleural cavity and thus the extrapulmonary veins (vena cava mainly) and right atrium. Circulating volume status will also

affect the relationship between IPPV and venous return. On the contrary, SB maintains a negative intrathoracic pressure, with the larger negative pressures during inspiration promoting venous return and thus maintaining cardiac output (Shekerdemian & Bohn 1999). Although CPAP relies on thoracic muscular activity to generate a breath, the higher $P_{mean\text{-}A}$ (as compared to SB) will likely dampen the beneficial effect of a spontaneously generated breath on venous return. Although the negative intrathoracic pressures during SB also have negative effects on left ventricular afterload and function (through increases in aortic transmural pressures), the beneficial effect on right heart venous return with overall improvement in cardiac output predominates in health (Shekerdemian & Bohn 1999). Even at the same level of PEEP, higher $P_{mean\text{-}A}$ associated with IPPV, as compared to CPAP, has a more detrimental effect on cardiac output (Shah et al. 1977; Simonneau et al. 1982).

An increase in pulmonary vascular resistance also decreases right-sided cardiac output. Pulmonary vascular resistance displays a u-shaped curve when plotted against lung volume, with an increased resistance at both low (hypoxic pulmonary vasoconstriction and mechanical collapse of extra-alveolar vessels) and high (alveolar blood vessel compression) lung volumes (Whittenberger et al. 1960; Sipmann et al. 2018). Pulmonary vascular resistance is optimised at normal FRC (Cortes-Puentes et al. 2018). Thus, the effect of a ventilation type on pulmonary vascular resistance will depend on the balance between alveolar recruitment and alveolar overdistension. As the muscular generated breaths (SB and CPAP) appear to better maintain $\dot{V}/\dot{Q}$ matching than IPPV at equal levels of trans-pulmonary pressure, they may help prevent elevations in pulmonary vascular resistance. The variability in the ability of IPPV, SB and CPAP to maintain normocapnia may also impact cardiac function. This is because hypoxic pulmonary vasoconstriction is influenced by $PaCO_2$.

1.3.4 Measuring ventilation-perfusion disturbances

The gold standard of assessing the range and extent of $\dot{V}/\dot{Q}$ present in the lung (including true right-to-left intrapulmonary shunt and alveolar dead space) is by use of the multiple inert gas elimination technique (Wagner et al. 1974). This technique is, however, technically difficult, requiring not only six inert gases but access to gas chromatography, computer analysis and knowledge of cardiac output (Wagner et al. 1974). An easy bed-side method of estimating the extent of low $\dot{V}/\dot{Q}$ (< 1.0) is by calculating the extent of venous admixture ($\dot{Q}s/\dot{Q}t$):

$$\dot{Q}_s/\dot{Q}_t = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$$

Where CcO_2 is the alveolar capillary blood O_2 content (mL dL^{-1}), CaO_2 is the arterial blood O_2 content (mL dL^{-1}) and CvO_2 is the mixed venous blood O_2 content (mL dL^{-1}).

This value, however, cannot differentiate true intrapulmonary shunt from areas of low $\dot{V}/\dot{Q}$ when FiO_2 is less than 1.00 (Cruz & Metting 1987). Also, to calculate $\dot{Q}s/\dot{Q}t$, measurement of mixed venous O_2 content is required and therefore pulmonary artery catheterisation needs to be performed. Even with short term pulmonary artery catheterisation there is a risk for potential life threating complications, including pulmonary artery rupture and life threatening cardiac arrythmias on catheter placement (Hadian & Pinsky 2006). Besides the risks associated with pulmonary artery catheterisation, the cost of the catheter placement and skilled required to do so also preclude the routine use in veterinary science, especially in low-income countries.

Alternatively, an estimate of shunt fraction (Est $\dot{Q}s/\dot{Q}t$) can be made by assuming a fixed arterial to mixed venous O_2 difference of 3.5 mL dL^{-1} which is typical in mammalian species (Harrison et al. 1975; Wandrup 1995; Bigeleisen 2001; Araos et al. 2012; van Loon et al. 2018).

Using an assumed O_2 difference may be a limitation if cardiac output is different amongst the different types of ventilation because the arterial to mixed venous content is influenced. Together with Est $\dot{Q}s/\dot{Q}t$, indices of oxygenation such as the ratio of PaO_2 to FiO_2 (P:F ratio) and the alveolar to arterial O_2 partial pressure difference [$P(A\text{-}a)O_2$], can help identify other causes of altered arterial oxygenation (Mellemgaard 1966; Hess & Maxwell 1985).

Calculating physiological dead space can provide insight into the magnitude of regions with high $\dot{V}/\dot{Q}$ ratios. Typically, the Bohr equation is used to calculate physiological dead space:

$$V_D/V_t = (P_ACO_2 - P_{\bar{E}}CO_2)/P_ACO_2$$

Where P_ACO_2 is the average partial pressure of CO_2 in the alveoli and $P_{\bar{E}}CO_2$ is the partial pressure of CO_2 in the mixed expired breath. A bedside estimate of P_ACO_2 requires the use of volumetric capnography, while $P_{\bar{E}}CO_2$ requires the use of volumetric capnography or evaluation of collected expired gas over a 1-minute period (Kallet et al. 2005; Tusman et al. 2011). To simplify calculating physiological dead space, Enghoff replaced P_ACO_2 with $PaCO_2$. This substitution creates a problem of not only including the effects of regions of high $\dot{V}/\dot{Q}$ but also regions of low $\dot{V}/\dot{Q}$ and right-to-left intrapulmonary shunting (Tusman et al. 2012). This phenomenon occurs as the higher partial pressure of CO_2 of mixed venous blood ($PvCO_2$) will influence $PaCO_2$ when significant blood flows past alveoli with low $\dot{V}/\dot{Q}$. By further substituting $P_{\bar{E}}CO_2$ in the Enghoff modification of the Bohr equation with end-tidal carbon dioxide ($P_E'CO_2$), alveolar dead space can be estimated (Nunn & Hill 1960; Hardman & Aitkenhead 1999). Again, this value is affected by alveoli with low $\dot{V}/\dot{Q}$. The $P_E'CO_2$ can be measured with time or volumetric capnography. As time capnography and arterial blood gas analysers, to determine $P_E'CO_2$ and $PaCO_2$ respectively, are readily available to most

anaesthesiologists, these substitutions to the Bohr equation provide an easy bedside estimate of $\dot{V}/\dot{Q}$ mismatch.

1.3.5 Biomarkers of perfusion

Cardiovascular function is often evaluated in a research setting by measuring cardiac output. However, there are many technical, expense and morbidity related factors limiting cardiac output measurements. As such, direct cardiac output measurement was not an option in this study. The value of blood lactate, venous to arterial CO_2 content difference, arterial to venous O_2 content differences and central venous oxyhaemoglobin saturation ($ScvO_2$) as indicators of cardiac output are briefly discussed.

One reason for an increased blood lactate is tissue hypoxia, where lactate is produced faster than it is metabolised (Phypers & Pierce 2006). This situation, however, will only occur below critical O_2 delivery, as such blood lactate may not be useful to detect subtle changes in O_2 delivery above this critical point, as may be expected with IPPV, CPAP or PEEP (Bakker & Vincent 1991).

According to the Fick equation applied to CO_2, the mixed venous to arterial CO_2 content difference is dependent on cardiac output and CO_2 production under stable conditions (de Boode et al. 2007; Mallat et al. 2016):

$$CvCO_2 - CaCO_2 = \dot{V}CO_2/\dot{Q}$$

where $CvCO_2$ is the content of CO_2 in mixed venous blood (mL L^{-1}), $CaCO_2$ is the content of CO_2 in arterial blood (mL L^{-1}), $\dot{V}CO_2$ is CO_2 production (mL $minute^{-1}$) and $\dot{Q}$ is cardiac output (L $minute^{-1}$)

Because of the almost linear relationship between CO_2 content and CO_2 partial pressures, central venous ($PcvCO_2$) to $PaCO_2$ difference can also be used as an indicator of cardiac output under stable conditions (Lamia et al. 2006; Mallat et al. 2016). As a low $PaCO_2$ decreases the perfusion of certain tissues through vasoconstriction, hyperventilation-induced hypocapnia has the potential to widen the $PcvCO_2$ to $PaCO_2$ difference without affecting cardiac output (Morel et al. 2011; Morel et al. 2017). The exact values of $PaCO_2$ at which this widened $PcvCO_2$ to $PaCO_2$ occurs is uncertain, however this occurrence may hinder the use of this indicator of cardiac function when $\dot{V}_E$ is different between ventilation types.

As with CO_2, the Fick equation can be applied to O_2, where $CaO_2 - CcvO_2$ is dependent on cardiac output when O_2 consumption remains constant (Fick 1870). As blood O_2 content (CbO_2) is primarily dependent on haemoglobin (Hb) saturation, when arterial Hb saturation with O_2 is close to 100% and Hb concentrations remain constant, $ScvO_2$ can also be used as an indicator of cardiac output (Shepherd & Pearse 2009). As with CO_2, there are also potential limitations to using $CaO_2 - CcvO_2$ to assess cardiac function while levels of alveolar ventilation are different. This is because respiratory alkalosis has been shown to increase tissue O_2 consumption through unknown mechanisms, while respiratory acidosis can inhibit mitochondrial function, thereby decreasing O_2 consumption (Khambatta & Sullivan 1973; Jubrias et al. 2003). It is, however, uncertain within what range of pH and $PaCO_2$ this described effect will interfere with interpretation of cardiac function.

To the best of the author's knowledge, these biomarkers of tissue perfusion have not been compared between CPAP, PCV+PEEP and SB. As such, $CaO_2 - CcvO_2$ will be compared amongst ventilation types in this study.

1.3.6 Summary and problem statement

There are potential advantages with the use of CPAP over IPPV with PEEP. These include better $\dot{V}/\dot{Q}$ matching and less severe effects on cardiac output. The disadvantages of CPAP in comparison to IPPV are potential hypoventilation within 20 minutes of applying CPAP (Simonneau et al. 1982). In comparison to SB, CPAP may have the potential to improve $\dot{V}_E$ through the reduction in WOB and improve arterial oxygenation through better recruitment of atelectatic lung.

Most investigations focused on CPAP have been done in humans with respiratory failure. However, lung functionality and response to ventilation modes will be different in health and disease. Also, it is difficult to extrapolate data among species. Studies using CPAP in dogs have been performed, however, they have not included invasive delivery of CPAP, nor compared CPAP to IPPV or SB (Staffieri et al. 2014; Meira et al. 2018). Lastly, most modern anaesthesia workstations and ICU ventilators have the option of ventilating with CPAP, thus the potential advantages of this mode of ventilation needs to be investigated.

1.4 Aims and objectives

The aim of this study was to compare the cardiopulmonary effects of CPAP, PCV with PEEP and SB in healthy dogs under general anaesthesia with a primary focus of their effects on $PaCO_2$ and PaO_2.

The study aim was achieved by the following objectives:

1. Collecting arterial and central venous blood gas samples immediately before (T0) the start and at the end (T20) of each ventilatory treatment for comparison.

2. Collecting routinely measured physiological, airway gas and spirometry variables immediately before (T0) the start, at five-minute intervals (T5, T10, T15) and at the end (T20) of each treatment.

1.5 Hypothesis

H0 - There will be no difference in cardiopulmonary variables within or among treatments.

H1 - There will be a difference in cardiopulmonary variables within or among treatments.

Chapter 2

2.1 Materials and Methods

2.1.1 Animals

The study was approved by the Animal Ethics Committee of the University of Pretoria (REC 216-19). A group of 15 intact male dogs (various breeds) of mean (± standard deviation) age, mass and body condition score of 25 (± 19) months, 21.7 (± 9.9) kg and 5 (± 1) out of 9, respectively, were used. A sample size of 15 dogs was calculated by using the following estimations and assumptions: the mean $PaCO_2$ was used for comparison amongst the treatments whereby distribution was considered normal with a standard deviation 2 mmHg $PaCO_2$, a confidence interval of 95%, a margin of error 1mmHg $PaCO_2$, an alpha level of 0.05 and beta level of 0.2 (MiniTab 18; Minitab; USA). This sample size was also similar to that used in other studies incorporating a crossover design (Staffieri et al. 2014; Meira et al. 2018). The dogs were deemed healthy by clinical examination, measurement of serum creatinine concentration (73 ± 21 umol L^{-1}), packed cell volume (44 ± 5%) and refractometric total plasma protein concentration (65 ± 6 g L^{-1}). The dogs were fasted from food but not water for 8 hours before premedication.

2.1.2 Study design

The study was designed as a prospective, controlled, randomised sequence, crossover clinical study to evaluate three ventilation treatments. The dogs underwent all treatments once in a randomised order. The investigators were not blinded to the treatments. The order of the treatments was randomised using a single block design (Sealed Envelope;

www.sealedenvelope.com/simple-randomiser/v1/lists [accessed 3 July 2020]). Each treatment was carried out for 20 minutes with a five-minute period of SB between treatments. All treatments were carried out under the same anaesthetic period. The treatments were:

CPAP - CPAP was applied using the CPAP/Pressure support ventilation (PSV) mode of the electronic anaesthetic workstation. The parameters were set as follows: Pressure support switched off and PEEP of 4 cmH_2O.

PCV+PEEP - IPPV was applied with the pressure-controlled ventilation mode of the electronic anaesthetic workstation. The parameters were set as follows: inspiratory pressure of 10 cmH_2O, PEEP of 4 cmH_2O, Inspiratory-to-Expiratory (I: E) ratio at 1:2 and f_R of 10 breaths $minute^{-1}$. If the $P_E'CO_2$ dropped below 35 mmHg, then the f_R was decreased by 2 breaths $minute^{-1}$.

SB – spontaneous breathing with the electronic anaesthetic workstation set to manual and no pressure applied to the airways.

Dogs were excluded from the study if one or more of the following were detected: abnormalities in clinical examination, paying attention to heart rate, respiratory rate, pulmonary auscultation, cardiac auscultation, peripheral pulse quality, mucous membrane colour, capillary refill time and rectal temperature; serum creatinine concentration higher than 159 umol L^{-1}; packed cell volume less than 35 %; total serum protein concentration of less than 55 g L^{-1} or if the dog had not been starved for 8 hours.

No exclusion criteria were set for data. If data appeared grossly abnormal the measurement was repeated to confirm the measurement.

2.1.3 Anaesthesia, instrumentation and sample collection

Prior to initiating the study, the airway module of the electronic anaesthetic workstation (Carestation 650 Anaesthesia Delivery System; Datex-Ohmeda Inc; USA) used in the study was calibrated, using a proprietary calibration gas canister, as per manufacturer's instructions. Each morning of the study, the built-in flow sensor, pressure sensor and circuit O_2 cell of the same workstation were calibrated as per manufactures instructions. The accuracy of the V_T measures was confirmed by slowly injecting and aspirating room air from the breathing system, to simulate breathing, using a 60 mL catheter syringe. Measurements of 60 ± 4 mL on 4 simulated breaths was considered adequately accurate.

The study was completed over multiple days with 1 to 3 dogs participating sequentially, one at a time, in the study each day. Premedication of each dog was carried out with buprenorphine (0.03 mg kg^{-1}; Temgesic; Reckitt Benckiser Healthcare; UK) and medetomidine (0.01 mg kg^{-1}; Domitor; Zoetis; RSA) administered intramuscularly into the gluteal muscle group by separate injections. The dogs were subsequently left undisturbed for 30 minutes prior to cephalic vein cannulation (20 Ga; Jelco; Smiths Medical International; UK). Anaesthesia was induced with propofol (Fresenius Propoven 1%; Fresenius Kabi AB; Sweden) administered intravenously to effect, in order to allow endotracheal intubation using a cuffed polyvinyl chloride endotracheal tube (internal diameter ranged from 9 to 12 mm; Ho-lee tube; JC Medical; RSA). Following intubation, general anaesthesia was maintained with isoflurane (Isofor; Safeline Pharmaceuticals (Pty) Ltd; RSA) administered in 100% O_2 at a fresh gas flow rate of 2.0 L $minute^{-1}$ delivered via a circle breathing system. The dogs were kept in right lateral recumbency for the duration of the study. A single dose of meloxicam (0.2 mg kg^{-1}; Metacam; Labiana Life Sciences S.A.; Spain) was administered subcutaneously. Cannulation

of a dorsal pedal artery was performed (22 Ga; Jelco; Smiths Medical International; UK). A three-lumen central venous catheter (CVC; 20 cm 8fr; CENTRA-LINE; Biometrix b.v; Netherlands) was aseptically inserted into the left jugular vein using a modified Seldinger technique (Beal & Hughes 2000). The CVC was advanced over the guidewire until the presence of a central venous pressure waveform (B125 Patient Monitor; GE Medical Systems; USA) was obtained (de Laforcade & Rozanski 2001). Once prepared, the dogs were moved to an operating theatre and connected via a circle breathing system to the previously calibrated electronic anaesthetic workstation. Isoflurane in a gas mixture of medical air (1.1 L minute^{-1}) and O_2 (0.7 L minute^{-1}), to achieve a FiO_2 of 0.5 (± 0.01), was administered for the duration of the study. As it is generally recommended to keep the FiO_2 below 0.6 to avoid oxygen induced lung damage, a FiO_2 of 0.5 was selected (Kallet & Matthay 2013). The end-tidal isoflurane concentration (F_E´Iso) was maintained between 1.2% to 1.4% (Barletta et al. 2016). The oesophageal temperature (T) of the dogs was maintained between 36.0 to 37.5 °C using a forced-air warming device (Bair Hugger Warming Unit-Model 505; Arizant Healthcare Inc; USA) and blankets.

Each dog was instrumented to monitor physiological variables using two different monitors. The multiparameter monitor (CARESCAPE Monitor B450; GE Healthcare, Finland) was used to determine the heart rate (by electrocardiogram; HR), direct systolic, diastolic and mean arterial blood pressure (SAP, DAP and MAP), peripheral oxyhaemoglobin saturation (SpO_2) and T. Direct arterial blood pressure was recorded with the use of an electronic pressure transducer (Art-Line; Biometrix Ltd; Israel) connected to the dorsal pedal artery catheter via a heparinised pressurised (300 mmHg) saline column housed in non-compliant tubing. The electronic pressure transducer was calibrated to atmospheric pressure at the level of the sternum for each dog prior to initiating data collection. Airway gas variables (F_E´Iso, FiO_2, P_E'

CO_2) and spirometry measurements (expired V_T, expired $\dot{V}_E$, peak pressure, PEEP, mean airway pressure ($P_{mean\text{-}AW}$), f_R) were obtained from the built-in monitor of the anaesthetic workstation.

The time from induction to completion of instrumentation was 29.6 ± 8.4 minutes. Following instrumentation, an isotonic crystalloid (Ringer-Lactate Solution; Fresenius Kabi; RSA) was infused at 5 mL kg^{-1} $hour^{-1}$ for the remainder of the study. Once instrumentation was complete, a 15-minute period elapsed before the ventilation treatments began.

In addition to collecting physiological variables, arterial and central venous blood was sampled simultaneously using a standardised procedure. First, a waste arterial (2 mL) and venous (5 mL) sample was drawn and discarded, then 1 mL of arterial and central venous blood was anaerobically drawn into heparinised syringes (BD A-Line; Becton, Dickinson and Company; UK) over 3 respiratory cycles. Samples were analysed within 5 minutes after collection using a self-calibrating benchtop blood gas analyser (RAPIDPoint 500; Siemens Healthcare Diagnostics Inc; USA).

2.1.4 Recovery

Following all treatments, the study was concluded. If the last treatment was CPAP or PCV+PEEP, the dog was switched to SB. At this point the arterial catheter and CVC were removed and haemostasis obtained with digital pressure. Prior to terminating anaesthesia, routine orchidectomies were performed. As part of the analgesic plan, lidocaine (2 mg kg^{-1}; Lignocaine Injection 2%; Bayer (Pty) Ltd; RSA) was used to perform a line block at the surgical site and injected into the spermatic chord of each testis. Once surgeries were complete, intravenous fluid administration was terminated, the dogs disconnected from the multiparameter monitor and anaesthetic workstation and moved to a recovery area. Vital

parameters were monitored at 5-minute intervals until extubation could be performed with the return of a swallowing reflex.

2.1.5 Data analysis

Physiological variables were recorded at start, immediately prior to initiating each treatment (T0) and then at 5 minutes intervals (T5, T10, T15) until treatment end at 20 minutes (T20). Blood gas analysis was performed at T0 and T20 for each treatment.

The P:F ratio, $P(A\text{-}a)O_2$, $CaO_2\text{-}CcvO_2$, Est $\dot{Q}_s/\dot{Q}_t$ and $PaCO_2\text{-}P_E'CO_2/PaCO_2$ were calculated. The following formulae were used to calculate P_AO_2, CbO_2 and Est $\dot{Q}_s/\dot{Q}_t$ respectively:

$P_AO2 = FiO_2 \times (Pbar - P_{H2O}) - (PaCO_2/RQ)$

Where FiO_2 is the inspired fraction of O_2, Pbar is the barometric pressure where the study was performed (650 mmHg), P_{H2O} is the saturated vapour pressure of water at 37 °C (47 mmHg) and RQ is the respiratory quotient of 0.8.

$CbO_2 = (SbO_2 \times Hb \times 1.36) + (PbO_2 \times 0.003)$

Where b is a place holder for arterial (a) or central venous (cv) blood, SbO_2 is the functional saturation of Hb with O_2, Hb is the haemoglobin concentration (g dL^{-1}), 1.36 is amount of O_2 that one gram of Hb is capable of carrying [Hüfner's constant; 1.36 (Morrison & Hisey 1935; Larimer 1959)], PbO_2 is the partial pressure of O_2 in the blood and 0.003 is the solubility coefficient for dissolved O_2 (mL dL^{-1} $mmHg^{-1}$).

Est $\dot{Q}_s/\dot{Q}_t = (CcO_2 - CaO_2) / (CcO_2 - CcvO_2)$

Where CcO_2 is the alveolar capillary blood content of O_2, $CaCO_2$ is the arterial blood O_2 content and $CcvO_2$ is the central venous blood O_2 content. The partial pressure of O_2 in the capillary blood was assumed to be equal to the P_AO_2, functional Hb O_2 saturation was taken as 100% and Hb concentration was assumed to equal that of the arterial blood.

Data was assessed for normality by inspection of histograms, descriptive statistics and the Anderson-Darling test for normality. Data distribution patterns were not parametric and therefore all variables were reported as median (1st quartile, 3rd quartile). The expired $\dot{V}_E$ and expired V_T were calculated per kg. Data collected at T0 were compared among treatments using Kruskal-Wallis. For each variable where data was collected over time, a change in value was calculated by subtracting the T5, T10, T15 and T20-value from the T0 value. Additionally, the percentage change in a variable was calculated by dividing the change in value by the T0 value and converting to a percent. All data collected or calculated over time were rank transformed prior to any further analysis to improve model fits. These data were then compared among treatments and over time using a general linear mixed model (Interactions: time, treatment, treatment x time; Fixed factors: time, treatment; Random factors: dogs). Model fits were assessed by visually inspecting residual plots to assess linearity, homogeneity of variances, normality, and outliers. Significant outcomes were further investigated by pairwise comparisons using the Tukey method. Data were compared using commercially available software (MiniTab 18; Minitab; USA) and significance interpreted at $p < 0.05$.

Chapter 3

3.1 Results

Full data sets were obtained from all dogs enrolled in the study. Amongst the variables at T0, only T was significantly different between ventilation treatments, where the dog's T before PCV+PEEP treatment (36.3°C) was significantly higher than CPAP (35.9°C) and SB (36.0°C) (p = 0.02). This difference was not considered clinically relevant. For all ventilation treatments at all time points F_E'Iso was 1.3 (1.3, 1.3)% and the FiO_2 was 0.50 (0.50, 0.51).

The actual values, change in value and percent change over time of the blood gas and calculated gradient variables are presented in Table 3-1. The PaO_2 significantly increased with PCV+PEEP from T0 to T20 ($p < 0.001$), and PaO_2 at T20 was significantly higher with PCV+PEEP than with CPAP and SB (both: $p < 0.001$). The PaO_2 was no different between T0 and T20 for CPAP (p = 0.203; 95% confidence interval, CI: -2.05; 17.50) and SB (p = 0.940; CI: -6.70; 12.86); or between CPAP and SB at T20 (p = 1.000; CI: -10.08; 9.48). The $PaCO_2$ significantly decreased with PCV+PEEP from T0 to T20 ($p < 0.001$), and $PaCO_2$ at T20 was significantly lower with PCV+PEEP than with CPAP ($p < 0.001$) and SB ($P < 0.001$). The $PaCO_2$ was no different between T0 and T20 for CPAP (p = 0.747; CI: -2.51; 6,91) and SB (p = 0.391; CI: -1.60; 7,83); or between CPAP and SB at T20 (p = 0.697; CI: -2.38; 7.05). Confidence interval plots highlighting the change and percent change of PaO_2 and $PaCO_2$ among the treatments are shown in Figure 3-1.

There were no significant differences in arterial Hb saturation with O_2 (SaO_2) from T0 for all ventilation treatments (p = 0.066) or between ventilation treatments at T20 (p = 0.228), however the change in value and percent change in value, was significantly greater for

PCV+PEEP as compared to CPAP and SB (p = 0.022). The arterial haematocrit (aHt) was no different between T0 and T20 for all ventilation treatments (p = 0.072) or between all ventilation treatments at T20 (p = 0.15). The degree of change in aHt was significantly different between all ventilation strategies (p < 0.001), with the greatest change seen with CPAP followed by SB then PCV+PEEP.

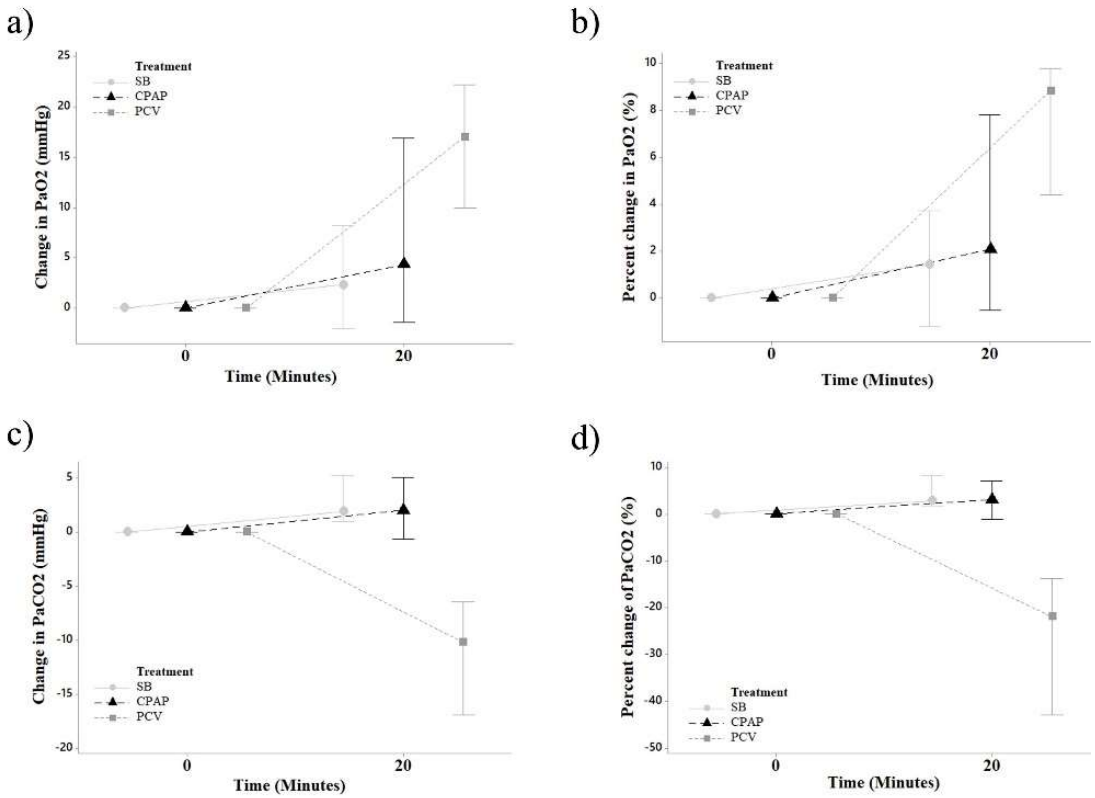

Figure 3-1 Confidence interval plots (median ± 95% confidence interval) highlight the change in a) arterial partial pressure of oxygen (PaO_2), c) arterial partial pressure of carbon dioxide ($PaCO_2$), and percent change of b) PaO_2 and d) $PaCO_2$ among the ventilation treatments in 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix. SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV, pressure-controlled ventilation with positive end expiratory pressure. The values at time 0 and 20 are staggered along the x-axis for clarity.

Mirroring $PaCO_2$, the central venous CO_2 partial pressure ($PcvCO_2$) significantly decreased with PCV+PEEP from T0 to T20 ($p < 0.001$), and $PcvCO_2$ at T20 was significantly lower with PCV+PEEP than with CPAP ($p < 0.001$) and SB ($P < 0.001$). The $PcvCO_2$ was no different between T0 and T20 for CPAP and SB ($p = 1.000$) or between CPAP and SB at T20 ($p = 0.804$). During PCV+PEEP, a significant decrease in central venous O_2 partial pressure ($PcvO_2$) ($p = 0.001$) and $ScvO_2$ ($p = 0.01$) from T0 to T20 was seen, and both $PcvO_2$ and $ScvO_2$ were significantly lower compared to SB and CPAP at T20 ($p < 0.001$ and $p = 0.026$, respectively). Confidence interval plots highlighting the change and percent change in $PcvCO_2$ and PcvO2 are shown in Figure 3-2. There were no significant differences in central venous haematocrit (cvHt) from T0 for all ventilation treatments ($p = 0.226$), or between ventilation treatments at T20 ($p = 0.728$).

During PCV+PEEP, a significant increase in P:F ($p < 0.001$) and CaO_2-$CcvO_2$ ($p = 0.003$) from T0 to T20 was observed and both P:F and CaO_2-$CcvO_2$ were significantly higher compared to SB and CPAP at T20 (both: $p < 0.001$). Confidence interval plots highlighting the change and percent change in P:F and CaO_2-$CcvO_2$ among the treatments are shown in Figure 3-3. A significant decrease in Est $\dot{Q}_s/\dot{Q}_t$ ($p = 0.001$) and $P(A\text{-}a)O_2$ from T0 to T20 ($p = 0.001$) occurred with all ventilation treatments, however, no significant differences were observed amongst them ($p = 0.337$ and $p = 0.287$ respectively) . Furthermore, no differences from T0 ($p = 0.258$) or amongst ventilation treatments ($p = 0.227$) were noted with $PaCO_2$-P_E' $CO_2/PaCO_2$.

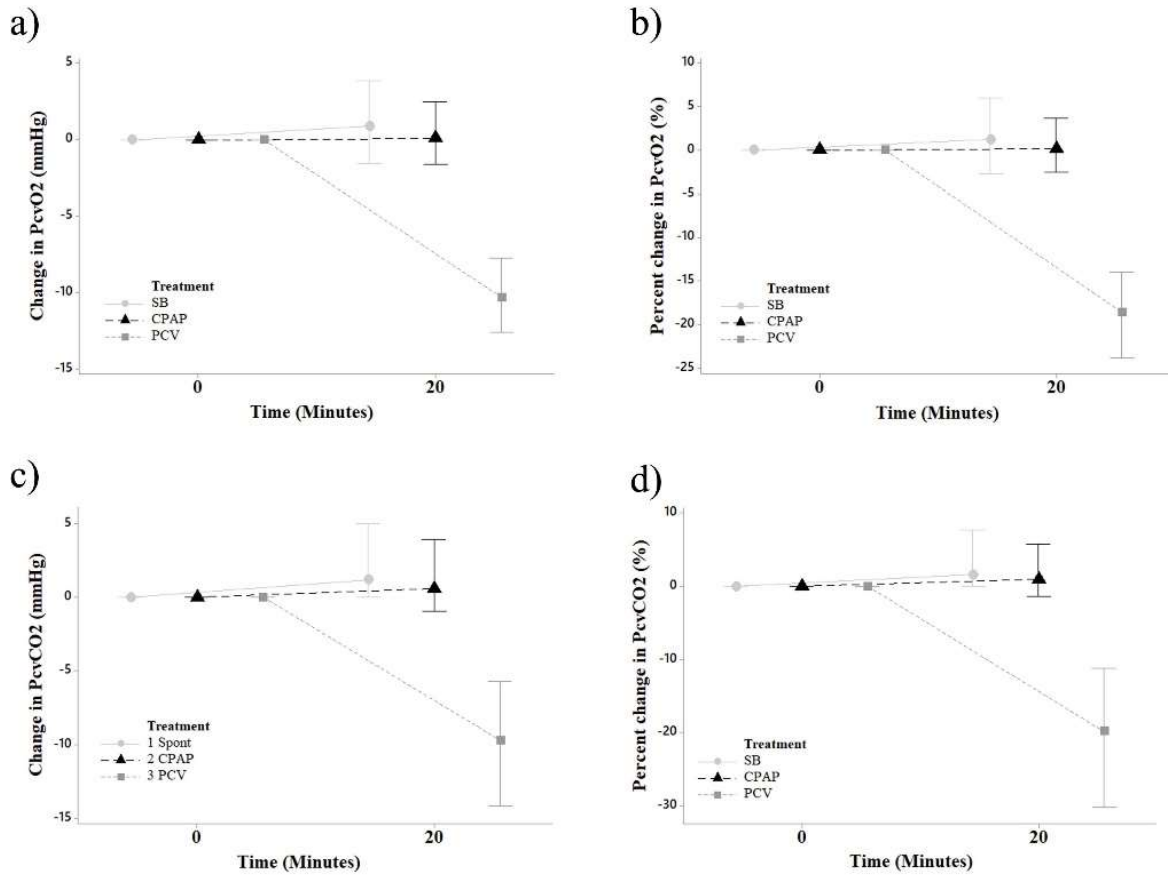

Figure 3-2 Confidence interval plots (median ± 95% confidence interval) highlight the change in a) central venous partial pressure of oxygen ($PcvO_2$), c) central venous partial pressure of carbon dioxide ($PcvCO_2$), and percent change of b) $PcvO_2$ and d) $PcvCO_2$ among the ventilation treatments in 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix. SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV, pressure-controlled ventilation with positive end expiratory pressure. The values at time 0 and 20 are staggered along the x-axis for clarity.

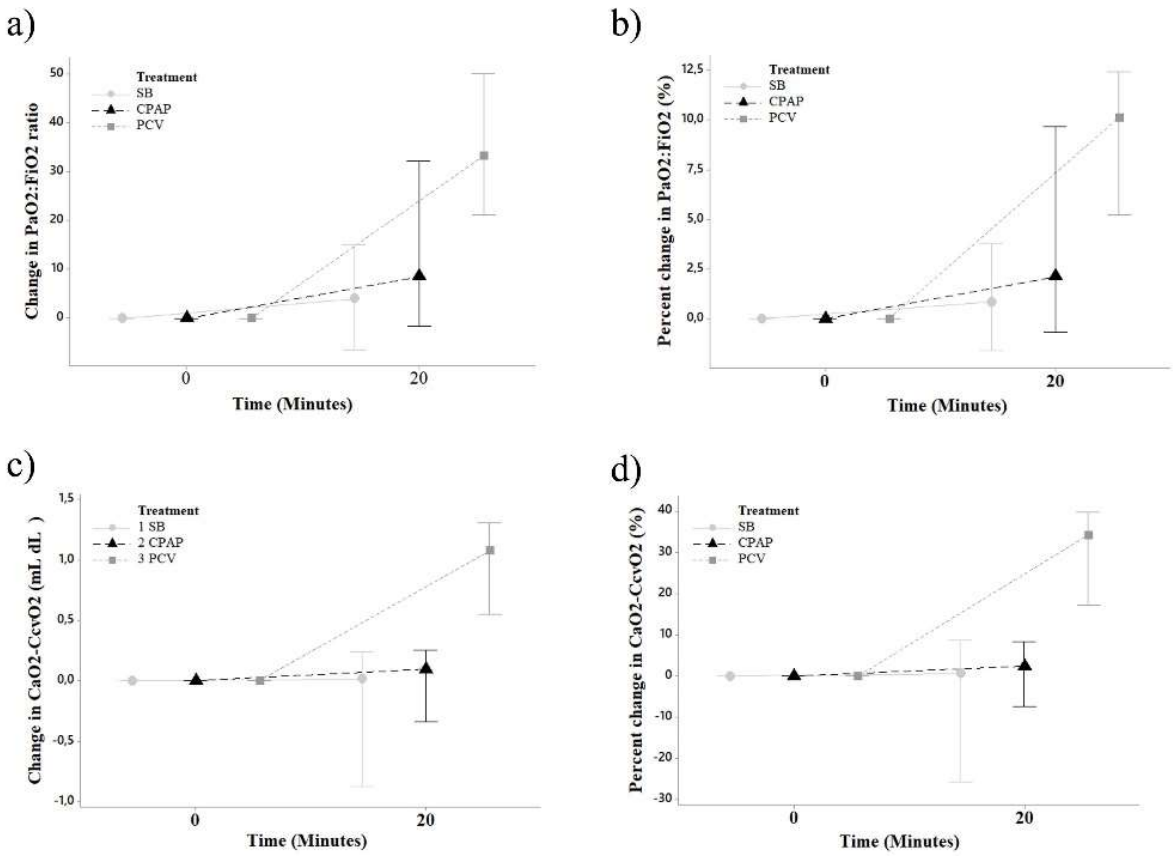

Figure 3-3 Confidence interval plots (median ± 95% confidence interval) highlight the change in a) the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen (P: F), c) the arterial to central venous oxygen content difference ($CaO_2 – CcvO_2$), and percent change of b) P: F and d) $CaO_2 – CcvO_2$ among the ventilation treatments in 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix. SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV, pressure-controlled ventilation with positive end expiratory pressure. The values at time 0 and 20 are staggered along the x-axis for clarity.

Table 3-1 Blood gas measures (median (1st and 3rd quartile)) and associated calculations (median (1st and 3rd quartile)) obtained from 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix undergoing 3 different methods of ventilation (SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV+PEEP, pressure-controlled ventilation with positive end expiratory pressure)

			Time		Change in variable	
Variable	**Unit**	**Treatment**	**0**	**20**	**Change in value**	**Change in percent**
$PaCO_2$	mmHg	SB	54 (53, 58)	56 (54,63)	2 (0, 7)	2.9 (0.2, 11.9)
		CPAP	57 (55, 61)	58 (56, 66)	2 (-2, 3)	3.0 (-3.6, 4.7)
		PCV+PEEP	57 (54, 61)	48 (40, 52) *†	-10 (-18, -3) †	-21.9 (-45.0, -5.1) †
PaO_2	mmHg	SB	203 (192, 212)	208 (197, 224)	2 (-3, 9)	1.5 (-1.7, 4.1)
		CPAP	195 (178, 208)	202 (191, 219)	4 (-2, 13)	2.1 (-0.8, 6.5)
		PCV+PEEP	209 (191, 219)	222 (204, 237) *†	17 (7, 23) †	8.9 (3.1, 9.7) †
SaO_2	%	SB	99.7 (99.7, 99.8)	99.7 (99.7, 99.8)	0 (0, 0)	0.0 (0.0, 0.0)
		CPAP	99.7 (99.6, 99.8)	99.7 (99.7, 99.8)	0 (0, 0.1)	0.0 (0.0, 0.1)
		PCV+PEEP	99.7 (99.6, 99.8)	99.8 (99.7, 99.8)	0 (0, 0.3)	0.0 (0.0, 0.3) †
aHt	%	SB	45 (36, 47)	44 (36, 47)	-1 (-1, 0) †	-1.1 (-3.0, 0.0) †
		CPAP	44 (37-48)	44 (37, 46)	-1 (-2, 0) †	-2.3 (-4.2, 0.0) †
		PCV+PEEP	43 (38, 46)	45 (37, 46)	0 (-1, 0)	0.0 (-1.3, 0.0)
$PcvCO_2$	mmHg	SB	57 (54, 62)	60 (57, 64)	1 (0, 5)	1.6 (-0.53, 8.14)
		CPAP	60 (55, 64)	61 (58, 64)	1 (0, 2)	1.0 (-0.6, 4.0)
		PCV+PEEP	59 (58, 64)	53 (43, 57) *†	-10 (-12, -3) †	-19.8 (-28.1, -6.3) †
$PcvO_2$	mmHg	SB	64 (59, 71)	65 (62-70)	1 (-2, -4)	1.2 (-3.4, 6.3)
		CPAP	63 (61, 67)	64 (60, 67)	0 (-2, 2)	0.2 (-2.6, 2.5)
		PCV+PEEP	65 (63, 68)	54 (52, 56) *†	-10 (-12, -8) †	-18.6 (-25.2, -14.6) †
$ScvO_2$	%	SB	84 (82, 87)	85 (83, 87)	0 (-1, 3)	-0.4 (-1.6, 3.5)
		CPAP	84 (81, 88)	84 (81, 87)	-1 (-2, 1)	-1.0 (-2.7, 0.6)
		PCV+PEEP	85 (83, 87)	80 (79, 83) *†	-5 (-7, -2) †	-5.5 (-8.8, -2.3) †
cvHt	%	SB	44 (37, 46)	43 (35, 45)	-1 (-1, 0)	-2.2 (-2.6, 0.0)
		CPAP	42 (37, 46)	42 (37, 45)	-1 (-1, 0)	-2.2 (-2.9, 0.0)
		PCV+PEEP	41 (37, 46)	43 (37, 45)	0 (-1, -1)	0.0 (-2.4, 2.5)
P: F	N/A	SB	406 (381, 429)	408 (394, 438)	4 (-7, 17)	0.8 (-1.6, 4.3)
		CPAP	385 (355, 419)	400 (383, 439)	9 (-2, 26)	2.1 (-0.6, 7.0)
		PCV+PEEP	415 (389, 432)	453 (408, 478) *†	33 (15, 54) †	10.1 (3.4, 13.4) †
P(A-a) O_2	mmHg	SB	30 (17, 40)	19 (7, 39) *	-7 (-14, 1)	-15.5 (-48.4, 36.4)
		CPAP	33 (18, 44)	20 (9, 39) *	-10 (-17, 0)	-27.9 (-61.6, 4.9)
		PCV+PEEP	23 (11, 46)	16 (13, 38) *	-4 (-10, 4)	-13.2 (-24.9, 33.8)
Est $\dot{Q}_s/\dot{Q}_t$	%	SB	2.4 (1.5, 3.8)	1.9 (0.7, 4.2) *	-0.7 (-1.0, 0.1)	-16.7 (-38.0, 32.9)
		CPAP	3.0 (1.3, 4.3)	1.5 (0.7, 3.4) *	-0.7 (-1.7, 0.0)	-30.2 (-59.6, 11.3)
		PCV+PEEP	2.0 (0.8, 4.4)	1.1 (0.7, 3.0) *	-0.6 (-1.4, 0.0)	-16.0 (-39.7, 45.6)
CaO_2-$CcvO_2$	mL dL^{-1}	SB	3.3 (3.0, 3.9)	3.2 (2.9, 4.1)	0.0 (-0.8, 0.2)	0.7 (-18.8, 6.7)
		CPAP	3.4 (3.1, 4.0)	3.5 (3.2, 3.7)	0.1 (-0.3-0.2)	2.4 (-8.8, 7.3)
		PCV+PEEP	3.3 (3.1, 3.8)	4.4 (3.9, 4.8) *†	1.1 (0.7, 1.3) †	34.2 (18.0, 40.6) †
$PaCO_2$- P_E' CO_2/ $PaCO_2$	N/A	SB	0.02 (-0.02, 0.05)	0.06 (-0.01, 0.09)	-0.01 (-0.07, 0.01)	23 (-28, 167)
		CPAP	0.07 (0.02, 0.08)	0.04 (0.01, 0.09)	-0.00 (-0.02, 0.05)	35 (-8, 95)
		PCV+PEEP	0.04 (-0.02, 0.06)	0.04 (0.00, 0.08)	-0.01 (-0.06, 0.04)	30 (-72, 194)

$PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; aHt, arterial haematocrit; $PcvCO_2$, central venous partial pressure of carbon dioxide; $PcvO_2$, central venous partial pressure of oxygen; $ScvO_2$, central venous haemoglobin saturation with oxygen; cvHt, central venous haematocrit; P:F, ratio of arterial partial pressure of oxygen to inspired fraction of oxygen; P(A-a)O_2, alveolar to arterial oxygen partial pressure gradient; Est $\dot{Q}_s/\dot{Q}_t$, estimated right-to-left intrapulmonary shunt fraction; CaO_2-$CcvO_2$, arterial to venous oxygen content difference; $PaCO_2$- P_E' CO_2/$PaCO_2$, estimate of alveolar dead space. * Statistically significant change from T0 ($p<0.05$). † Statistically different from all other treatments at the same evaluation point ($p<0.05$).

The physiological, airway gas and spirometry variable actual values, change and percent change over time are presented in Table 3-1. During PCV+PEEP, dogs had a significantly lower $P_E'CO_2$ (p = 0.001), and higher V_T (p = 0.008) and $\dot{V}_E$ (p = 0.002) at all time points compared to T0, and compared to SB (p < 0.001) and CPAP (p < 0.001) at all time points. There were no statistically significant differences in f_R from T0 for all ventilation treatments (p = 0.939) or among the ventilation treatments at all time points (p = 0.418). Confidence interval plots highlighting the change in $P_E'CO_2$, $\dot{V}_E$, V_T and f_R with time among the treatments are shown in Figure 3-4. During PCV+PEEP, the dogs' HR was significantly lower at T10, T15 and T20 compared to T0 (p = 0.023), and when compared to SB and CPAP at these time points (both: p < 0.001). Dogs HR were similar at all time points for CPAP and SB (p = 0.195). Dogs experienced a significant increase in DAP from T0 during PCV+PEEP at all time points (p = 0.018), and at T5 and T10, DAP was significantly higher during PCV+PEEP compared to both CPAP an SB (both: p < 0.001). The dogs' DAP during SB was significantly lower at T15 compared to PCV+PEEP and CPAP (both: p < 0.001). No differences from T0 or among ventilation treatments were observed for MAP (p = 0.469 and p = 0.089 respectively) and SAP (p = 0.837 and p = 0.300 respectively). The dogs experienced a significant drop in T from T0 during PCV+PEEP at T10, T15 and T20 (p = 0.042), and T was lower during PCV+PEEP compared to SB and CPAP at these time points (both: p < 0.001). T was similar between CPAP and SB at all time points (p = 0.713). There were no significant differences in SpO_2 readings from T0 for all ventilation treatments (p = 0.201) or between ventilation treatments at all time points (p = 0.999).

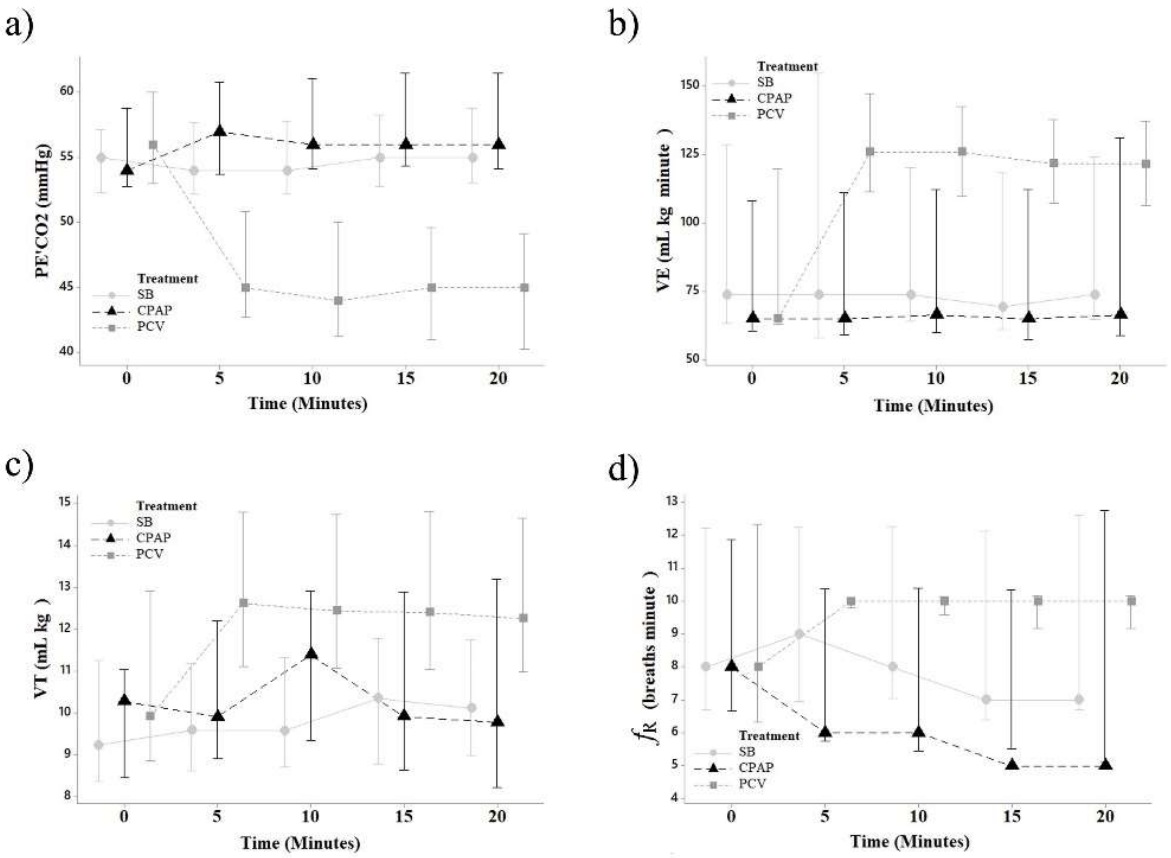

Figure 3-4 Confidence interval plots (median ± 95% confidence interval) highlighting the change in a) end-tidal carbon dioxide (PE' CO_2), b) expired minute volume ($\dot{V}_E$), c) expired V_T and d) respiratory rate (f_R) with time among the ventilation treatments in 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix. SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV, pressure-controlled ventilation with positive end expiratory pressure. The values at all time points are staggered along the x-axis for clarity.

Table 3-2 Physiological, airway gas and spirometry variables (median (1st and 3rd quartile) obtained from 15 healthy laterally recumbent anaesthetised dogs receiving a 50% oxygen-air mix undergoing 3 different methods of ventilation (SB, spontaneous breathing; CPAP, continuous positive airway pressure; PCV+PEEP, pressure-controlled ventilation with positive end expiratory pressure).

			Time				
Variable	**Unit**	**Treatment**	**0**	**5**	**10**	**15**	**20**
$P_E'CO_2$	mmHg	SB	55 (50, 57)	54 (51, 58)	54 (52, 57)	55 (52, 59)	55 (52, 59)
		CPAP	54 (51, 59)	57 (53, 61)	56 (55, 59)	56 (54, 60)	56 (53, 60)
		PCV+PEEP	56 (53, 58)	45 (42, 52) *†	44 (38, 51) *†	45 (39, 51) *†	45 (37, 50) *†
$\Delta P_E'CO_2$	mmHg	SB		0 (0, 1)	0 (-1, 1)	1 (0, 2)	1 (0, 2)
	[%]			[0.0 (0, 1.7)]	[0.0 (-1.8, 2.0)]	[1.6 (0.0, 3.5)]	[1.7 (0.0, 3.9)]
		CPAP		0 (0, 3)	1 (0, 3)	1 (1, 5)	1 (1, 4)
				[0.0 (0.0, 4.9)]	[1.9 (0.0, 4.1)]	[2.0 (1.7, 7.9)]	[2.0 (1.7, 5.3)]
		PCV+PEEP		-9 (-15, -4)	-10 (-17, -4)	-10 (-19, -4)	-10 (-20, -5)
				[-20.5 (-31.8, -9.1)] †	[-23.3 (-38.1, - 9.1)] †	[-22.2 (-41.5, -9.1)] †	[-22.2 (-45.0, -11.6)] †
$\dot{V}_E$	mL kg^{-1} $minute^{-1}$	SB	74 (54, 110)	74 (60, 100)	74 (54, 95)	70 (60, 95)	74 (62, 95)
		CPAP	65 (48, 102)	65 (49, 99)	67 (53, 103)	65 (46, 103)	67 (59, 103)
		PCV+PEEP	65 (54, 144)	126 (108, 160) *†	126 (107, 146) *†	122 (106, 134) *†	122 (105, 134) *†
$\Delta\dot{V}_E$	mL kg^{-1} $minute^{-1}$	SB		0 (0, 6)	0 (0, 7)	0 (-9, 6)	4 (-5, 8)
	[%]			[0.0 (0.0, 10.0)]	[0.0 (0.0, 6.5)]	[0.0 (-11.1, 4.6)]	[4.2 (-11.1, 9.1)]
		CPAP		0 (-6, 8)	4 (-8, 8)	0 (-7, 8)	0 (-7, 12)
				[0.0 (-10.0, 11.1)]	[4.2 (-21.4, 11.1)]	[0.0 (-13.3, 11.1)]	[0.0 (-10.0, 19.2)]
		PCV+PEEP		44 (7, 67)	44 (0, 64)	44 (0, 57)	41 (0, 57)
				[41.0 (4.6, 57.1)] †	[41.0 (0.0, 55.6)] †	[41.0 (0.0, 47.4)] †	[38.5 (0.0, 47.4)] †
V_T	mL kg^{-1}	SB	9 (8, 11)	10 (9, 11)	10 (9, 11)	10 (9, 11)	10 (9, 12)
		CPAP	10 (8, 12)	10 (8, 13)	11 (8, 13)	10 (7, 14)	10 (7, 14)
		PCV+PEEP	10 (8, 14)	13 (11, 16) *†	12 (11, 16) *†	12 (11, 17) *†	12 (11, 16) *†
ΔV_T	mL kg^{-1}	SB		0 (-1, 1)	0 (0, 1)	0 (0, -1)	0 (0, -1)
	[%]			[1.2 (-4.4, 5.5)]	[1.7 (-0.6, 4.8)]	[2.7 (-3.5, 10.6)]	[3.0 (-2.9, 8.5)]
		CPAP		1 (0, 2)	1 (1, 2)	1 (0, 3)	1 (0, 3.0)
				[11.5 (7.1, 14.7)] †	[13.5 (5.4, 20.4)] †	[12.9 (4.9, 19.0)] †	[15.3 (2.8, 22.5)] †
		PCV+PEEP		2 (0, 4)	2 (0, 4)	2 (0, 4)	2 (0, 4)
				[17.3 (3.1, 27.3)] †	[17.3 (4.4, 26.6)] †	[17.1 (3.8, 27.3)] †	[16.0 (3.2, 27.6)] †
f_R	breaths $minute^{-1}$	SB	8 (6, 14)	9 (5, 13)	8 (6, 12)	7 (5, 13)	7 (6, 13)
		CPAP	8 (6, 14)	6 (4, 12)	6 (4, 13)	5 (4, 13)	5 (5, 13)
		PCV+PEEP	8 (5, 12)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)
Δf_R	breaths $minute^{-1}$	SB		1 (-1, 1)	1 (-1, 1)	0 (-1, 1)	0 (0, 2)
	[%]			[4.8 (-14.3, 11.1)]	[9.1 (-7.1, 20.0)]	[0.0 (-15.4, 9.1)]	[0.0 (0.0, 16.7)]
		CPAP		-1 (-2, 0)	-1 (-3, 0)	-1 (-3, 0)	-1 (-3, 0)
				[-11.8 (-22.2, 0.0)]	[-18.8 (-33.3, 0.0)]	[-18.8 (-50.0, 0.0)]	[-20.0 (-33.3, 0.0)]
		PCV+PEEP		2 (-2, 5)	1 (-2, 5)	0 (-2, 5)	0 (-2, 5)
				[20.0 (-20.0, 50.0)]	[12.5 (-20.0, 50.0)]	[0.0 (-20.0, 50.0)]	[0.0 (-20.0, 50.0)]
$P_{mean\text{-}AW}$	cmH2O	SB	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)	1 (1, 1)
		CPAP	1 (1, 1)	5 (5, 6) *†	5 (5, 6) *†	5 (5, 6) *†	5 (5, 6) *†
		PCV+PEEP	1 (1, 1)	8 (8, 8) *†	8 (8, 8) *†	8 (8, 8) *†	8 (8, 8) *†
HR	beats $minute^{-1}$	SB	79 (69, 92)	77 (75, 96)	80 (77-96)	78 (75-94)	80 (75-92)
		CPAP	80 (74, 91)	78 (71, 90)	80 (70-86)	79 (71-84)	79 (66-82)
		PCV+PEEP	80 (76, 88)	75 (62, 85)	73 (63-83) *†	70 (61-79) *†	69 (61-80) *†
ΔHR	beats $minute^{-1}$	SB		2 (0, 6)	2 (-1, 9)	2 (-1, 4)	3 (-2, 6)

	[%]			[2.3 (0.0, 8.0)]	[2.8 (-1.3, 10.1]	[2.6 (-1.5, 4.6)]	[4.2 (-2.1, 8.0)]
		CPAP		-1 (-3, 0)	-1 (-4, 2)	-3 (-7, 0)	-5 (-8, 1)
				[-1.3 (-4.2, 0.0)]	[-1.1 (-4.8, 2.6)]	[-3.3 (-8.8, 0.0)]	[-5.7 (-11.6, 1.2)]
		PCV+PEEP		-6 (-12, -5)	-11 (-14, -4)	-13 (-18, -8)	-14 (-16, -9)
				[-11.6 (-18.3, -6.7)] †	[-15.7 (-25.0, -4.4)] †	[-18.5 (-31.2, -10.5)] †	[-20.0 (-31.2, -11.3)] †
MAP	mmHg	SB	73 (67, 80)	71 (66, 76)	70 (67, 74)	69 (67, 72)	71 (67, 75)
		CPAP	70 (66, 78)	72 (68, 77)	70 (68, 75)	70 (67, 74)	69 (65, 73)
		PCV+PEEP	69 (67, 72)	70 (69, 80)	72 (68, 81)	72 (68, 82)	72 (67, 80)
SAP	mmHg	SB	102 (96, 110)	101 (96, 111)	100 (93, 109)	100 (95, 110)	101 (98, 108)
		CPAP	99 (96, 111)	106 (97, 118)	102 (96, 115)	103 (96, 115)	100 (94, 110)
		PCV+PEEP	102 (95, 107)	102 (93, 116)	102 (96, 118)	104 (94, 118)	101 (93, 119)
DAP	mmHg	SB	57 (53, 66)	57 (54, 62)	56 (54, 60)	56 (53, 59) †	57 (54, 60)
		CPAP	56 (53, 65)	57 (55, 64)	57 (55, 62)	58 (54, 61)	57 (52, 60)
		PCV+PEEP	56 (55, 59)	60 (57, 67) *†	60 (56, 68) *†	60 (56, 65) *	60 (55, 66) *
T	°C	SB	36.0 (35.5, 36.4)	35.9 (35.5, 36.3)	36.0 (35.6, 36.3)	36.0 (35.6, 36.4)	36.0 (35.6, 36.4)
		CPAP	35.9 (35.7, 36.7)	36.0 (35.7, 36.4)	36.1 (35.7, 36.4)	36 (35.8, 36.4)	36.1 (35.8, 36.3)
		PCV+PEEP	36.3 (35.8, 36.5) †	35.8 (35.4, 36.2)	35.7 (35.4, 36.2) *†	35.7 (35.3, 36.2) *†	35.6 (35.3, 36.1) *†
SpO_2	%	SB	95 (94, 95)	94 (94, 95)	94 (94, 95)	94 (93, 95)	94 (93, 95)
		CPAP	95 (94, 96)	94 (94, 95)	95 (94, 95)	94 (94, 95)	94 (94, 95)
		PCV+PEEP	95 (94, 96)	94 (94, 96)	95 (94, 96)	95 (94, 96)	94 (94, 96)

P_E' CO2, end-tidal carbon dioxide partial pressure; Δ P_E' CO2, change in end-tidal carbon dioxide partial pressure from T0; $\dot{V}_E$, minute volume normalised to body mass; $\Delta\dot{V}_E$, change in minute volume normalised to body mass from T0; V_T, tidal volume normalised to body mass; Δ V_T, change in tidal volume normalised to body mass from T0; $P_{mean\text{-}AW}$, mean airway pressure; Δf_R, respiratory rate; Δ f_R, change in respiratory rate from T0; HR, heart rate; ΔHR, change in heart rate from T0; MAP, mean arterial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; T, oesophageal temperature; SpO_2, arterial haemoglobin oxygen saturation measured by pulse oximetry. * Statistically significant change from T0 ($p<0.05$). † Statistically different from all other treatments at the same evaluation point ($p<0.05$).

Chapter 4

4.1 Discussion

The administration of short-term, invasive CPAP to healthy, laterally recumbent, anesthetised dogs demonstrated no advantage or disadvantage over SB in terms of the arterial oxygenation, CO_2 elimination and other cardiopulmonary variables evaluated in this study. Invasive PCV+PEEP was advantageous over CPAP and SB in terms of arterial oxygenation and CO_2 elimination. Nevertheless, the lower $ScvO_2$, $PcvO_2$ and higher CaO_2-$CcvO_2$ noted with PCV+PEEP, as compared to CPAP and SB, suggests increased tissue O_2 extraction. This increased O_2 extraction was most likely due to a reduction in cardiac output, which itself was partly due to a lower HR with PCV+PEEP.

The variability in PaO_2 in anaesthetised patients without alveolar diffusion impairments and receiving an equivalent FiO_2, depends on the extent of tissue O_2 extraction, level of alveolar ventilation, extent of intrapulmonary right-to-left shunting and variability in ventilation to perfusion ($\dot{V}/\dot{Q}$) ratios (Nunn 1964; Nunn et al. 1965). The value of P_AO_2 determines the maximum achievable PaO_2. The P_AO_2 achieved depends on the balance between O_2 delivery to the alveoli through ventilation and O_2 removal by pulmonary circulation (Petersson & Glenny 2014). Thus, if alveolar perfusion remains constant, the P_AO_2 will depend on alveolar ventilation. In the present study, $\dot{V}_E$, as a result of an increased V_T, was significantly greater with PCV+PEEP. This greater $\dot{V}_E$ likely contributed to the higher PaO_2 and P:F ratio noticed with this ventilation treatment. The $\dot{V}_E$ was similar between CPAP and SB, which is one reason to explain similar levels of PaO_2 between these ventilation treatments. The value of Est $\dot{Q}s/\dot{Q}t$ in this study represents a theoretical value of venous admixture, including both true right-to-left intrapulmonary shunting and areas of low $\dot{V}/\dot{Q}$ ratios. The estimated shunt fraction in the

present study was calculated using central venous O_2 content as a surrogate for mixed venous O_2 content. Although individual values of oxygenation derived from central venous samples vary from mixed venous samples, the two correlate well and are generally close to one another, even under conditions of varying cardiac output (Reinhart et al. 1989; Berridge 1992; Shepherd & Pearse 2009). Shunt fraction calculation using venous O_2 content derived from jugular samples has also been shown to correlate with shunt fraction calculation using mixed venous O_2 content in anaesthetised horses (van Loon et al. 2018). Given that there was no significant difference in Est $\dot{Q}s/\dot{Q}t$ amongst the ventilation treatments, it is unlikely that a reduction in intrapulmonary right-to-left shunt or areas of low $\dot{V}/\dot{Q}$ contributed to the improved PaO_2 noted with PCV+PEEP. The trans-alveolar pressures achieved with PCV+PEEP and CPAP in this study were probably too low to significantly improve ventilation to the few alveoli with low or absent ventilation (Rothen et al. 1999). A narrowing of $P(A\text{-}a)O_2$ would be expected with a reduction in the number of alveoli with low $\dot{V}/\dot{Q}$ ratios or with recruitment of atelectatic alveoli. No difference in $P(A\text{-}a)O_2$ amongst the treatments suggests that improvement in alveolar ventilation was the predominate factor causing improved PaO_2 and P:F ratios in the PCV+PEEP group. The decrease in $P(A\text{-}a)O_2$ and Est $\dot{Q}s/\dot{Q}t$ from T0 to T20 in all treatments groups suggests alveolar recruitment with time. The most probable explanation for this alveolar recruitment was the change in FiO_2 from 1.0 to 0.5 prior to initiating the study.

A lower body temperature, decreased muscular energy expenditure and improved alveolar ventilation may have contributed to a lower $PaCO_2$, $PcvCO_2$ and $P_E'CO_2$ observed with PCV+PEEP (Henneberg et al. 1987; Manthous et al. 1995; Bacher 2005; Treger et al. 2010). The significantly higher $\dot{V}_E$ with PCV+PEEP was likely the primary factor contributing to the lower $PaCO_2$, $PcvCO_2$ and $P_E'CO_2$. The increase in FRC that is known to occur with CPAP, may

only be of benefit on pulmonary ventilation if it results in recruitment of atelectatic lung, shifting tidal ventilation to a more compliant part of the static pressure-volume curve (Katz & Marks 1985). A more compliant lung results in a greater V_T for a given respiratory effort (change in P_{trans}). In our study it is probable that the gain in FRC with CPAP resulted in very little improvement in pulmonary compliance, thus no significant differences in V_T were noted from SB. Even when the addition of CPAP does improve V_T, $PaCO_2$ does not seem to change as there is also a concomitant reduction in f_R as seen here (Katz & Marks 1985). This phenomenon is not surprising given that the neural mechanisms responding to pH, $PaCO_2$ and PaO_2 are still in control of ventilation with CPAP as they are with SB. Theoretically, when CPAP improves compliance and subsequently decreases the WOB, it may prevent earlier respiratory fatigue and thus be able to maintain a given $PaCO_2$ for a longer period of time as compared to SB at a lower pulmonary compliance. $PaCO_2$-$P_E'CO_2/PaCO_2$ was used to assess variability in alveolar dead space in our study (Nunn & Hill 1960; Hardman & Aitkenhead 1999). Although no significant differences in $PaCO_2$-$P_E'CO_2/PaCO_2$ were noted amongst the ventilation treatments, it is difficult to make meaningful conclusions in terms of equivalence in alveolar dead space. This is because of the influence of multiple factors affecting the relationship between $PaCO_2$-$P_E'CO_2/PaCO_2$ and alveolar dead space. For example, increasing $P_{mean\text{-}AW}$ results in an increase in both alveolar and anatomical dead space, both of which have opposing effects on the value of $PaCO_2$-$P_E'CO_2/PaCO_2$ (Dueck et al. 1977; Hedenstierna et al. 1979; Marini & Ravenscraft 1992b; Hardman & Aitkenhead 1999).

The O_2 content of blood is dependent primarily on Hb content and the extent of its saturation with O_2. In terms of SaO_2 and haematocrit, no significant differences were found between ventilation treatments. Therefore, CaO_2 was likely similar among treatments. Similarly, cvHt was also similar amongst treatments. Thus, we speculate that the primary cause of the

increase in CaO_2-$CcvO_2$ with PCV+PEEP was due to the decrease in $ScvO_2$. A decrease in $ScvO_2$ is due either to a decrease in delivery of O_2 to the tissues, as occurs with a decrease in cardiac output, or an increase in tissue O_2 consumption (Shepherd & Pearse 2009). With regards to tissue O_2 consumption, even though tissue O_2 consumption can be expected to increase as the severity of respiratory acidosis deceases (with improved $\dot{V}_E$ that occurs with IPPV), it has been shown that tissue O_2 consumption decreases with institution of IPPV, most likely due to removal of the work performed by the respiratory musculature (Khambatta & Sullivan 1973; Manthous et al. 1995; Jubrias et al. 2003). Another factor affecting tissue O_2 extraction and consumption is body temperature, with lower temperatures, as with PCV+PEEP, decreasing O_2 extraction and consumption (Badeer 1956; Oda et al. 2002). However, the most likely factor contributing to the decrease in $ScvO_2$ and increase in CaO_2-$CcvO_2$ with PCV+PEEP was a decrease in O_2 delivery, more specifically a decrease in cardiac output (Lutch et al. 1972). There are three mechanisms that are most likely responsible for a reduction in cardiac output with PCV+PEEP. Namely, a reduction in sympathetic tone through a decrease in $PaCO_2$, an increase in intrathoracic pressures having both mechanical and autonomic effects, and an increased pulmonary vascular resistance (Morgan et al. 1966; Norman & Atkinson 1970; Fietze et al. 2004). Elevated $P_{mean\text{-}A}$ with CPAP could be expected to have the same effect on decreasing cardiac output. However, the level of CPAP used in this study was likely too low to raise intrathoracic pressures enough to affect cardiovascular function. The initial effect of a decreased cardiac output during mechanical ventilation is arteriolar vasoconstriction, preserving or slightly increasing blood pressure, (Selldén et al. 1989; Peters et al. 1997). The suggested mechanism responsible for arteriolar vasoconstriction is a decreased transmural pressure of the low-pressure cardiopulmonary baroreceptors located in the heart (Selldén et al. 1989). This arteriolar vasoconstriction may have contributed to the significantly higher DAP

noticed with PCV+PEEP. However, with greater decreases in cardiac output, arterial blood pressure will eventually drop and HR will increase (Mirro et al. 1987; Canfrán et al. 2013). Increased pulmonary stretch, as would occur with higher V_T, is associated with decreased sympathetic supply to the heart and subsequent reduction in HR (Seals et al. 1990; Fietze et al. 2004). Increased pulmonary stretch with the higher V_T seen with PCV+PEEP may have contributed to the significantly lower HR, which itself could have contributed to a decrease in cardiac output. Besides reduction in HR, a reduction in myocardial performance and systemic vascular resistance also occurs with increased pulmonary stretch (Glick et al. 1969). The effect on the sympathetic nervous system likely varies with the degree of lung inflation (Greenwood et al. 1980). Lastly, the elevated V_T with PCV+PEEP may have contributed to an increase in pulmonary vascular resistance. In summary, the overall effect of increased $P_{mean\text{-}A}$ on cardiovascular variables will likely depend on an interaction between mechanical factors and the autonomic nervous system.

Heat loss through the respiratory system occurs via evaporation, convection and CO_2 decompression from carbonic acid (H_2CO_3), all of which are increased with an increase in $\dot{V}_E$ (Burch 1945). Thus, it is not surprising that T was significantly lower with PCV+PEEP.

4.2 Limitations

There are a number of limitations of this study. The sample size of this study was calculated only to detect significant changes in $PaCO_2$. Thus, it may not have been large enough to detect changes in all the evaluated variables. The sample size was however, similar to other dog studies evaluating a similar level of CPAP (also taking the crossover design into consideration),

that did find significant changes in other cardiopulmonary variables (Staffieri et al. 2014; Meira et al. 2018).

As the three treatments were tested sequentially in each dog, there was the potential for the preceding treatment to affect the results of the subsequent treatment. Although it is impossible to be certain if the 5-minute SB period between treatments was enough time for all evaluated variables to reach a new equilibrium, no significant differences were detected been treatments at T0 (except for temperature). A five minute period after the removal of applied airway pressures (PCV+PEEP or CPAP) would have at least been sufficient for a new equilibrium to have be established for the oxygenation variables measured (Chiumello et al. 2013). From induction of anaesthesia to instrumentation, the dogs were kept on a FiO_2 of 1.0 with sufficient time for absorption atelectasis to develop in some alveoli (Dantzker et al. 1975). As no recruitment manoeuvre was applied before the reduction in FiO_2, absorption atelectasis may have persisted into the study. With the reintroduction of nitrogen into the lungs (with reduction of FiO_2) subsequent recruitment may have occurred with time, blunting any treatment effects that may have been seen if FiO_2 was kept constant. Each treatment was applied for 20 minutes, thus, it is difficult to extrapolate what might occur with prolonged administration of each treatment, as may be the case in clinical practice.

The dogs were kept in a lateral recumbency to simulate what may occur in an ICU, however, different positioning is known to affect the distribution of ventilation and perfusion during anaesthesia (Nyrén et al. 2010; Ambrisko et al. 2017).

As medetomidine has profound physiological effects, its effect on our study results should be briefly discussed. Most notably, at doses used in this study, medetomidines causes a significant reduction in cardiac output (Pypendop & Verstegen 1998). This decrease in cardiac

output has been shown to result in increase in tissue oxygen extraction, potentially lowering $ScvO_2$ and subsequently PaO_2 (Lawrence et al. 1996; Ko et al. 2000). The effects of medetomidine on ventilation perfusion matching in the dog are not well described. However, the administration of medetomidine appears to have little vasoactive effects on the pulmonary vasculature in the dog (Pypendop & Verstegen 1998). In humans undergoing one lung ventilation, the infusion of dexmedetomidine has been shown to improve ventilation-perfusion matching independent of its direct effects on the alpha 2 adrenoceptors or on lowering isoflurane requirements (Xia et al. 2015). In terms of ventilation, medetomidine has not been shown to effect minute ventilation and thus $PaCO_2$ (Kuusela et al. 2000). Given the time period from medetomidine administration to initiation of ventilation treatments, these physiological effects mentioned would have persisted into the study as well as decreased with time (Pypendop & Verstegen 1998). Thus, the overall $\dot{V}/\dot{Q}$ ratio of the lung may have decreased with time as the effects of medetomidine diminished. In terms of our study, the actual values for arterial oxygenation, venous oxygenation and calculated variables may have been different if medetomidine was not used. However, due to the time standardisation of the study procedures and the randomisation of ventilation treatments, it is unlikely that the use of medetomidine would have influenced study conclusions.

Lastly, as mentioned previously, the FiO_2 will influence the extent of alveolar atelectasis, thus using an FiO_2 higher than 0.5 may have had different results.

4.3 Conclusion

In healthy anaesthetised dogs positioned in right lateral recumbency, the administration of short-term, low-level, invasive CPAP resulted in comparable levels of oxygenation, ventilation

and cardiac function to that seen with SB. The use of PCV+PEEP resulted in significantly improved arterial oxygenation and CO_2 elimination as compared to both CPAP and SB. This improvement was attributed to greater alveolar minute ventilation as a result of an increased V_T. A notable effect associated with PCV+PEEP was a reduction in venous O_2 tensions and saturations, resulting in a greater arterial to venous O_2 content difference. The most likely cause of this observation was a decrease in cardiac output. The clinical benefit of short-term CPAP over SB in the healthy anaesthetised dog remains uncertain.

4.4 Future research and recommendations

Future research needs to be conducted to establish the role of CPAP in dogs with diseased lungs (such as patients with pneumonia, pulmonary oedema and acute respiratory distress syndrome) where a greater amount of atelectatic lung can be expected to exist. Similarly, in patients receiving a higher FiO_2, CPAP may have produced a different outcome to SB in terms of both oxygenation and CO_2 elimination (when anaesthetic periods are long enough to produce respiratory fatigue). In patients with left ventricular failure, the increase in intrathoracic pressures associated with IPPV decreases left ventricular afterload with subsequent increase in cardiac output (Corredor & Jaggar 2013). Thus, patients with altered cardiac function may have also demonstrated different outcomes from this study. Also, patients with cardiac failure may present with pulmonary oedema, thus there are also theoretical benefits of CPAP with spontaneously generated breaths through improved alveolar recruitment. Thus, future research is needed to identify what the value of CPAP in comparison to PCV+PEEP may be in these patients.

In terms of recommendations derived from the current study, in healthy laterally anesthetised dogs receiving an FiO_2 of 0.5, there does not appear to be a clinical benefit or disadvantage of using CPAP over SB. If hypoventilation is significant, IPPV should be initiated to manipulate blood gas tensions.

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Addendum

Animal ethics approval certificate

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Veterinary Science
Animal Ethics Committee

7 April 2020

Approval Certificate
New Application

AEC Reference No.:	REC216-19
Title:	The cardiorespiratory effects of constant positive airway pressure and pressure controlled ventilation with positive end expiratory pressure in anaesthetised dogs.
Researcher:	Dr KJ Boustead
Student's Supervisor:	Prof GE Zeiler

Dear Dr KJ Boustead,

The **New Application** as supported by documents received between 2019-10-11 and 2020-04-03 for your research, was approved by the Animal Ethics Committee on its quorate meeting of 2020-04-03.

Please note the following about your ethics approval: Please use current UP letterhead for the informed consent document.

1. The use of species is approved:

Species and Samples	Number
Dogs	18
Arterial blood	6 ml each
Venous blood	6 ml each

2. Ethics Approval is valid for 1 year and needs to be renewed annually by 2021-04-07.
3. Please remember to use your protocol number (REC216-19) on any documents or correspondence with the AEC regarding your research.
4. Please note that the AEC may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.
Yours sincerely

Prof V Naidoo
CHAIRMAN: UP-Animal Ethics Committee

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Fakulteit Veeartsenykunde
Lefapha la Diseanse tša Bongakadiruiwa

Informed consent form

INFORMED CONSENT FORM

We, the undersigned, hereby agree that the animal(s), as specified below, may be used by the researcher(s), as specified below, in the procedures as explained below:

1. To be completed by the researcher(s)

- **NAME OF THE RESEARCHER(S):** Dr Keagan Boustead**,** Prof Gareth Zeiler

- **NAME OF RESEARCH PROJECT:** Cardiopulmonary effects of three different ventilation treatments in healthy anaesthetised dogs

- **PURPOSE OF RESEARCH PROJECT:** CPAP and PCV are two different ways of ventilating a dog under anaesthesia with a mechanical ventilator. The one supports the dog's normal ventilation while the other takes complete control over respiration. This study will help identify if the use of CPAP can keep up with PCV in terms of ventilation as well as if it is advantageous over PCV in terms of improving blood oxygenation and oxygen delivery to body cells in ventilated patients. This will be knowledge will be valuable in anaesthetic and ICU cases requiring ventilation.

- **DETAILED PROCEDURE(S) TO BE PERFORMED:** The dog will be premedicated (drug administered before anaesthesia to provide pain prevention and sedation) with buprenorphine (pain killer) (im; 0.02 mg/kg; Temgesic 0.3 mg/ml) and medetomidine (sedative and pain killer) (im; 5ug/kg; Domitor 1000ug/ml). Thirty minutes after premedication, an over the needle catheter (18G; Jelco) will be placed in one of the cephalic veins (a vein of the front leg) and

anaesthesia will be induced with Propofol (a general anaesthetic) (iv; to effect; Propoven 10 mg/ml). An endotracheal tube (a tube specifically designed for tracheal placement) will be placed into the trachea via the mouth. The endotracheal tube will be connected to an anaesthetic machine in order to provide oxygen and the inhalational anaesthetic agent isoflurane (Isofor, Safeline) via circle breathing system. A drip (lactated Ringer's Solution) will be administered at 5 ml/kg/hour for the duration of the general anaesthetic. These procedures described above are routine procedures that are normally performed on all dogs requiring anaesthesia.

Once asleep, the dog will be instrumented as follows:

1) a three-lumen central venous catheter (25 cm; 12Fr) will be placed into the left jugular vein. This is a type of catheter with a larger lumen that will allow blood to be drawn through it without having to prick the patient multiple times. We normally place these catheters in dogs that require frequent blood sampling, long term drips and large amount of intravenous fluids.
2) an arterial catheter (5 cm; 22G) will be placed into a dorsal pedal artery. This is a small catheter that is placed in to the artery on top of the foot to allow sampling of arterial blood without pricking the patient multiple times.
3) a multiparameter monitor (Carescape B450) will be used to monitoring physiological variables (such as heart rate, respiratory rate, blood pressure etc.) continuously but recorded at study intervals as per the data collection requirements.

Treatments

Once instrumented and spontaneously breathing the experiment will begin. PCV + PEEP and CPAP will be applied via the ventilator built into the anaesthetic machine (Carestation 650).

Castration

Dogs will be castrated once the experiment is complete. Five minutes prior to removing the testicles a local anaesthetic (2mg/kg, lignocaine 20mg/ml) will be injected into the spermatic chord where the nerves of the testicle run. This is an additional measure to assist in pain control.

Recovery

Once all treatments have been performed the experiment will end. If the last treatment was PCV + PEEP or CPAP the dog will be weaned from the ventilator, to make sure they are

adequately ventilating before termination of general anaesthesia. At this point intensive monitoring will end and all instruments and probes will be removed. Once the patient is spontaneously breathing the inhalation agent will be switched off and the patient will be disconnected from the breathing system. The cuff of the endotracheal tube deflated and the dog will then be moved to a recovery area. The following parameters will be monitored during the recovery period: heart rate, respiratory rate, peripheral pulse quality, capillary refill time and rectal temperature. Heating through warm air circulating blankets will be stopped once a rectal temperature reaches 37 degrees Celsius.

- **RISK(S) INVOLVED IN SPECIFIED PROCEDURE:** Potential complication of this study includes haematoma (bruise) formation at the arterial and venous catheter sites. To prevent this digital pressure will be applied for five minutes after catheter removal. In cases where excessive haemorrhage occurs at the central venous catheter site, a suture will be placed in the skin after catheter removal. The volumes and pressures used for ventilation in this study are considered to be safe. Many dogs and humans are routinely ventilated under anaesthesia with the same parameters without any complication. The dogs will be shaved in the neck region and both on the front and hind limbs.

- **IDENTIFICATION OF ANIMAL TO BE USED:**

- **UNMISTAKEABLE DISTINGUISHING DESCRIPTION OF ANIMAL TO BE USED:**

2. To be completed by the animal's owner or person duly authorized to sign on his/her behalf:

- **NAME OF OWNER:**

- **HAVE YOU RECEIVED DETAILED INFORMATION REGARDING THE PROPOSED STUDY?**

- **HAVE ALL THE RISKS INVOLVED IN THE PROCEDURE BEEN EXPLAINED TO YOU AND DO YOU FULLY UNDERSTAND THESE RISKS?**

- **DO YOU GRANT FULL CONSENT FOR THE PROCEDURE TO BE PERFORMED?**

3. The undersigned parties further agree that no compensation will be payable to the animal's owner or anybody else and that all research associated costs will be covered by the researcher(s).

4. The undersigned parties further agree that this form would serve to fully indemnify the University of Pretoria and the undersigned researcher(s) against any future claims resulting from the specified procedure by or on behalf of the animal's owner.

5. The undersigned parties further agree that no material of any kind, including data and research findings, obtained or resulting from the procedure, would be passed on to any third party or used for any purpose other than that specified in this form, except with the written consent of the undersigned owner of the animal.

_____ _____

SIGNATURE RESEARCHER(S) **SIGNATURE OWNER**

_____

SIGNATURE WITNESS

DATE: _____

Data collection form

Comparison of the cardiopulmonary effects of three different ventilation treatments in healthy anaesthetised dogs

Researcher: Dr K Boustead

Patient detail

Patient number	
Age	
Breed	
Weight	
Thoracic Conformation	
BCS	
Fasted Y/N	

Pre experimental examination

Heart rate		Peripheral pulse quality	
Respiratory rate		Packed cell volume	
Mucous membrane colour		Serum creatinine	
CRT		Blood smear	
Temperature			

Premedication, induction and instrumentation. NO MIX

Drug	Volume	Time
Buprenorphine (0.03mg/kg)		
Medetomidine (10ug/kg)		

30 minutes

Task	Completed tick
Cephalic catheter	
Propofol induction to effect	**Time:**
Maintain on isoflurane 100% O_2 at 20ml/kg FGF	
Administer LRS at 5ml/kg/hr	
Central venous catheter left Jugular	
Arterial catheter dorsal pedal	
Move to theatre and instrument	**Time:**

Give 15 minutes to equilibrate

MAC for dogs is 1.23-1.27% (Keep ET ISO between 1.2 – 1.4%) NB requires 15 min to equilibrate
Air 1.1L/min, oxygen 0.7L/min

Checklist prior to Treatment	**Treatment 1**	**Treatment 2**	**Treatment 3**
Et Iso at MAC			
PEEP < 1cmH20			

ABG and VBG data capture confirmation

Time	Treatment 1 S: _____ F: _____		Treatment 2 S: _____ F: _____		Treatment 3 S: _____F: _____	
	ABG	VGB	ABG	VBG	ABG	VBG
0						
20						

Physiological variables data capture confirmation

Time	Treatment 1		Treatment 2		Treatment	
	Mon 1	Mon 2	Mon 1	Mon 2	Mon 1	Mon 2
0						
5						
10						
15						
20						
NB* 10 to 15 minutes Iso MAC establishment before study starts Waiting period of spontaneous breathing between treatments.						

NOTES:

_____

_____

_____

_____

Publications

Title: Comparative blood gas effects of invasive CPAP, PCV with PEEP and spontaneous breathing in healthy anaesthetised dogs

Authors: Keagan Boustead, Roxanne Buck, Justin Grace, Gareth Zeiler

Journal: Under review: Veterinary Anaesthesia and Analgesia

Presentation

Event: IVECCS 2021 - International Veterinary Emergency and Critical Care Symposium

Date: 11/09/2021 – 15/09/2021

Title: Comparative blood gas effects of invasive CPAP, PCV with PEEP and spontaneous breathing in healthy anaesthetised dogs