

AN ABSTRACT OF THE THESIS OF

Chiara De Caro Carella for the degree of Master of Science in Veterinary Science presented on June 9, 2016

Title: Effect of Intravenous Tiletamine-zolazepam for Induction of General Anesthesia Prior to and during Maintenance with Isoflurane on Cardiorespiratory Parameters and Acid-base Status in Healthy Dogs: A Comparison with Alfaxalone, Ketamine-diazepam, and Propofol.

Abstract approved:

Ronald E. Mandsager

Abstract:

The effects of alfaxalone (A-HPCD), propofol (P), ketamine-diazepam (KD) and tiletamine-zolazepam (TZ) administered IV in dogs on cardiovascular and respiratory systems, acid-base balance and electrolytes have been reported in the literature, but a study that compares IV TZ to the other induction protocols (IP) is needed. Six dogs enrolled in a randomized-crossover study were anesthetized with sevoflurane and instrumented. After at least 30 minutes post-recovery, baseline values for cardiovascular and respiratory parameters were determined, cardiac output (CO) measured via thermodilution, and arterial (Art) and mixed venous (MV) blood samples collected. Anesthesia was

induced with A-HPCD (4 mg/kg), P (6 mg/kg), KD (7 and 0.3 mg/kg, respectively), or TZ (5 mg/kg) administered IV in quarter increments to effect, and maintained with isoflurane ($Et_{Iso} 1.14 \pm 0.32\%$) for 60 minutes. Immediately post-induction (PI) and at 10, 20, 40, and 60 minutes all measurements were repeated and blood sampled. Derived hemodynamic parameters were calculated. Cardiorespiratory and acid-base parameters compared with RM-ANOVA and a post-hoc t-test were considered significant when $p < 0.05$. The parameter most affected by protocol was heart rate (HR), with TZ producing the highest HR PI and at 40 and 60 minutes. Oxygen delivery (DO_2) was best maintained by TZ in the first 20 min, while A-HPCD maintained the highest DO_2 at 60 minutes. No significant differences for CO, cardiac index, mean arterial pressure, and systemic vascular resistance were found among IP. Although still within normal limits, mean MV pH, Art and MV potassium were similarly increased with TZ and KD compared to P and A-HPCD. Although statistical significance was found for $EtCO_2$, pH, lactate, and serum potassium, values stayed in the normal clinical range. TZ produced comparable respiratory changes to KD. Intravenous induction of general anesthesia with TZ maintained on isoflurane is a safe alternative to A-HPCD, KD, and P in healthy dogs and it is recommended for short anesthetic procedures.

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Prior to and during Maintenance with Isoflurane on Cardiorespiratory Parameters and
Acid-base Status in Healthy Dogs: A Comparison with Alfaxalone, Ketamine-diazepam,
and Propofol

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APPROVED:

Major Professor, representing Veterinary Science

Dean of the College of Veterinary Medicine

Dean of the Graduate School

I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

Chiara De Caro Carella, Author

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TABLE OF CONTENTS

	<u>Page</u>
1. Introduction.....	2
2. Objectives and Hypothesis.....	6
3. Literature Review.....	8
3.1. General Anesthesia.....	8
3.2. Anesthetic Risk.....	9
3.3. Respiratory Physiology for Anesthesia.....	10
3.4. Cardiovascular Physiology for Anesthesia.....	17
3.5. Acid-Base Balance and Electrolytes and Anesthesia.....	27
3.6. Anesthetic Agents.....	34
3.6.1. Tiletamine-Zolazepam.....	34
3.6.2. Alfaxalone-HPCD.....	38
3.6.3. Ketamine-Diazepam.....	42
3.6.4. Propofol.....	46
3.6.5. Isoflurane.....	48
3.6.6. Recovery from General Anesthesia.....	49
4. Materials and Methods.....	62
4.1. Ethical Approval.....	62
4.2. Study Design.....	62
4.3. Animals.....	62
4.4. Techniques.....	63
4.4.1. Arterial Blood Pressure Measurements.....	63
4.4.2. Cardiac Output Measurement.....	65
4.5. Phase I: Instrumentation.....	69
4.6. Phase II: Recovery from phase I.....	71
4.7. Phase III: Measurements.....	72
4.8. Phase IV: Recovery from Phase III.....	77
4.9. Post-hoc Calculated Parameters.....	78
4.10. Recovery Scores.....	78

	<u>Page</u>
4.11 Statistical Analysis.....	79
5. Results.....	88
5.1. Cardiovascular Effects.....	89
5.2. Respiratory Effects.....	92
5.3. Effects on Acid-base and Electrolytes.....	93
5.4. Recovery.....	94
6. Discussion.....	111
7. Conclusion.....	124
8. References.....	125
9. Appendix.....	151
9.1. Abbreviations.....	151

LIST OF FIGURES

<u>Figure</u>	<u>Page</u>
Figure 1. Oxyhemoglobin dissociation curve.....	53
Figure 2. Determinants of oxygen delivery.....	54
Figure 3. Frank Starling's curve showing physiologic relationship between stroke volume and preload (solid line) in normal cardiac function.	55
Figure 4. Relationship of oxygen saturation to oxygen content.....	56
Figure 5. Gamblegram of the electrolyte distribution in normal canine plasma.....	58
Figure 6. Relationship between oxygen delivery (DO_2) and consumption (VO_2).....	59
Figure 7. Characteristic pressure waveforms of right atrium, right ventricle, pulmonary artery, and wedged pulmonary artery encountered while advancing a pulmonary arterial catheter into the pulmonary artery.....	83
Figure 8. Cardiac output dilution curve by thermodilution technique. In orange the area under the curve (AUC).....	84
Figure 9. Cardiac output dilution curves. (a) represents a normal cardiac output, (b) a high cardiac output (small area under the curve), and (c) a low cardiac output (large area under the curve).....	85
Figure 10. Fluroroscopy image of a pulmonary arterial catheter (PAC) in place before and during cardiac output measurements.....	87
Figure 11. Sample cardiac output measurement performed during the study. Values with variation > 10% in absolute value were discarded and three accepted measurements averaged.....	88
Figure 12. Keys for plot interpretation.....	103

Figure 13. Plots showing trends of heart rate (HR), cardiac output (CO), oxygen delivery (DO ₂), and oxygen consumption (VO ₂) from baseline (-10) to 60 minutes post-induction with four different induction regimens.....	104
Figure 14. Plots showing trends of systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP), mean arterial blood pressure (MABP), and total arterial Hb (Hb _a) from baseline (-10) to 60 minutes post-induction with four different induction regimens.....	105
Figure 15. Plots showing trends of systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) from baseline (-10) to 60 minutes post-induction with four different induction regimens.....	106
Figure 16. Plots showing trends of oxygen saturation of arterial blood (SaO ₂), partial pressure of oxygen (PaO ₂) and carbon dioxide (PaCO ₂) in arterial blood, and end-tidal partial pressure of carbon dioxide (EtCO ₂) from baseline (-10) to 60 minutes post-induction with four different induction regimens.....	107
Figure 17. Plots showing trends of serum potassium of arterial (K ⁺ arterial) and mixed-venous (K ⁺ mixed) blood, and arterial and mixed venous concentrations of lactate from baseline (-10) to 60 minutes post-induction with four different induction regimens.....	108
Figure 18. Plot showing the relationship between average recovery scores and recovery time for six dogs anesthetized in 24 episodes with four different induction regimens. Lowest recovery scores are concentrated in a recovery time ranging between 10 and 16 minutes.....	109
Figure 19. Stripchart showing distribution of recovery times according to drug administered for induction of anesthesia in 6 dogs maintained under anesthesia with isoflurane at MAC values.....	110

LIST OF TABLES

<u>Table</u>	<u>Page</u>
Table 1. American Society of Anesthesiology patient physical status classification.....	51
Table 2. Clinical application of mixed-venous oxygen saturation (S _{mv} O ₂) values....	57
Table 3. Causes of hyperlactatemia A.....	60
Table 4. Criteria for scoring recoveries over a period of 15 minutes. Higher scores were indicative of poorer quality of recovery.....	86
Table 5. Mean ± SD values for cardiovascular parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane 1.14 ± 0.32%	97
Table 6. Mean ± SD values for cardiorespiratory parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane 1.14 ± 0.32%	99
Table 7. Mean ± SD values for acid-base parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane 1.14 ± 0.32%	101

DEDICATION

To my family. You are the light that shines and saves me when darkness descends.

Effect of intravenous tiletamine-zolazepam for induction of general anesthesia prior to and during maintenance with isoflurane on cardiorespiratory parameters and acid-base status in healthy dogs: a comparison with alfaxalone, ketamine-diazepam, and propofol

1. Introduction

General anesthesia is a state in which unconsciousness is produced by reversible drug-induced depression of the central nervous system. Ideally, agents inducing and maintaining anesthesia should also produce amnesia, muscular relaxation, and suppression of reflex responses to noxious surgical stimuli. In veterinary medicine, general anesthesia finds its application in facilitating performance of various diagnostic, therapeutic, and surgical procedures, and can be induced with different techniques. In clinical practice, veterinary practitioners' preference on induction regimens is dictated by familiarity with the protocol, pre-anesthetic examination findings, expense, and duration of the anesthetic episode (Enouri et al. 2008). Additionally, it is of paramount importance for the anesthetist to have a deep understanding of the effects that anesthetic agents produce on oxygen delivery to tissues. Oxygen delivery is the product of cardiac output and arterial oxygen content. Many anesthetic and sedative compounds have been shown to depress cardiac output via different mechanisms (Grimm et al. 2015), whereas factors such as hypoventilation can decrease the arterial oxygen content, and therefore further impair oxygen delivery.

Several injectable anesthetic agents that are routinely used in clinical practice by veterinary practitioners are often used off label due to lack of drug labeling that covers multiple species and multiple routes of administration because of the expenses associated with the approval process through the US Food and Drug Administration (O'Horo et al.). Probably the four most common injectable agents used for induction of general anesthesia in this field are propofol, alfaxalone, ketamine, and tiletamine. The two latter compounds

are referred to as dissociative agents, and they are similar to alfaxalone in producing sedation and anesthesia when administered intramuscularly (IM). Tiletamine and ketamine produce dissociation of the limbic and thalamocortical systems, producing a state defined as “dissociative anesthesia”. Benzodiazepines and alpha-2 adrenergic receptor agonist agents have been used to decrease the degree of muscle rigidity produced by the use of dissociative agents (Grimm et al. 2015). Tiletamine is marketed as a combination with the benzodiazepine zolazepam as Telazol[®] (Zoetis Inc., Kalamazoo, MI) in the United States, and as Zoletil[®] (Virbac, Carros cedex, France) in Europe, Latin America, Asia, and the Pacific Area. Although in other countries tiletamine-zolazepam is registered for use in dogs and cats for both IM and intravenous (IV) use, in North America, Telazol[®] is registered for IM use only. This drug is widely used to produce chemical restraint in zoo and exotic medicine, small and large animal practice, and shelter medicine, especially in combination with other agents (Lin et al. 1993a; Lin et al. 1993b; Wilson et al. 1993; Cuvelliez et al. 1995; Carroll et al. 1997; Sweitzer et al. 1997; Vachon et al. 1999; Massolo et al. 2003). For example, the addition of dexmedetomidine and butorphanol to tiletamine-zolazepam administered IM has been shown to provide safe and affordable anesthesia for neutering procedures lasting 30 to 45 minutes, and that lower doses of this combination can be used for induction of anesthesia in shelter populations prior to maintenance with inhalant agents (Ko & Berman 2010).

The combination of ketamine-diazepam has been historically used in veterinary medicine to induce general anesthesia in several species, such as domestic carnivores, equids, ruminants, camelids, swine, laboratory animals and a variety of wildlife and avian species, and it has been shown to provide rapid onset and short duration of action while

supporting cardiovascular function (Green et al. 1981; Moreland & Glaser 1985; Chen et al. 1989; Haskins & Patz 1990; HELLYER et al. 1991; Abrahamsen 2009; Ghurashi et al. 2009; Klöppel & Leece 2011; Reynolds et al. 2012; Casoni et al. 2015).

Alfaxalone is a neuroactive steroid similar to progesterone, which has recently made its return into the North American veterinary market under the name Alfaxan[®] in a new aqueous formulation lacking the side effects of the previously available formulation Saffan[®]. Until the return of alfaxalone into the veterinary market, dissociative anesthetic agents were the only agents to be effective via both IM and IV routes, in contrast with other injectable anesthetic compounds such as barbiturates and propofol.

Propofol is a very popular induction agent in both human and veterinary anesthesia (Grimm et al. 2015) due to its rapid induction (Henaó-Guerrero & Riccó 2014) and recovery from anesthesia with minimal residual effects (Ferreira et al. 2015). After induction with this agent, general anesthesia can be maintained with either injectable or inhalation agents.

Isoflurane is a halogenated ether that is currently considered the most widespread inhalation agent in North America (Grimm et al. 2015). Although its utilization requires specialized equipment to achieve vaporization, an oxygen source, and a patient breathing circuit, isoflurane allows for rapid adjustments in anesthetic depth, which contributed to its diffusion in the veterinary practice.

Recovery from anesthesia starts when administration of anesthetic agents (injectable or inhalant) is discontinued, and their pharmacologic effects on target receptors within the central nervous system cease. Superior recovery quality has been associated with the administration of propofol for induction of general anesthesia when compared to

induction with ketamine-diazepam, etomidate (Sams et al. 2008), and alfaxalone (Maney et al. 2013).

2. Objectives and Hypothesis

The cardiorespiratory effects of these drugs individually have been widely studied in the past. However, a study that compares cardiorespiratory effects, and effects on acid-base balance and electrolytes of tiletamine-zolazepam administered IV for induction of anesthesia to the ones produced by alfaxalone, ketamine-diazepam, and propofol is lacking.

This study was designed to resemble clinical conditions found in daily practice of veterinary anesthesia (induction of anesthesia via IV route, and maintenance with isoflurane in oxygen for 60 minutes). The purpose of this study was to compare the effects of tiletamine-zolazepam (5 mg/kg) administered IV for induction of general anesthesia prior to maintenance with isoflurane in non-sedated, healthy dogs, to those produced by alfaxalone (4 mg/kg), ketamine-diazepam (respectively 7 and 0.3 mg/kg), and propofol (6 mg/kg), administered by the same route in doses sufficient to achieve tracheal intubation. Effects that were evaluated were cardiorespiratory parameters, acid-base balance and electrolytes, and recovery time and quality. Specifically, we hypothesize that anesthesia induced in healthy adult dogs with tiletamine-zolazepam, alfaxalone, ketamine-diazepam, or propofol prior to maintenance of anesthesia with isoflurane for 60 minutes would be:

1. No significant difference in the cardiovascular parameters produced by tiletamine-zolazepam and those produced by the comparison drugs, with particular attention to oxygen delivery;
2. No significant difference in the respiratory parameters produced by tiletamine-zolazepam and those produced by the comparison drugs;

3. No significant difference in the acid-base status of dogs induced with tiletamine-zolazepam and alfaxalone, ketamine-diazepam, and propofol;
4. No significant difference in quality of recovery from anesthesia induced with tiletamine-zolazepam or alfaxalone, ketamine-diazepam, and propofol and maintained with isoflurane for 60 minutes.

3. LITERATURE REVIEW

3.1. General Anesthesia

General anesthesia is a drug-induced state characterized by controlled, reversible depression of the central nervous system. During general anesthesia, the patient's sensory, motor, and autonomic reflex functions are generally attenuated, with various degree of depression, depending on drugs and techniques used (Grimm et al. 2015). Dissociative anesthesia is a state accomplished through the use of drugs such as ketamine and tiletamine, which are referred to as dissociative agents. The name originates from the effects produced by these drugs on the central nervous system: after administration, the thalamocortical and the limbic system become in fact "dissociated", causing a cataleptoid state in which eyes are centrally located, pupils dilated, and intact palpebral reflex and swallowing reflexes.

The three ideal features of general anesthesia are unconsciousness, analgesia, and muscle relaxation. Unfortunately, no drug administered as a single anesthetic agent to produce general anesthesia is able to provide all three features without producing significant side effects. To overcome this limitation, balanced anesthesia, a technique that combines the use of multiple drugs and techniques, such as sedatives, muscle relaxants, hypnotics, and inhalant anesthetics, is often adopted in veterinary medicine. For example, since ketamine may cause muscle rigidity and spontaneous movement of limbs or head, it is often co-administered along with a benzodiazepine or an α_2 -agonist to improve muscle relaxation (Green et al. 1981).

3.2. Anesthetic Risk

Anesthetic death in small animal anesthesia is usually caused by cardiovascular and respiratory complications, such as cardiac arrest resulting from cardiac arrhythmias, myocardial hypoxia, pre-existing pathology, and myocardial depression from anesthetic overdose, complications during endotracheal intubation, and respiratory failure (Grimm et al. 2015). In three large studies (Clarke & Hall 1990; Dyson et al. 1998; Brodbelt et al. 2008), anesthesia-related death occurred respectively in 6 % of canine and 8% feline during induction, while 30 % of feline and 46% of canine deaths occurred during maintenance of anesthesia. Renal, gastrointestinal, neurologic and hepatic-related deaths have also been reported as other causes of anesthetic death in veterinary anesthesia.

In human and veterinary medicine, preoperative assessment of patient health status is an important tool to evaluate preanesthetic risk. The American Society of Anesthesiology (ASA) has developed a five-category (I to V) classification of patient physical status in order to assess the patient's overall preanesthetic risk (Table 1). However, the literature has consistently shown that higher ASA status grade is associated with increased risk of death in small companion animals (Clarke & Hall 1990; BVSC 1998; Dyson et al. 1998; Brodbelt et al. 2006; Brodbelt 2006; Brodbelt et al. 2007; Gil & Redondo 2013), horses (Johnston et al. 2004), and humans (Morita et al. 2001). Along with ASA status, hematologic and biochemical assessments may help the anesthesiologist in identifying systemic illness, and to identify abnormalities of significance for general anesthesia, such as anemia, hypoproteinemia, hepatic or renal disease, etc..

3.3 Respiratory Physiology for Anesthesia

A deep understanding of cardiovascular and respiratory physiology is of paramount importance for the anesthetist. The respiratory and cardiovascular systems work in concert to provide hemoglobin with oxygen that is transported to tissues to maintain physiologic functions. Ventilation is defined as the inward and outward movement of air into and from the lungs, while respiration is defined as the process of exchange of oxygen from the atmosphere to the erythrocytes, and of carbon dioxide (CO_2) from the bloodstream to the atmosphere (Lough 2015). Respiration depends on ventilation since the former cannot occur without movement of air to and from the lungs. Once air reaches the lungs, gases move by diffusion from areas of high partial pressure to areas of low partial pressure. Oxygen partial pressure in the alveoli ($P_{\text{A}}\text{O}_2$) approaches 100 mmHg at 1 atmosphere, while the partial pressure of oxygen in venous blood is about 40 mmHg. This pressure gradient permits movement of oxygen from the alveoli into the capillary blood and vice versa. In contrast, arterial blood that enters the capillaries with a $P_{\text{a}}\text{O}_2$ of about 100 mmHg encounters tissues having a P_{O_2} of about 30 mmHg. Movement of oxygen according to gradient facilitates its diffusion into the mitochondria for adenosine triphosphate (ATP) formation. At this level, oxygen is consumed and its partial pressure decreases, reaching lower levels, and the cycle continues. Normal levels of $P_{\text{a}}\text{O}_2$ in healthy dogs are 99.5 ± 6.8 mmHg (Haskins et al. 2005).

The gradient between alveolar ($P_{\text{A}}\text{CO}_2$) and venous partial pressure of carbon dioxide ($P_{\text{v}}\text{CO}_2$) is about - 6 mmHg, given that the former is usually about 40 mmHg and the latter 46 mmHg. Although the gradient between the partial pressure of carbon dioxide in tissues (P_{CO_2}) and the arterial partial pressure of carbon dioxide ($P_{\text{a}}\text{CO}_2$) is about 10 mmHg (40

mmHg in arterial blood and 50 mmHg in tissues), carbon dioxide (CO₂) solubility facilitates diffusion. It is common practice in veterinary medicine to provide anesthetized patients with an inspired fraction of oxygen (FiO₂) of 1 (in contrast with room air which has a FiO₂ of 0.21), which to some extent allows additional oxygen to compensate for decreased oxygen delivery. Normal values of PaCO₂ in dogs are 40.2 ± 3.4 mmHg (Haskins et al. 2005).

Arterial oxygen content is determined by the oxygen bound to hemoglobin as oxyhemoglobin (97%), and the oxygen dissolved in plasma (3%). In fact, in order to dissolve 0.31 ml of oxygen in 100 ml of blood, a PaO₂ of 100 mmHg is required; if this was the only form in which oxygen was carried in blood, a cardiac output incompatible with life would be necessary to maintain homeostasis between delivery and demand. In healthy dogs, 17.8 ± 2.3 ml of oxygen are contained in 100 ml of blood (Haskins et al. 2005).

Hb is a protein formed by a globin and a heme-group (four iron-porphyrin), and since each heme-group can bind one molecule of oxygen, each molecule of hemoglobin can carry four molecules of oxygen. Each gram of hemoglobin binds a maximum amount of 1.34 ml of oxygen (Haskins et al. 2005). The binding of oxygen to hemoglobin is a rapid and dynamic process, where oxygen is reversibly bound and unbound based on tissue needs, pH, 2,3-disphosphoglycerate (2,3-DPG), PCO₂, and temperature. Hemoglobin oxygen saturation (SO₂) is expressed as the ratio (in percentage) of the hemoglobin saturated with oxygen to the total hemoglobin content in 100 ml, as shown in the following equation (a):

$$\text{a) } \text{SO}_2 = \frac{\text{HbO}_2}{\text{Hb} + \text{HbO}_2} \times 100$$

SO₂ can be measure in arterial blood (SaO₂) and in mixed venous blood sampled at the pulmonary artery (SmvO₂). The latter provides information on the extraction of oxygen occurring in tissues. This is because venous blood is sampled after returning to the right heart, before it is oxygenated in the lungs. In physiologic conditions, SmvO₂ averages values > 75%, with an overall tissue oxygen extraction of about 25%, while SaO₂ is 96.3 ±0.9% in healthy dogs (Haskins et al. 2005).

The oxyhemoglobin dissociation curve provides visual information on the existing relationship between PaO₂ and SaO₂ (Figure 1). This curve is sigmoid in shape, and reflects the optimal physiologic condition where binding and unbinding of oxygen occur.

The flat portion of the curve represents the oxygen uptake occurring in the lungs; as shown by the slope of the curve in this portion, a small change in PaO₂ causes only a small change in SaO₂ (60 < PaO₂ > 100 mmHg). The steep portion of the curve reflects the blood returning to the lung and releasing oxygen to the tissues. In this portion of the curve, even small changes in PaO₂ produce large alterations in SaO₂. If PaO₂ is below 30 mmHg, oxygen reserve is rapidly depleted. The abbreviation P50 has been used to describe the value at which 50% of the hemoglobin is saturated with oxygen, therefore representing hemoglobin's affinity for oxygen. For example, under standard conditions (pH 7.4, temperature 37°C, PaCO₂ 40 mmHg, and normal 2,3-DPG) a canine's P50 is similar to a human's (respectively 28.5 mmHg and 27 mmHg) (Clerbaux et al. 1993). Temperature, pH, CO₂, and 2,3-DPG affect P50 as follows:

- a. A decrease in pH will favor oxygen dissociation from hemoglobin (curve shifted to the right), causing a higher P_{aO_2} required to saturate 50% of hemoglobin (higher P50). Although there is a decrease in SaO_2 , the limited amount of oxygen in blood is released more easily to the tissues. An increase in pH causes the curve to shift to the left, producing opposite effects on P50, and therefore making hemoglobin release oxygen less readily (increased affinity). Many causes can alter pH, whereas perhaps the most common encountered in anesthetized patients is respiratory acidosis caused by decreased alveolar ventilation induced by sedative, anesthetic, or paralyzing agents. Normal values for arterial pH_a and mixed-venous pH_{mv} in dogs are 7.38 ± 0.025 and 7.362 ± 0.027 (Haskins et al. 2005).
- b. A PCO_2 increase will favor oxygen dissociation from hemoglobin (curve shifted to the right), causing a higher P_{aO_2} required to saturate 50% of hemoglobin (higher P50). Although there is a decrease in SaO_2 , the limited amount of oxygen in blood is released more easily to the tissues. A decrease in $PaCO_2$ causes the curve to shift to the left, producing opposite effects on P50, and therefore making hemoglobin releasing oxygen less readily (increased affinity).
- c. An increase in temperature will favor oxygen dissociation from hemoglobin (curve shifted to the right), causing a higher P_{aO_2} required to saturate 50% of hemoglobin (higher P50). Although there is a decrease in SaO_2 , the limited amount of oxygen in blood is released more easily to the tissues. An increase in temperature causes the curve to shift to the left, producing opposite effects on P50, and therefore making hemoglobin releasing oxygen less readily (increased affinity).

- d. 2,3-DPG is a product of erythrocyte metabolism. An increase in its concentration will favor oxygen dissociation from hemoglobin (curve shifted to the right), causing a higher PaO_2 required to saturate 50% of hemoglobin (higher P50). Although there is a decrease in SaO_2 , the limited amount of oxygen in blood is released more easily to the tissues. An increase in 2,3-DPG causes the curve to shift to the left, producing opposite effects on P50, and therefore making hemoglobin releasing oxygen less readily (increased affinity). Increases in 2,3-DPG have been encountered in human patients with hyperthyroidism, hypoxemia, and during pregnancy, while its decrease have been found in subjects with iron deficiency anemia and chronic acidosis (MACDONALD 1977).

Hypoxemia is defined as the presence of a PaO_2 lower than 80 mmHg (Grimm et al. 2015), and it has been reported to occur in 0.5% of anesthetized dogs breathing gas mixture with high FiO_2 . Causes of hypoxemia have been classically divided in five categories:

1. Low FiO_2 (i.e. altitude, equipment malfunction) causes;
2. Hypoventilation (i.e. excess anesthetic depth, neuromuscular impairment, airway obstruction, abdominal distention, pneumothorax, pleural space-filling disorders);
3. Ventilation/perfusion mismatch (i.e. pulmonary disease, atelectasis, bronchospasm, pulmonary thromboembolism);
4. Diffusion impairment (i.e. thickened alveolar wall, pulmonary fibrosis);
5. Right-to-left shunting (i.e. ventricular septal defect, left-to-right patent ductus arteriosus, tetralogy of Fallot);

Hypoxemia is a condition that leads to tissue hypoxia, and is not always accompanied by cyanosis. Hypoxemia can rapidly cause lactic acidosis arrhythmias, organ injury, and finally death, making its recognition and treatment of great importance for the anesthetist. Hypoventilation and venous admixture occurring in areas of low ventilation/perfusion (V/Q) ratio or atelectasis are perhaps the most common causes of hypoxemia in anesthetized veterinary patients (personal observation). Hypoventilation occurs when alveolar ventilation is low compared to metabolic rate, therefore causing PaCO₂ to rise. This phenomenon can occur at any respiratory frequency, although it is often observed during apnea. In studies on respiratory effects of sedative and anesthetic agents, apnea has been defined as the absence of respiratory effort for > 30 to 60 seconds (Keates & Whitem 2012; Amengual et al. 2013; Robinson & Borer- Weir 2013; Martinez- Taboada & Leece 2014). During anesthesia, hypercapnia and hypoventilation are more likely to occur in spontaneously breathing patients because of the effect of sedative and anesthetic drugs on the central control of alveolar ventilation (Grimm et al. 2015). Furthermore, all anesthetic agents currently used in veterinary medicine have been shown to produce a dose dependent decrease in response to CO₂, reducing responsiveness of physiologic mechanisms controlling alveolar ventilation in non-anesthetized patients (Pavlin & Hornbein 1986; Muir III & Hubbell 2008; Miller 2010), and to affect cardiac output which ultimately can lead to hypoxemia by reduced venous oxygen content (CvO₂) as occurs during severe vasodilation or shock (Grimm et al.).

Venous admixture in areas of low V/Q and atelectasis occurs due to the fact that blood fails to come in contact with well-ventilated alveoli and gas exchange fails to take

place. Furthermore, venous blood that was partially arterialized now mixes with arterialized blood, decreasing the overall net PaO_2 (Grimm et al. 2015). Alveoli that are fully expanded can potentially hyperventilate to compensate for areas of poor ventilation, although not efficiently enough to avoid hypoxemia. However, due to its greater solubility compared to oxygen, alveolar and arterial concentrations of CO_2 equilibrate quickly; therefore, PaCO_2 (and P_ACO_2) can be used as a measure of alveolar ventilation. Normal PaCO_2 is around 40 mmHg, while hypercapnia is defined as a $\text{PaCO}_2 > 60$ mmHg. Since respiratory complications have been ascribed as the cause of up to 50% of canine and 66% of feline deaths (Dyson et al. 1998; Gaynor et al. 1999), and severe hypoventilation has been observed to occur in 66% of anesthetized dogs (Redondo et al. 2007), it is important for the anesthetist to monitor patient respiratory status, and maintain acid-base status, temperature, and oxygenation to prevent occurrence of tissue hypoxia, malignant arrhythmias, lactic acidosis, and ultimately death (Grimm et al. 2015).

3.4 Cardiovascular Physiology for Anesthesia

The cardiovascular system provides the physical medium that carries gases and the actual driving force that moves the medium, blood, to tissues and back to the pump, the heart. Cardiac output represents this driving force. Two of the main goals during anesthesia are to maintain adequate patient's oxygen delivery to tissues and perfusion. Oxygen delivery is determined as (b):

$$\text{b) } \text{DO}_2 = \text{CO} * \text{CaO}_2$$

And it is measured in ml of oxygen delivered per minute (if the formula is multiplied by 10). In the equation, DO_2 indicates oxygen delivery, cardiac output, and CaO_2 arterial oxygen content. An algorithm showing the determinant factors for oxygen delivery is illustrated in Figure 2.

Cardiac output represents the volume of blood that is ejected by the left ventricle in one minute, and it is usually measured in milliliters per minute (ml/min). Normal values of cardiac output in healthy dogs are 3360 ± 1356 ml/min (Haskins et al. 2005). Cardiac output is the product of heart rate and stroke volume, and its relationship with arterial blood pressure can be illustrated in the following equation (b):

$$c) \quad BP = CO * SVR$$

with SVR indicating systemic vascular resistance. Arterial blood pressure is defined as the pressure exerted on the blood vessel walls by blood circulating in the arterial system. Stroke volume depends on three further factors: contractility, preload, and afterload.

Heart rate is determined by the electrical depolarization of the sinus node, ultimately resulting in cardiac contraction. In a study including 97 healthy dogs, mean HR and standard deviation (SD) were 87 ± 22 beats per minute (Haskins et al. 2005). Alteration in rate and rhythm can adversely affect cardiac output due to the relationship shown in Figure 2. Presence of tachycardia may indicate a compensatory response for hypotension/hypovolemia, or hypoxemia (Lough 2015). Injectable and inhalant anesthetic agents have the potential of causing changes in heart rate via different mechanisms, such as the increase in sympathetic outflow and catecholamines release seen with ketamine and tiletamine, and the myocardial depression and baroreceptor response seen with propofol and alfaxalone

(Haskins et al. 1985a; Brüssel et al. 1989; Goodchild & Serrao 1989; HELLYER et al. 1989; Muir et al. 2008; Grimm et al. 2015; Okushima et al. 2015).

Contractility, or inotropy, is an intrinsic property of the myocardium that allows for increase in strength of shortening, independently from preload and afterload. Parasympathetic and sympathetic discharge decrease and increase contractility respectively, as well as myocardial oxygen supply (Hall & Guyton 2011). Decrease in contractility in anesthetized patients has been shown to have the potential to induce heart failure in subjects with cardiac disease, and in subjects administered high amount of anesthetic drugs. Ketamine has been shown to have direct negative inotropic effects in dogs (Diaz et al. 1976), although the clinical effects of this phenomenon are not usually appreciated due to the predominance of the central sympathetic stimulation. Negative inotropy has been reported to be dose-dependent (Dowdy & Kaya 1968; GOLDBERG et al. 1970). Increase in myocardial oxygen requirements, cardiac output, systemic vascular resistance, pulmonary vascular resistance, heart rate, and cardiac work have also been observed after administration of ketamine (Haskins et al. 1985a). Although a study on dogs administered tiletamine-zolazepam and alfaxalone reported respectively increased and maintained contractility after injection (HELLYER et al. 1989; Muir et al. 2008; Rodríguez et al. 2012) in dogs, studies conducted on “load-independent” conditions are lacking to the author’s knowledge. Propofol has been shown to cause myocardial depression and vasodilatation in a dose-dependent fashion (Goodchild & Serrao 1989), although in experimentally-controlled hemodynamic conditions in dogs the negative inotropic effect of propofol remains slightly smaller than the one produced by ketamine (Pagel et al. 1992).

Preload is the volume that fills the ventricle at end-diastole, just before the semi-lunar valves close, and it is determined by venous return and myocardial fiber stretch (Lough 2015). Preload can be conceptually divided in right ventricular and left ventricular preload. Left ventricular preload can be indirectly measured by pulmonary artery wedge pressure (PAWP) by use of a Swan-Ganz pulmonary arterial catheter. Pulmonary capillary occlusion pressure are synonyms and PAWP. For the purposes of this manuscript, the former will be used. Left ventricular preload is essential in dictating cardiac output. Alteration in preload can alter cardiac output due to the Starling's law. This law states that myocardial stretch, within limits, causes an increase in the force of cardiac contraction. A visual representation of this law is provided by the Starling's curve (Figure 3). The x axis represents preload (right or left), while the y axis represents stroke volume. As the curve shows by its flat portion, the relationship between pressure (x) and volume (y) is not linear. In fact, if the ventricle becomes overdistended, stroke volume and cardiac output will decrease because myocytes will lose contraction force, and unusually high pressure will develop in the ventricle. A classic example of decreased cardiac function shown in the Starling's curve is heart failure due to dilated ventricles, where the ejection fraction will decrease and end-diastolic volume will increase, impeding further filling of the ventricle during the following cardiac cycle. Propofol and alfaxalone have been proven to decrease preload (Goodchild & Serrao 1989; Muir et al. 2008), although any anesthetic drug affecting vasomotor tone and venous return are able to affect preload. Ketamine and tiletamine seem to have no effect on preload (Grimm et al. 2015), although their effect on pulmonary and systemic vascular resistance is inconsistent in the literature (Diaz et al. 1976; Haskins & Patz 1990; Pagel et al. 1992).

Right ventricular and left ventricular afterload represent the impedance that blood being ejected by ventricles encounters, and can be measured by calculating pulmonary vascular resistance and systemic vascular resistance by dividing mean arterial blood pressure by cardiac output. Normal values for pulmonary resistance index in dogs are 0.065 ± 0.026 mmHg/ml/kg/min. Values of systemic vascular resistance index (SVRI) are higher than pulmonary vascular resistance index (PVRI) (0.641 ± 0.173 mmHg/ml/kg/min), reflecting different thickness of right and left ventricular walls (Haskins et al. 2005). In order to standardize cardiac output and stroke volume based on surface area or weight, these are usually divided respectively by m^2 or kilograms, obtaining a parameter called cardiac index (CI) and stroke volume index (SVI). Normal values of CI in dogs are 4.42 ± 1.24 L/min/ m^2 and 165 ± 43 ml/kg/min, and of SVI are 51.9 ± 13.5 ml/beat/ m^2 and 1.93 ± 0.46 ml/beat/kg (Haskins et al. 2005). For the purposes of this study, the latter unit of measure will be used. Mean arterial blood pressure (MABP), mean pulmonary artery pressure (PAP), mean right atrial pressure (MRAP), and mean pulmonary artery wedge pressure (MPAWP) values in healthy non-sedated dogs reported by (Haskins et al. 2005) are respectively 103 ± 15 mmHg, 14 ± 3.2 mmHg, 3.1 ± 4.1 cmH₂O, and 5.5 ± 2.9 mmHg, and are consistent with previously reported reference ranges (Cox et al. 1976; Arndt et al. 1984; Bennett et al. 1989).

Complex and continuous interaction between parasympathetic and sympathetic nervous systems provide control of heart rate, vascular tone, inotropy, and resistance respectively via release of acetylcholine, and norepinephrine, which act at several receptors as needed to maintain homeostasis. Anesthetic agents often exert effects on these mechanisms, resulting in alteration of vascular tone (vasodilation/vasoconstriction), heart rate

(bradycardia/tachycardia), contractility (negative/positive inotropy), and therefore modifying cardiac output and oxygen delivery. Additionally, mechanoreceptors sensitive to changes in pressure (baroreceptors) located at the base of the heart and great vessels work in concert with the autonomic nervous system and the neuro-hormonal systems (i.e. renin-angiotensin-aldosterone system, natriuretic peptides, antidiuretic hormone) to regulate and maintain homeostasis of the cardiovascular system and its volume (Lough 2015). Propofol, alfaxalone, and isoflurane have been reported to depress baroreceptor reflex activity (Toda et al. 1992; McCallum et al. 1993; Grimm et al. 2015).

Arterial oxygen content is determined by the sum of the oxygen dissolved in plasma ($\text{PaO}_2 * 0.0031$) and the FiO_2 actually bound to hemoglobin (SaO_2), which is expressed in percentage and depends on the concentration and affinity of hemoglobin. The equation is (d):

$$\text{d) } C_a\text{O}_2 = 1.36 * \text{Hgb} * \frac{\text{S}_a\text{O}_2}{100} + 0.0031 * \text{P}_a\text{O}_2$$

In the formula, Hb represents hemoglobin, 1.36 is termed Hüfner's constant, which represents the amount of oxygen (ml at 1 atmosphere) bound per gram of hemoglobin. PaO_2 is multiplied by 0.0031 which is a constant used to calculate the amount of dissolved oxygen in plasma. Normal arterial oxygen content is about 20.1 ml/100 ml of blood in humans, and 17.8 ± 2.3 in canines (Muggenburg & Mauderly 1974; ABDUL-RASOOL et al. 1987; Nelson et al. 1987; Haskins et al. 2005), with normal concentration of hemoglobin of 13.6 ± 1.8 g/dl in dogs. Therefore we can derive that 17.8 ± 2.3 ml/dl of oxygen are present in arterial blood when SaO_2 is 100%.

We can linearly predict arterial oxygen content because the relationship between content and SaO_2 is linear, as shown in Figure 4, but only if hemoglobin concentration is normal. At room air, the dissolved oxygen portion is minimal compared to SaO_2 , although in case of anemia or high FiO_2 , this becomes more significant. Oxygen content in mixed venous blood (CmvO_2) can also be calculated with the same formula (d), substituting for SaO_2 with SmvO_2 , and PaO_2 for PmvO_2 . Normal CmvO_2 values are 14.2 ± 2.2 ml of oxygen for 100 ml of blood (Haskins et al. 2005).

Mixed venous oxygen saturation (SmvO_2) represents the oxygen remaining in the blood after tissue extraction, and it has been suggested as an indirect indicator of tissue oxygenation (Kandel & Aberman 1983). Normal SmvO_2 values range from 60 to 80%, with 70% in humans, and have been reported by Haskins et al to be $77.1 \pm 5.5\%$ (Haskins et al. 2005). When SmvO_2 values are decreased below 40%, oxygen demand exceeds supply, and we can assume that oxygen is relatively unavailable to tissues to be used. In two studies in human critical care, low SvO_2 was a predictor of poor outcome (Kasnitz et al. 1976; Kandel & Aberman 1983), whereas it has been shown that normal or supra-normal values fail to guarantee adequate tissue oxygenation (Arnold et al. 2009; Perz et al. 2011) such in the case of low tissue extraction observed during sepsis and cellular death. Despite these findings, SmvO_2 has been shown to be superior as an indicator of substantial hemodynamic deterioration compared to MABP and heart rate in humans undergoing cardiac surgery, although predictor values were inconsistent (Waller et al. 1982; Magilligan et al. 1987). Finally, SmvO_2 has been shown to positively predict mortality in people that underwent cardiac surgery (Pölonen et al. 2000; Holm et al. 2010; Holm et al. 2011), and to decrease the incidence of organ failure in humans when oxygen extraction ratio (O_2ER) <

27% is used as a goal-directed therapy end point (Donati et al. 2007). A summary of the variation of $S_{mv}O_2$ and its causes are available in Table 2.

Oxygen demand is the total oxygen necessary to meet metabolic requirement of tissues in order for them to function in an aerobic metabolic state. This demand is affected by temperature, metabolic state, and muscular activity. In order for tissues to maintain homeostasis, oxygen delivery must meet oxygen demand. Oxygen consumption (VO_2) is the amount of oxygen that actually gets utilized by the tissues, and in physiologic conditions, demand and consumption are equal. For instance, mechanisms behind myocardial contractility are great oxygen consumers of the myocardial oxygen supply (Brashers & McCance 2010). Normal values of oxygen delivery and oxygen consumption in dogs are respectively 29.5 ± 8.8 ml/kg/min and 6 ± 2.6 ml/kg/min (Haskins et al. 2005), which means that only 20 to 30% of the delivered oxygen is actually used by tissues and organs. However, in pathologic states, oxygen demand may exceed oxygen consumption, causing oxygen deprivation and increased anaerobic metabolism in the cell. The formula to calculate oxygen consumption is derived by the reverse/inverse Fick principle, as described below (e):

$$e) \quad VO_2 = (CaO_2 - C_{mv}O_2) * (CI/100)$$

where CaO_2 is arterial oxygen content, $C_{mv}O_2$ oxygen content in mixed-venous blood, and CI is cardiac index. This balance between demand and delivery can be disrupted by two mechanisms: a) an increase in oxygen consumption (muscle tremors, fever, seizures), or b) a decrease in supply due to decreased cardiac output, decreased hemoglobin, or decreased SaO_2 (cardiac insufficiency, anemia, hypoxemia). The first attempt of the body to

compensate for disruption of homeostasis is to increase cardiac output (up to threefold) to improve oxygen delivery, since oxygen consumption cannot be promptly decreased. If this compensatory mechanism is not effective in meeting tissue energy needs, oxygen extraction increases from arterial blood by tissues, causing S_{mvO_2} to decrease. If this second attempt also fails, a third mechanism, increase in anaerobic metabolism, takes place, becoming the only source for ATP production, although inefficient. If this state persists for prolonged time, the waste product of anaerobic metabolism, lactic acid, is produced in abundance but not cleared as fast, producing a condition called metabolic lactic acidosis. For this reasons, this state has been adopted as evidence of tissue hypoxia (Allen & Holm 2008), and associated with poor prognosis is several species (Moore et al. 1976; Lagutchik et al. 1998). To help areas of high oxygen demand survive, vasoactive compounds are activated and afferent vessels of these areas are dilated, providing increased blood flow. In contrast, areas of poor oxygen extraction are vasoconstricted, increasing vascular resistance and diverting flow to higher need areas. Oxygen consumption has been reported to remain unchanged and decrease after ketamine administration in anesthetized hypovolemic (Weiskopf et al. 1981; Haskins & Patz 1990) and normovolemic dogs (Weiskopf et al. 1981), and to decrease in normovolemic dogs anesthetized with isoflurane (Weiskopf et al. 1981), although some references report oxygen consumption to be decreased in anesthetized people (McLellan & Walsh 2004).

Many anesthetic agents and sedatives have been reported to depress cardiac output in dogs, via different mechanisms such as previously described. Since compensatory mechanisms to regulate hemoglobin and SaO_2 are physiologically limited, a fall in cardiac output is perhaps the most dangerous threat to tissue homeostasis. Respiratory depression

under general anesthesia is commonly estimated by evaluating PaCO₂. Clinically significant respiratory depression can be seen at PaCO₂ > 60 mmHg, whereas normocarbica can be accompanied by some degree of hypoxemia (SaO₂ < 90% and PaO₂ < 60 mmHg) (Grimm et al. 2015).

Because of the sigmoid shape of the oxyhemoglobin dissociation curve and because most patients are maintained on an FiO₂ of 1.0 under anesthesia, SaO₂ and arterial oxygen content are usually maintained in adequate levels; therefore it is important to ensure appropriate hemodynamic component of delivery. Anemic patients have reduced oxygen-carrying capacity due to the reduced content of hemoglobin in blood. Since in clinical settings measuring cardiac output is often difficult, expensive, and requires invasive monitoring, MABP has been adopted as a more practical parameter to measure in the daily practice. However, it should be kept in mind that large variations in cardiac output can occur with no absolute variation in MABP values. Furthermore, the anesthetist needs to keep in mind that neither of these two parameters can accurately describe regional flow and shunting of flow to other regions.

Oxygen extraction ratio is a measure of the total oxygen extracted from the tissues and is calculated by dividing oxygen consumption by oxygen delivery. Normal values for dogs are $20.5 \pm 5.7\%$ (Haskins et al. 2005). Oxygen extraction ratio increases in tissues receiving inadequate blood flow (Thurmon et al. 2007), which can be confirmed by concomitant lower levels of SmvO₂ in mixed venous blood. Unfortunately, this measures the overall extraction but doesn't reflect the extraction of oxygen of a single organ or system, since it is known that some organs such as kidneys are very largely supplied by blood but are actually poor consumers of oxygen for their function. In contrast, the brain is supplied

by a large flow rate matched by a large oxygen consumption. When oxygen supply becomes limited, mechanisms intrinsic of the cardiovascular system redirect blood flow where more is needed, to tissues with high oxygen extraction ratio to preserve physiologic function, although these regulatory mechanisms have limits. Increased oxygen extraction ratio occurs whenever oxygen delivery is decreased in the face of constant oxygen consumption, and it is associated with decreased $S_{mv}O_2$ (Haskins et al. 2005).

In general and for the purpose of this study, hemodynamic instability has been defined as a condition where clinical features indicate lack of global and regional perfusion, such as in patients with circulatory shock and heart failure (Weil 2005).

3.5 Acid-Base Balance and Electrolytes and Anesthesia

Acid-base abnormalities causing deviation of blood pH result from changes in strong ion difference (SID), PCO_2 , and weak acids (A_{tot}). Changes in other variables, such as bicarbonate concentration ($[HCO_3^-]$), can therefore be explained by variations of the independent variables (SID, PCO_2 , and A_{tot}) according to the law of electroneutrality. Some of the patient's acid-base derangements are typical of the perioperative period, such as respiratory acidosis and alkalosis, respectively due to decrease (hypoventilation, insufficient mechanical ventilation, narcosis, excessive anesthetic depth) and increased alveolar ventilation (hyperventilation, pain, anxiety). Common metabolic causes of acidosis in the perioperative period are reduced SID (hyperchloremia) and dilution of the extracellular space with isotonic fluids such as NaCl 0.9%, lactated Ringer's solution (LRS), or dextrose, and consequent fall in pH due to increase CO_2 dissociation and relative decrease in HCO_3^- . Metabolic alkalosis in the anesthetized patient can occur in the case of increased

SID (hypernatremia, hypochloremia) (Miller et al. 2014). The aforementioned acid-base conditions are common occurrence in healthy patients, and are often simple disturbance of iatrogenic origin; in critical ill patients more complicated, mixed disturbances are expected. The present study was conducted on healthy dogs; therefore only simple respiratory disturbances caused by anesthetic techniques were expected.

Normal arterial $[pH_a]$ and mixed-venous $[pH_{mv}]$ pH of non-sedated healthy dogs are respectively 7.381 ± 0.025 and 7.362 ± 0.027 (Haskins et al. 2005). pH_{mv} has been reported to be lower than pH_a (Garg et al.) by 0.02 due to the higher partial pressure of carbon dioxide ($P_{mv}CO_2$) contained in mixed-venous blood. Arterial (P_aCO_2) and mixed-venous ($P_{mv}CO_2$) partial pressures of carbon dioxide in blood differ slightly in healthy dogs by about 4 mmHg, with normal values of P_aCO_2 of 40.2 ± 3.4 and $P_{mv}CO_2$ of 44.1 ± 3.8 (Haskins et al. 2005). Although metabolic compensation starts within an hour from the start of a primary respiratory disorder, this is not complete before 2 to 5 days (DiBartola 2011), which makes it imperative for the anesthetist to preserve normal alveolar ventilation to avoid uncompensated pH deviations during the short perioperative term.

The main buffer systems for CO_2 in the body are Hb, plasma proteins, and bicarbonate (HCO_3^-). In fact, in human blood 65% of the CO_2 is in the form of HCO_3^- and hydrogen ions bound to hemoglobin, 27% bound to carbaminohemoglobin, and 8% in the dissolved form. Mixed-venous ($HCO_3^-_{mv}$) bicarbonate has been reported to be higher than arterial bicarbonate ($HCO_3^-_a$) by 1 mEq/L in average, which can be justified by the fact that erythrocytes also act as CO_2 buffers. Normal $HCO_3^-_a$ is 23.1 ± 2 and $HCO_3^-_{mv}$ 24.2 ± 2.1 in healthy dogs (Haskins et al. 2005). Traditionally, a decrease in $[HCO_3^-]$ has been interpreted as an indication of metabolic acidosis, whereas an increase would indicate the

presence of metabolic alkalosis. However, the traditional approach has the limitations of a) not accounting for the fact that the change in HCO_3^- is a direct consequence of a change in total CO_2 in the body, and b) failing to explain why deviations in strong ions (Na^+ and Cl^-) and plasma proteins (A_{tot}) affect pH. A more complete picture can be offered by integrating this approach with the ones taking in account base deficit (semi-quantitative approach) and SID (Stewart-Fencl approach).

Base excess (BE) is defined as the amount of strong acid required to return pH to 7.4 at 37 °C and normal PaCO_2 (40 mmHg), and it is a variable independent from PaCO_2 and HCO_3^- , which is considered to reflect the status of the metabolic component of an acid-base disturbance. The major limitation of the BE equation is that it assumes that A_{tot} is normal, which is a false assumption in the case of hypoproteinemia and dehydration states. Mixed-venous base excess (BE_{mv}) is almost identical to arterial (BE_a) (Feigl & D'Alecy 1972; Wise 1973; Mauderly 1974; Muggenburg & Mauderly 1974; Rose & Carter 1979; Reeves et al. 1982; Arndt et al. 1984; Atchison et al. 1986; Mathias et al. 1988; Samsel et al. 1988; Bennett et al. 1989; Ilkiw et al. 1989; Ilkiw et al. 1991; Pypendop & Versteegen 1999; Haskins et al. 2005). Normal values are -2.1 ± 2.3 mEq/L in arterial blood and -1.9 ± 2.3 mEq/L in mixed-venous blood (Haskins et al. 2005). These values do not change during acute respiratory acidosis/alkalosis in the absence of metabolic alterations.

Na^+ and Cl^- are the two electrolytes present in high concentration in the body. For the law of electroneutrality, changes in their concentrations, and changes in concentration of other cations and anions will produce alteration in SID, which will affect pH. Potassium, Ca^{++} , and Mg^{++} are present in small concentrations in the body compare to sodium

and chloride, therefore causing minimal changes in pH when altered compare to Na^+ even if the alteration in their concentration is great. Chloride will affect and will be affected by alteration in HCO_3^- , lactate, phosphates, sulfates, plasma proteins, and other organic anions (Haskins et al. 2005). A graphic representation of the electrolyte distribution in normal canine plasma is provided by the Gamblegram. Two columns indicating the totality of the cations (left column) and the anions (right column) represent electroneutrality. The most abundant cations in plasma is Na^+ , followed by potassium, calcium, magnesium, and unmeasured cations (γ -globulins). As shown in the right column, Cl^- is the main anion, followed by HCO_3^- , plasma proteins (albumin), lactate, phosphates and sulfates.

The composition of plasma electrolytes is mainly affected in the perioperative period by administration of IV fluids such as NaCl 0.9%, LRS, dextrose, and normosol-R. The latest guidelines provided from the American Animal Hospital Association recommends that anesthetized animals receive perioperative administration of IV fluids at 5 ml/kg/hr. The reasoning behind it is to prevent and treat anesthetic-related hypotension (mainly caused by vasodilation and therefore relative hypovolemia), hypoperfusion, and preserve renal function (Kudnig & Mama 2002). However, these solutions possess different electrolyte composition compared to canine plasma, which can lead to shifting of plasma electrolytes. Solutions with a SID of 24 mEq/L are considered balanced solutions and are unlikely to alter acid-base balance (Morgan & Venkatesh 2003). A study conducted on the effects of three different infusion rates of LRS in anesthetized dogs (10, 20, 30 ml/kg/hr IV) has shown a dose-dependent decrease in packed cell volume (PCV), total plasma proteins, and whole blood viscosity, with the greatest effects produced by the 30 ml/kg/hr rate, but no significant difference in serum Na^+ , K^+ , Cl^- , and ionized calcium

(iCa^{++}) at any of the rates for 60 minutes (Muir III et al. 2011). Because of these results and the fact that LRS SID is 27 mEq/L, LRS was chosen as the IV fluid to be administered to the anesthetized dogs in this study.

Changes in serum K^+ in dogs with respiratory acidosis have been quantified, with K^+ increasing 0.14 mEq/L per 0.1 decrease in pH (DiBartola 2011). This increase may be clinically significant in hyperkalemic patients that need to undergo procedures requiring general anesthesia or profound sedation which can induce respiratory acidosis.

Lactate is a strong acid produced mainly in skeletal muscle, brain, skin, erythrocytes, and gastrointestinal tract as a result of glycolysis in homeostatic conditions (Kreiserberg 1980; Toffaletti 1991; Lagutchik et al. 1996). During glycolysis, glucose is converted into pyruvate, which, in aerobic conditions, can cross into the mitochondria and is converted into acetyl coenzyme A to enter the citric acid cycle and produce energy via ATP production. The biological process involving production and clearance of lactate are referred to as the Cori cycle. Liver and kidneys are the two main organs where 50% and 30% of lactate clearance respectively occurs. Although a small portion of pyruvate is produced in aerobic conditions, lactate production is considered mainly an anaerobic event. This is because pyruvate is converted to lactate and it allows quick production of ATP molecules through anaerobic glycolysis. Lactic acidosis is a metabolic derangement that occurs when lactate is generated via anaerobic metabolism more rapidly than it can be metabolized, causing hyperlactatemia. Hyperlactatemia has been classified by Cohen and Woods as type A and type B (Cohen & Woods, 1976) based on pathophysiology. The former is due to increased lactate production and it has been reported to be the most com-

mon in human and veterinary medicine (Toffaletti 1991; Lagutchik et al. 1996). Its pathophysiology resides in inadequate oxygen delivery and consequent tissue hypoxia. Type B hyperlactatemia encompasses all the causes of increased lactate levels that are not due to hypoxia. This condition is seen in case of certain disease processes, such as diabetes mellitus, severe liver disease, sepsis, neoplasia, and pheochromocytoma, in the presence of toxins and drugs, such as cyanide, acetaminophen, salicylates, and morphine, or as an inborn abnormal mitochondrial function (Karagiannis & Reniker 2006). Hypoglycemia, thiamine deficiency, and D-lactate hyperlactatemia are other causes of type B hyperlactatemia that do not fall into any of the three aforementioned categories (Karagiannis & Reniker 2006).

Type A hyperlactatemia is caused by impaired cellular oxygen delivery. As previously mentioned, oxygen delivery depends on two components: a) arterial oxygen content, and b) cardiac output. As shown in Figure 4, oxygen consumption is independent from oxygen delivery in physiologic situations, where they can fail to match in a wide range to a certain point called “critical delivery threshold” or “critical delivery point”. Beyond this point, oxygen consumption becomes dependent on oxygen delivery, resulting in tissue hypoxia (Tuchschmidt et al. 1991; Mizock & Falk 1992) and lactic acidosis (shaded area in Figure 4). In dogs, critical oxygen delivery ranges between 6 and 11 ml/kg/min (Thurmon et al. 2007). Causes of type A hyperlactatemia are included in Table 3. Tissue hypoxia can also be caused by increased oxygen consumption, even when adequate oxygen delivery is provided. Clinically this event is seen during seizure activity, extreme exercise, and trembling, and it seems to be due to increased glycolysis in the skeletal muscles with conversion of pyruvate and consequently, in lactate formation.

Blood lactate measurements can also be used along with $SmvO_2$, PvO_2 , oxygen extraction ratio, BE, and anion gap (AG) to acquire greater information on tissue oxygenation (Karagiannis & Reniker 2006). Lactate has been shown to correlate with prognosis in several human and veterinary studies, with trends being more predictive than single measurement on outcome (Mizock & Falk 1992; Lagutchik et al. 1996; Porter & Ivatury 1998). Although statistically significant differences have been found for different sampling sites in lactate measurements, with the cephalic vein containing the highest levels, followed by femoral artery and the jugular vein (Hughes et al. 1999), there is no evidence that arterial sampling is superior to venous sampling in obtaining accurate lactate levels (Gallagher et al. 1997; Middleton et al. 2006). Also, no difference has been found in samples stored for up to 30 minutes in lactate levels (Hughes 2000). Despite these considerations, lactate measurement has limitations; it lacks in sensitivity and specificity in certain circumstances. In fact, type A hyperlactatemia is not the only cause of increased lactate levels, and other causes must be considered for an accurate differential diagnosis. Furthermore, regional hypoperfusion close to the sampling site can cause the false perception that global hypoperfusion exists (Allen & Holm 2008). Normal values for lactate in dogs have been reported to range between 0.7 and 2.8 mmol/L (Allen & Holm 2008). Elevations up to 4.9 mmol/L are considered non-normal in unstressed patients and mild in pathologic states. Levels between 5 and 7 mmol/L are considered moderate, whereas levels higher than 7 mmol/L are considered severe (Kreisberg 1980; Hughes 2000). However, levels of lactate > 2.5 mmol/L in anesthetized dogs have been reported to be indicator of impaired tissue perfusion (Hughes 2006).

3.6 Anesthetic Agents

3.6.1 Tiletamine-Zolazepam

Tiletamine-zolazepam, the former a phencyclidine, the latter a benzodiazepine, are combined at a fixed ratio (50:50) in a product marketed as a lyophilized powder which is reconstituted with 5 ml of saline, dextrose or water to obtain a concentration of 50 mg/ml of tiletamine and 50 mg/ml of zolazepam (100 mg/ml total dose). The obtained solution has a pH between 2 to 3.5, and it should be discarded after 4 days from reconstitution when kept at room temperature (Arrijoja-Dechert 2002). Although it is approved only for IM administration in dogs and cats, several studies report its effects after IV administration (Donaldson et al. 1989; HELLYER et al. 1989; Ilkiw 1992). This combination produces dose-dependent sedation, recumbency, and a cataleptic state when administered at increasing doses. Zolazepam improves muscle relaxation, decreases myoclonus, and has anticonvulsant properties. Palpebral, laryngeal, pharyngeal, and pedal reflexes are maintained, pupils are dilated, eye centrally positioned, and analgesia is adequate for mild to moderate pain (Arrijoja-Dechert 2002). This drug combination is particularly useful in immobilizing aggressive animals, and for diagnostic and minor surgical procedures (Pablo & Bailey 1999), and its use in combination with other sedative and analgesic compounds has been largely investigated (Jang et al. 2004; Krimins et al. 2012a; Krimins et al. 2012b; Gómez- Villamandos et al. 2013).

Tiletamine is similar to ketamine in its pharmacologic properties, although it has been reported to be more potent and to have a longer duration of action (Clarke & Trim 2013). Like after injection of inductive doses of ketamine, an increase in heart rate is noted

with tiletamine-zolazepam in dogs, leading to the assumption that tiletamine exerts the same stimulatory effects in the sympathetic nervous system via catecholamine release. The cardiorespiratory effects of IM tiletamine-zolazepam have been studied in response to several doses (10 to 20 mg/kg); cardiovascular depression is dose-dependent, sinus tachycardia is accompanied by a reduction in stroke volume, with an overall stable cardiac output, whereas after administration of 20 mg/kg IM, cardiac output decreased in the face of sinus tachycardia (Short 1987). Furthermore, at the latter dose, myocardial contractility and arterial blood pressure were decreased (Arrijoja-Dechert 2002). Hellyer and colleagues administered tiletamine-zolazepam IV to dogs and cats and studied its cardiorespiratory effects (HELLYER et al. 1988; HELLYER et al. 1989). In canines, three doses of tiletamine-zolazepam were investigated (6.6, 13.2, 19.8 mg/kg), administered twice to the same subject (once while subject was non-sedated, and once on residual isoflurane anesthesia). Hellyer describes a good, rapid induction of anesthesia, with time to sternal recumbency depending on the dose administered. Heart rate significantly increased (sinus tachycardia) after administration of tiletamine-zolazepam IV, and significantly higher cardiac output with the two higher doses used in the study was observed. Mean systolic (MSBP), MABP, and diastolic (DABP) arterial blood pressures were decreased at all dosages when measured 1 minute post-induction, to later increase from to baseline. Systemic vascular resistance was transiently increased 1 minute only after administration of 6.6 mg/kg, whereas it was decreased with higher doses. Decrease in arterial blood pressure has been attributed to decreased systemic vascular resistance in this study. No significant difference was found in central venous pressure (CVP), MPAP, MPAWP, or left and right ventricular pressures. The authors concluded that the maintained and increased cardiac output seen at

all doses was due to direct stimulatory effects of tiletamine-zolazepam on the sympathetic nervous system, although myocardial contractility and systemic vascular resistance were decreased. The latter was attributed to either direct effect of the drug, changes in vasomotor tone, or residual effects of isoflurane (Steffey & Howland Jr 1977). Interestingly, in calves administered IV tiletamine-zolazepam SVR, MABP, HR, PAWP were significantly decreased after induction and gradually returned to baseline, to then increase overtime, which seems to be in accordance with studies conducted in cats, and in contrast with studies in canines (HELLYER et al. 1988; Lin et al. 1989). Authors reported in both studies that the biphasic response is not completely understood in these species, and it may have depended on study design. Finally, tiletamine-zolazepam does not decrease the dose of epinephrine that elicits ventricular arrhythmias in dogs and cats anesthetized with halothane (Bednarski & Muir 3rd 1990).

Minute ventilation was decreased only when 19.8 mg/kg were used, and hypoventilation, cyanosis, and hypoxemia were observed (HELLYER et al. 1989). Non-sedated dogs administered 2 to 4 mg/kg IV showed normocapnia and border-line hypoxemia ($\text{PaO}_2 = 80\text{-}82$ mmHg) in absence of cyanosis (Donaldson et al. 1989). Respiratory depression with increased PaCO_2 and decreased PaO_2 has been also reported to occur in calves and cats anesthetized with tiletamine-zolazepam (HELLYER et al. 1988; Lin et al. 1989). Therefore, endotracheal intubation and insufflation with oxygen was recommended. Tiletamine seems to outlast zolazepam in dogs (Lin et al. 1993a), whereas the opposite occurs in felines. Respiratory acidosis has been reported in cats anesthetized with tiletamine-zolazepam (HELLYER et al. 1988), but unfortunately this information has not been reported in Hellyer's study in dogs. In a study evaluating the effects of tiletamine-

zolazepam on acid-base balance in canines via samples collected from an arterial catheter, investigators found that pH was decreased below 7.3 in all subjects after IM and IV injection, and that respiratory acidosis occurred in all groups. PaCO₂ was increased above 45 mmHg, PaO₂ decreased below 75 mmHg, and consequently SaO₂ dropped below 90%. Furthermore, hypoxemia was more severe with IV injection compared to IM injection, although it was completely resolved within 8 minutes from induction. Base excess and [HCO₃⁻] were within normal limits at all times and did not significantly change among groups. Therefore, authors concluded that drug effects on acid-base balance were minimal although enriched oxygen gas mixtures should be administered at least in the first 10 minutes post-induction (Savvas et al. 2005).

Difference in recovery quality seen between dogs and cats has been attributed to differences in pharmacokinetics (redistribution, metabolism, and clearance). Half-life of tiletamine has been reported to be 1.2 hours in dogs, whereas zolazepam half-life is about 4.5 hours (Lin et al. 1993a). Pablo and Bailey have suggested that maintenance with inhalational agents (halothane and isoflurane) markedly improve recovery quality, especially after long anesthetic episodes, and they have discouraged the use of tiletamine-zolazepam as a maintenance agent due to side effects and prolonged, rough recoveries associated with this practice (Pablo & Bailey 1999). A study conducted on the use of tiletamine-zolazepam for anesthesia for dental procedures has shown that recoveries were smoother with lower doses, and that they were quick and well despite the fact that it could not take place in a quiet, dark environment (van Foreest 1991).

Side effects observed during tiletamine-zolazepam anesthesia are ptyalism, myoclonus, involuntary movements, increased cerebral blood flow, and metabolic oxygen requirements which may be undesirable in ill patients (Pablo & Bailey 1999). A recent study has also failed to demonstrate increased intraocular pressure in dogs induced with IV tiletamine-zolazepam administered at 5, 10 and 20 mg/kg (Jang et al. 2015).

In the present study, tiletamine-zolazepam powder was diluted with 10 ml of sterile NaCl 0.9% to allow better titration due to greater volume. Therefore, this solution contained 50 mg/mg of tiletamine-zolazepam (25 mg/ml of tiletamine and 25 mg/ml of zolazepam). Furthermore, a dose similar to the low end of the IM dose recommended by the manufacturer for diagnostic procedures was used (5 mg/kg).

3.6.2 Alfaxalone-HPCD

Alfaxalone (3- β -hydroxy-5 β -11,20-dione) is a synthetic neuroactive steroid, non-barbiturate anesthetic, chemically similar to progesterone, which produces unconsciousness and smooth induction with rapid onset, muscle relaxation, and short duration of action (Estes et al. 1990; Ferré et al. 2006). Alfaxalone has been shown to act on the GABA_A receptor within the CNS. Recently, this drug has been reformulated and reintroduced in the veterinary market in several countries. Alfaxalone is poorly soluble, and therefore an emulsifier (Cremophor-EL) derived from castor oil, was used to improve solubility and distribution. This formulation called Saffan[®] for the veterinary market and Althesin[®] for the human market mostly contained alfadolone, a less potent neuro-steroid which was also used to improve solubility. However, the most frequent side effect of this formulation was

the development of anaphylactoid reactions in dogs and humans (Estes et al. 1990), and edema of forepaws and pinnae in cats (Middleton et al. 1982). Due to this undesirable effect, both drugs were withdrawn from the market. Recently, an Australian pharmaceutical company has reformulated alfaxalone with a cyclodextrin molecule (2-hydroxypropyl- β -cyclodextrin, HPCD). Cyclodextrins are sugar molecules shaped as a ring which encapsulate the steroid molecule in their hydrophobic core (Warne et al. 2015). This molecule is devoid of anaphylactoid reactions, and allows alfaxalone-HPCD to become soluble and exert quick action after intramuscular and intravenous injection. The solution is clear and colorless, and has a concentration of 10 mg/ml. Half-life of alfaxalone is in average 24 minutes (Ferchichi et al. 2013), and this formulation does not induce pain at IV injection (Michou et al. 2012). Mild coughing after induction with alfaxalone has been reported by (Maddern et al. 2010), although this phenomenon has been attributed to the use in this study of a lower dose of alfaxalone compared to what suggested by the manufacturer. Other studies reporting intubation quality have judge it to be excellent to good (Muir et al. 2008). Data on alfaxalone in non-premedicated Beagle dogs and Greyhounds have shown that there is no significant difference between pharmacokinetic parameters between breeds (Ferré et al. 2006; Pasloske et al. 2009).

Several studies on the cardiorespiratory effects of alfaxalone as the only treatment investigated, or in comparison with other induction protocols have been published in the last decade, with some of them also investigating the use of alfaxalone in debilitated and young patients (Psatha et al. 2011; O'Hagan et al. 2012; Amengual et al. 2013). Strong evidence shows that there is no significant difference in induction quality between propofol and alfaxalone when administered over 40 to 60 seconds (Michou et al. 2012;

Chiu et al. 2016). In another study conducted on dogs premedicated with fentanyl IV, alfaxalone was more likely to maintain or increase HR after induction than propofol, with no difference in incidence of apnea between groups (Okushima et al. 2015), which was attributed to baroreceptor response (Muir et al. 2008). Psatha et al. in a study conducted on debilitated dogs reported that induction with alfaxalone or fentanyl-diazepam-propofol combination were comparable in their cardiovascular effects and clinically acceptable for induction in this cohort of patients (Psatha et al. 2011).

Clinically used doses of alfaxalone (2 mg/kg IV) in premedicated dogs have been shown to maintain arterial blood pressure, and cause mild respiratory depression at induction doses (Muir et al. 2008). Hemodynamic and respiratory effects of alfaxalone have been compared to the ones produced by propofol in non-premedicated subjects (Maney et al. 2013), and diazepam-fentanyl in compromised dogs premedicated with methadone (Psatha et al. 2011) with no apparent difference in performance. Muir reported decreased myocardial oxygen consumption in dogs after induction with alfaxalone (Muir et al. 2008). There is moderate evidence that heart rate is not significantly different after administration of alfaxalone when compared to propofol (Ambros et al. 2008; Suarez et al. 2012; Chiu et al. 2016), although several studies have reported this finding (Muir et al. 2008; Andaluz et al. 2012; O'Hagan et al. 2012; Rodríguez et al. 2012; Amengual et al. 2013). Specifically, Amengual reported an increase in HR of 14 ± 33 beats/minute after alfaxalone and a decrease in HR after propofol administration of -2 ± 28 beats/minute. Systolic, and diastolic pressures decrease significantly as shown by moderate evidence (Chiu et al. 2016) with both propofol and alfaxalone (Amengual et al. 2013).

Many clinical studies have reported the occurrence of respiratory depression with alfaxalone, although the incidence of apnea was not significantly different at clinical doses (Ambros et al. 2008; Suarez et al. 2012; Maney et al. 2013). However, at supraclinical doses (6 and 20 mg/kg), alfaxalone showed dose-dependent respiratory depression, decrease in minute volume and respiratory rate, and PaO₂ at 6 and 20 mg/kg IV (Muir et al. 2008). Maney et al also reported a significant decrease in respiratory rate compared to baseline after an average induction dose of alfaxalone of 2.6 ± 0.4 mg/kg IV (Maney et al. 2013). A study conducted on IV dose escalation to verify the incidence of apnea with propofol and alfaxalone used several multiples of labeled doses (x1 to x 20 multiples), showing that propofol was more likely to induce apnea (at x2 multiple) compared to alfaxalone (x5 multiple) (Keates & Whitem 2012).

Acid-base changes after administration of alfaxalone have been described in sheep (Andaluz et al. 2012) where a significant decrease in pH was shown in the face of normal PaCO₂, accompanied by a decrease in SpO₂ for up to 15 minutes post-induction. Decreased pH was noted with both propofol and alfaxalone post-induction and after 5 minutes, although further data are not available because anesthesia was not maintained and dogs were allowed to recover after a single bolus (Maney et al. 2013). In the same study, propofol decreases SaO₂ and PaO₂, whereas PaCO₂ and HCO₃⁻ were higher with both agents. alfaxalone also resulted in lower body temperature compared to propofol, although this finding was not reputed clinically significant.

Recoveries have been described as quiet with alfaxalone (Ferré et al. 2006), although Maney et al. reported longer time to sternal recumbency and standing with alfaxalone compared to propofol after a single bolus (Maney et al. 2013). A study on recovery

quality from alfaxalone and propofol for induction of anesthesia in dogs with history of seizures showed superior recovery quality in dogs administered propofol, although this study has been criticized due to several flaws in the design (Ferchichi et al. 2013). However, investigators pointed out that they intended to evaluate differences between commonly used protocols in clinical practice (Jiménez et al. 2012). A systematic review on alfaxalone in cats and dogs reported that there is strong evidence that recoveries after propofol and alfaxalone are smooth before reaching sternal recumbency (Chiu et al. 2016).

Increased intraocular pressure was found in dogs premedicated with acepromazine and hydromorphone, and induced with propofol or alfaxalone, but not a significant difference between groups (Hasiuk et al. 2014).

To the author's knowledge, studies comparing tiletamine-zolazepam and alfaxalone on their cardiorespiratory and acid-base effects are missing.

3.6.3 Ketamine-Diazepam

Ketamine hydrochloride is a dissociative anesthetic chemically related to phencyclidine and cyclohexamine. It is commercially available as a racemic mixture of two enantiomers which have different anesthetic potency, effects on catecholamines reuptake, and emergence delirium (Reich & Silvey 1989), although purified S-ketamine formulations are available in some countries (Grimm et al. 2015). Ketamine's pH is 3.5-5.5; it is lipophilic, and has short onset and duration of action. This drug produces dose-dependent sedation to cataleptic state with functional disorganization of the limbic, thalamocortical, and reticular activating systems (Reich & Silvey 1989). It also acts on monoaminergic and

muscarinic receptors (Grimm et al. 2015). Analgesia is also produced via antagonism of several receptors, such as opioid (μ , δ , κ) and N-Methyl-D-Aspartate (NMDA) receptor, a glutamate-binding receptor responsible for spinal nociception (Parsons et al. 1988) and the “wind-up” phenomenon at the level of the central nervous system (Muir 2010). Half-life of ketamine in dogs after an IV bolus of 10 mg/kg is 122 ± 9 minutes (Schwieger et al. 1991).

Diazepam is a benzodiazepine with great liposolubility. Its mechanism of action is potentiation of the neurotransmitter Gamma-Amino-Butyric-Acid (GABA) at the GABA receptor within the CNS, but the drug itself does not exert a direct effect on the receptor. Its half-life in dog is 0.46 ± 0.10 hours (Klotz et al. 1976). The main cardiovascular effects of ketamine are increased heart rate, cardiac output, and mean arterial blood pressure with preservation of tissue perfusion as a result of sympathetic outflow (Wong & Jenkins 1974; Haskins et al. 1985b). Its administration IV before ketamine has been reported to produce excitement, restlessness, and to blunt the sympathetic outflow stimulation but not to annul it, as shown by a lower increase in cardiac output produced by ketamine-diazepam compared to ketamine alone (Haskins et al. 1986). In this study, Haskins et al concluded that diazepam is unreliable sedative in healthy dogs and should not be used alone without previous sedation in this species (Haskins et al. 1986). Ketamine-diazepam has been historically used in combination with ketamine to provide better muscle relaxation, decreased seizure activity and salivation observed with the use of ketamine as a sole anesthetic agent (Haskins et al. 1986). Increased incidence of vomiting has been reported in healthy dogs that were given diazepam before induction and after emergence (Haskins et al. 1986). Increased intraocular pressure have also been reported

as a side effect from administration of ketamine-diazepam (Hofmeister et al. 2006; Kovalcuka et al. 2013)

Cardiorespiratory effects of ketamine alone (Haskins et al. 1985a), and its combination with diazepam (HELLYER et al. 1991; White et al. 2001) have been studied in the past. The cardio-stimulatory effects of ketamine are the results of central inhibition of sympathetic outflow and the release of catecholamines via inhibition of norepinephrine reuptake (Traber et al. 1970), although negative inotropy is also a feature of this drug (Diaz et al. 1976; Appel et al. 1979). Ketamine has been shown to produce greater levels of myocardial depression when compared to etomidate and propofol, although the difference with the latter was small (Kawakubo et al. 1999), and to increase myocardial oxygen consumption (Grimm et al. 2015). Furthermore, a lack of cardiac output compensation for anemia in dogs anesthetized with ketamine has been shown by (Van der Linden et al. 1998). Diazepam alone has minimal effects on arterial blood pressure, and heart rate (Jones et al. 1979). However, Haskins et al. reported an increase in heart rate after diazepam administration IV attributed to awakening of the central nervous system and excitement (Haskins et al. 1986). Overall, ketamine produces beneficial cardiovascular effects in normovolemic and hypovolemic dogs, with an initial transient decrease in MABP for less than 1 minute, to then increase significantly overtime, with no changes in systemic vascular resistance (Haskins et al. 1986; Haskins & Patz 1990). Intravenous doses of ketamine-diazepam used by Haskins in his studies were higher (10 mg/kg of K, 0.5 mg/kg of diazepam) compared to the ones used in the present study. Lower doses of this combination (5-5.5 mg/kg of ketamine and 0.25-0.28 mg/kg of diazepam) compared to the ones used in the present study have been used with (Ko et al. 1998; Enouri et al. 2008; Hena-

Guerrero & Ricc6 2014) or without (HELLYER et al. 1991) addition of other agents. At these doses, intubation was prolonged in one study, while the use of 5 $\mu\text{g}/\text{kg}$ of medetomidine as a co-induction agent improved quality of anesthetic induction (Ko et al. 1998), although respiratory depression was significantly more marked in sedated dogs compared to non-sedated, especially with the use of α_2 -agonist agents in premedication (Enouri et al. 2008).

Ketamine has been traditionally considered as a mild respiratory depressant compared to barbiturates (Hirshman et al. 1977), although authors have reported clinically effective doses of ketamine to have caused apnea in some individuals (Haskins et al. 1986; Grimm et al. 2015). Minute ventilation and respiratory rate were decreased in healthy dogs anesthetized with ketamine-diazepam, although diazepam was blamed to potentiate the minimal respiratory depression produced by ketamine (Haskins et al. 1986). Diazepam does not affect oxygen consumption and delivery, and P_aCO_2 , whereas the addition of ketamine produces significant increase in these parameters up to 30 minutes after administration (Haskins et al. 1986). The combination ketamine-diazepam does not produce different oxygen extraction ratio compared to ketamine alone (Haskins et al. 1986). Another peculiarity of ketamine is that it can produce an “apneustic breathing” pattern, with the features of prolonged inspiratory phase and shortened expiratory phase (Jaspar et al. 1983).

Acid-base status in dogs made hypovolemic was not modified by ketamine administration, except from a transient mild respiratory acidosis with no changes in HCO_3^- and BE (Haskins et al. 1986).

Recoveries have been described to range from good to rough in dogs anesthetized with ketamine-diazepam, with marked improvement if inhalant anesthetics had been used for maintenance of anesthesia (Grimm et al. 2015).

3.6.4 Propofol

Propofol (2,6-diisopropylphenol) is a non-barbiturate hypnotic anesthetic. Its pH ranges between 6.5 and 8.5 for the solution containing 1% propofol, 19% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide (same formulation used in the current study). Use of propofol is characterized by smooth induction, rapid onset of unconsciousness, short duration of action (Morgan & Legge 1989), although muscle tremors, paddling, and limb rigidity in non-sedated dogs have been reported (Davies 1991; Watney & Pablo 1992; Muir 3rd & Gadawski 1998; Aarnes et al. 2009; Ferreira et al. 2015). This drug acts on the GABA_A receptor within the central nervous system, as does alfaxalone and etomidate (Garcia et al. 2010). Rapid distribution within the central nervous system occurs after injection and half-life in dogs after a single bolus IV ranges around 91 minutes (Ferchichi et al. 2013).

Its hemodynamic effects have been extensively studied in dogs (Goodchild & Serrao 1989; Morgan & Legge 1989; Weaver & Raptopoulos 1990; Muir 3rd & Gadawski 1998; Quandt et al. 1998). Decreased myocardial contractility, systemic vascular resistance, preload, and sympathetic activity have been shown to decrease cardiac output and be dose-dependent (Goodchild & Serrao 1989; Pagel & Warltier 1993; Short & Bufalari 1999). These effects are magnified in ill patients, such as in the case of hypovolemia,

and impaired left ventricular function (Pagel et al. 1998). The decrease in systemic vascular resistance and stroke volume is not compensated by an increase in heart rate with this drug. Furthermore, propofol has been shown to sensitize the myocardium to arrhythmias induced by epinephrine, although not arrhythmogenic (Kamibayashi et al. 1991). Critical oxygen excitation ratio in dogs anesthetized with propofol is $41.1 \pm 6.4\%$ (Van der Linden et al. 2000). In a study conducted on healthy dogs premedicated with acepromazine and oxymorphone, propofol has significantly lower heart rate, cardiac output, and oxygen delivery compared to ketamine-diazepam and ketamine-propofol combination (Henao-Guerrero & Ricc3 2014). Even when administered as a constant rate infusion, propofol and alfaxalone have been shown to produce minimal cardiovascular and moderate respiratory depression (Ambros et al. 2008).

After induction of anesthesia in dogs with propofol, respiratory depression and apnea are often seen (Muir 3rd & Gadawski 1998), especially subsequent to rapid injection (Amengual et al. 2013), where reduction in tidal volume and respiratory rate occur. In one study, propofol was more likely to cause apnea after induction of general anesthesia compared to alfaxalone (Keates & Whitem 2012).

Recovery quality from propofol is often good to excellent, with quietness being the main observable feature (Morgan & Legge 1989; Grimm et al. 2015), and it has been judged to be of similar and superior recovery quality to alfaxalone and etomidate respectively (Sams et al. 2008; Chiu et al. 2016). In a study comparing induction and recovery quality between propofol and ketamine-diazepam, the former produced better recovery quality, whereas the latter produced better induction quality, shorter induction time, and less myoclonus (Ferreira et al. 2015).

3.6.5 Isoflurane

Isoflurane (2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro-ethane) is a non-flammable halogenated inhalant anesthetic widely used in veterinary medicine. Its physical properties allow for quick induction and recovery from general anesthesia. Isoflurane has negative inotropic, dromotropic, and chronotropic effects, and dose-dependent decrease in preload, systemic vascular resistance and cardiac output in humans, dogs, cats, and other species (Steffey & Howland Jr 1977; Pagel et al. 1991; Vigani et al. 2011; Miller et al. 2014). Minimum alveolar concentration (MAC) of isoflurane is 1.28% in dogs (Steffey & Howland Jr 1977), although this value is relatively uniform across species. Isoflurane is a potent respiratory depressant, and apnea subsequent to its administration occurs in dogs at 2.4 MAC (Steffey & Howland Jr 1977). In a study conducted on the effect of isoflurane on tissue perfusion, authors found significant differences in oxygen delivery, cardiac output, mean arterial blood pressure, SvO₂ and oxygen extraction ratio, with concentrations of isoflurane of 2 MAC decreasing all the aforementioned parameters compared to 1.5 MAC, except for oxygen extraction ratio that was significantly increased at 2 MAC (Floriano et al. 2016). Cardiac output increased overtime during the experiment, attributed to increased preload due to IV fluid administration which was set at 10 ml/kg/hr explained by the Frank Starling's law. However, in the same study the authors did not find any significant difference between multiples of MAC in serum lactate, although this finding was attributed to isoflurane-induced vasodilation which may have actually increased perfusion of capillary beds, concluding that perfusion was impaired but not clinically significant (Floriano et al. 2016).

Recovery from isoflurane anesthesia has been evaluated with and without previous premedication in dogs (Bennett et al. 2008; Lopez et al. 2009; Keating et al. 2016) and with co-administration of nitrous oxide (Laing et al. 2009). Lopez et al. reported no difference between recovery quality of non-premedicated dogs between desflurane, sevoflurane, and isoflurane, although time to sternal recumbency was markedly shorter with the first agent. Absolute scores were not reported in the manuscript making impossible to know what the quality of recovery was. Laing et al. reported that recovery quality from isoflurane anesthesia was improved by nitrous oxide in premedicated dogs induced with propofol (Laing et al. 2009).

3.6.6 Recovery from General Anesthesia

In general, smooth and quiet emergence from general anesthesia is desirable because it allows for quick discharge in day case procedures requiring anesthesia, and because excitement causes increased levels of catecholamines and oxygen consumption that can be of harm for patients with cardiovascular, respiratory, and metabolically compromised, injury, increased pain, hemorrhage, and self extubation (Lepouse et al. 2006). In human medicine, excitement upon recovery from anesthesia is named “emergence delirium” or “emergence agitation”, and it has been defined as “a disturbance in a child’s awareness of and attention to his/her environment with disorientation and perceptual alterations, including hypersensitivity to stimuli and hyperactive motor behavior in the immediate post-anesthesia period” (Kwak et al. 2010). Good recovery quality has been judged as so when quiet, coordinated movements accompanied with a single attempt to

achieve sternal recumbency and standing occurs, whereas poor recoveries present vocalization, lack of coordination, thrashing of limbs, paddling, excitement, disorientation, lacrimation and salivation (Buback et al. 1996; Lerche et al. 2000; Love et al. 2007; Seliskar et al. 2007). Induction agent, premedication, maintenance agent, analgesia and body temperature have been all reported to affect recovery quality and duration (Laing et al. 2009).

ASA PS Classification*	Definition	Examples, including, but not limited to:
ASA I	Normal healthy patient	Healthy, non-smoking, no or minimal alcohol use
ASA II	Patient with mild systemic disease	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity ($30 < \text{BMI} < 40$), well-controlled DM/HTN, mild lung disease
ASA III	Patient with severe systemic disease	Substantive functional limitations; One or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity ($\text{BMI} \geq 40$), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, premature infant PCA < 60 weeks, history (>3 months) of MI, CVA, TIA, or CAD/stents.
ASA IV	Patient with severe systemic disease that is a constant threat to life	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
ASA V	Moribund patient who is not expected to survive without the operation	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction

ASA VI	Declared brain-dead patient whose organs are donated	
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Table 1. American Society of Anesthesiology patient physical status classification. Updated October 15, 2014. Acid reflux disease (ARD), American Society of Anesthesiologists (ASA), body mass index (BMI), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), cerebral vascular accident (CVA), disseminated intravascular coagulation (Arnold et al.), diabetes mellitus (DM), end-stage renal disease (ESRD), hypertension (HTN), myocardial infarction (MI), post conceptual age (PCA), physical status (PS), transient ischemic attack (TIA).

*The addition of “E” denotes Emergency surgery. (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part)

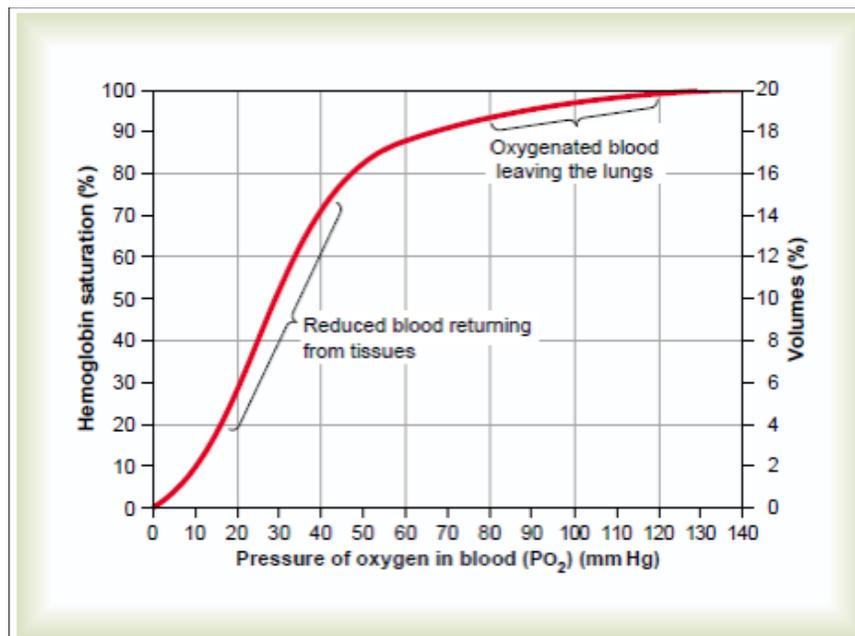


Figure 1. Oxyhemoglobin dissociation curve. From (Guyton & Hall 2006).

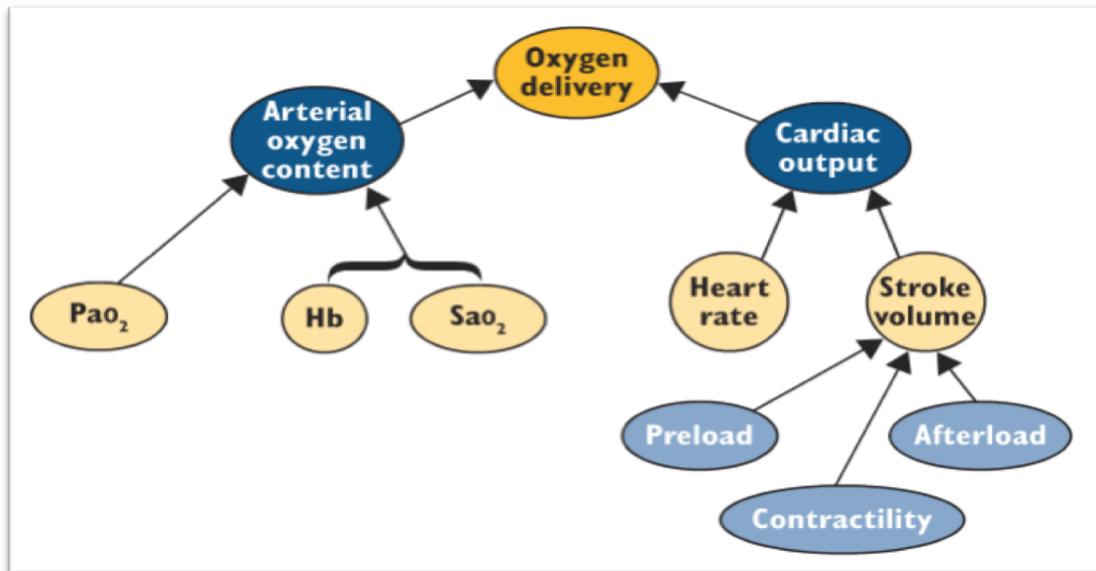


Figure 2. Determinants of oxygen delivery (DO_2) (Hb = Hemoglobin, PaO_2 = partial pressure of arterial oxygen, SaO_2 = arterial oxygen saturation) from (Karagiannis et al. 2006).

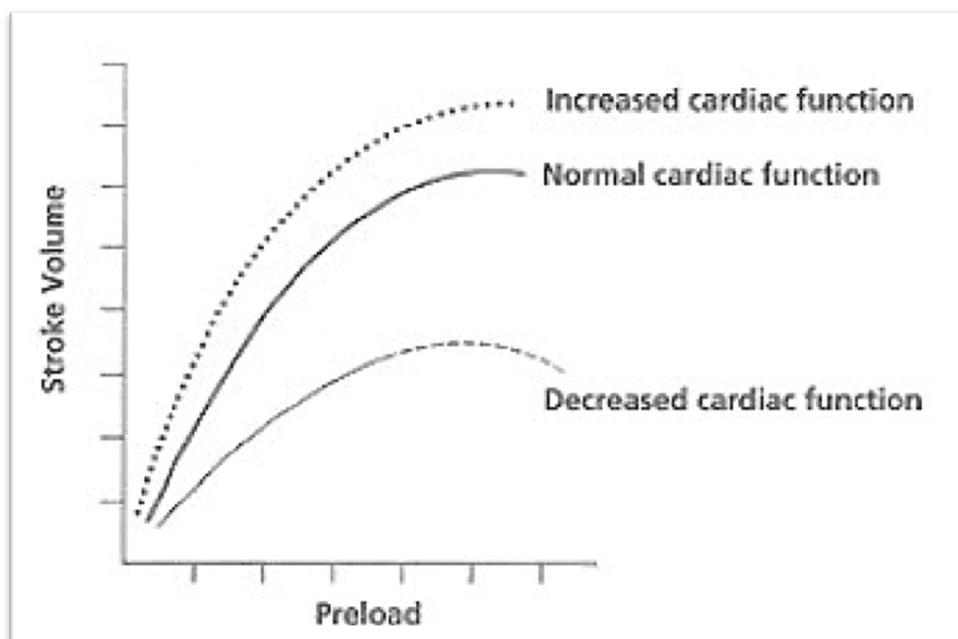


Figure 3. Frank Starling's curve showing physiologic relationship between stroke volume and preload (solid line) in normal cardiac function. From www.edwards.com

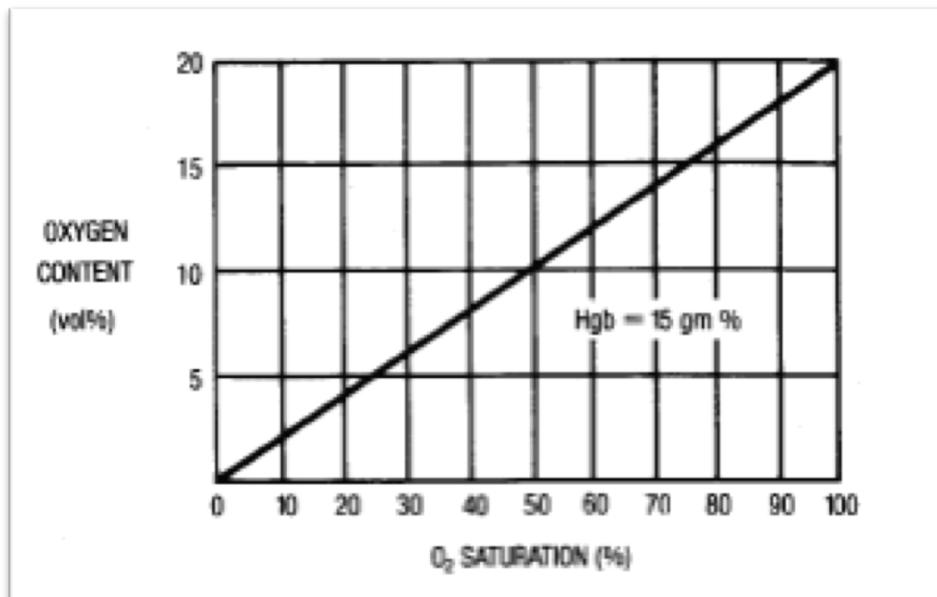


Figure 4. Relationship of oxygen saturation to oxygen content. From (To)

SvO₂	Mechanism	Cause
High	↑ DO₂	Increased FiO ₂ , Hyperoxia, Blood Transfusion, IV Fluids, Inotropic Agents Administration,
	↓ VO₂	Hypothermia, Sedation, Anesthesia, Hypothermia, Neuromuscular blocker use, Mechanical Ventilation, Sepsis (↓ O ₂ Extraction),
Low	↓ DO₂	
	↓ <i>Hb</i>	Anemia, Hemorrhage
	↓ <i>SaO₂</i>	Any condition causing hypoxia
	↓ <i>CO</i>	Hypovolemia, Shock, Arrhythmias, Heart Failure
	↑ VO₂	Hyperthermia, Pain, Shivering, Seizures, Respiratory Failure, ↑ Metabolic Demand

Table 2. Clinical application of mixed-venous oxygen saturation ($S_{mv}O_2$) values. Modified from (van Beest et al. 2011).

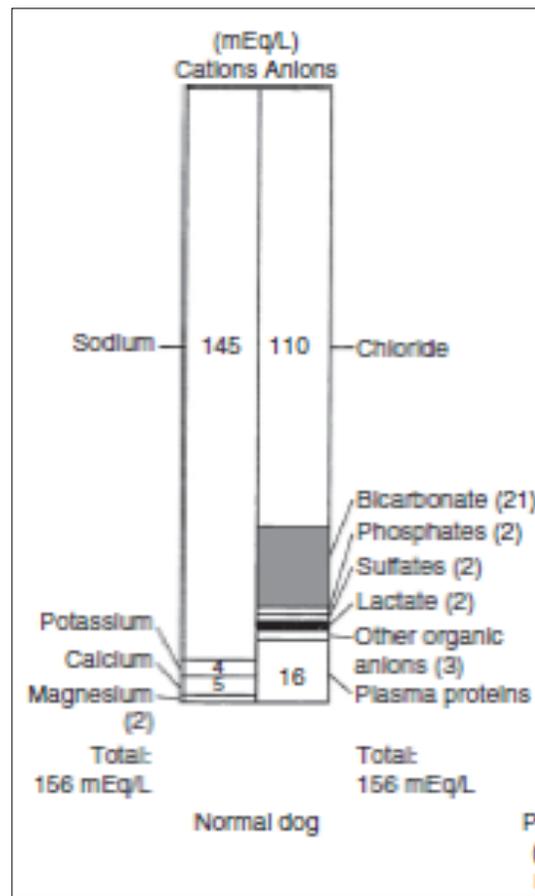


Figure 5. Gamblegram of the electrolyte distribution in normal canine plasma. From (DiBartola 2011)

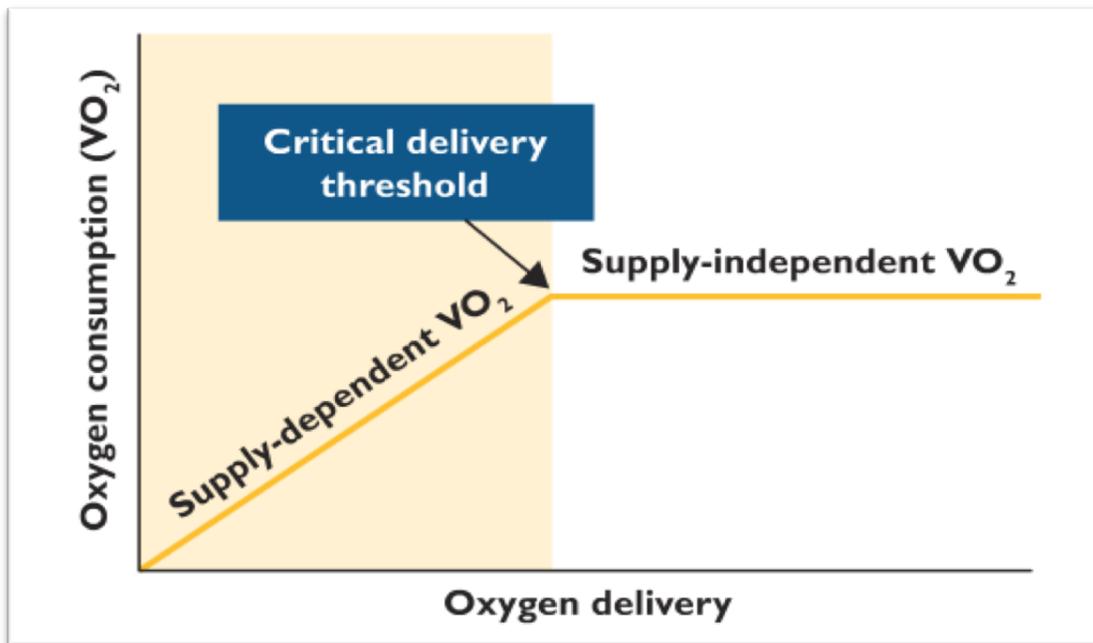


Figure 6. Relationship between oxygen delivery (DO_2) and consumption (VO_2). Modified from (Karagiannis & Reniker 2006)

Table 3. Causes of Type A Hyperlactatemia
<i>Systemic Hypoperfusion</i>
<ul style="list-style-type: none"> • Hypovolemia/hypovolemic shock • Distributive shock • Systemic inflammatory response syndrome, sepsis, anaphylaxis, neurogenic shock • Cardiogenic shock • Myocardial failure, valvular disease, arrhythmias • Obstructive shock • Cardiac tamponade, tension pneumothorax
<i>Local Hypoperfusion</i>
<ul style="list-style-type: none"> • Arterial thromboembolism • Gastric-dilatation volvulus • Mesenteric torsion • Tourniquet placement
<i>Impaired hemoglobin oxygen carrying capacity</i>
<ul style="list-style-type: none"> • Carboxyhemoglobin (carbon monoxide toxicosis) • Methemoglobin
<i>Excessive muscle activity</i>
<ul style="list-style-type: none"> • Exercise • Trembling • Seizures • Tremorgens
<i>Hypoxemia (PaO₂ < 40 mmHg), Anemia (PCV < 15%)</i>

Table 3. Causes of hyperlactatemia A. Modified from (Karagiannis et al. 2006)

4. MATERIALS AND METHODS

4.1. Ethical Approval

Ethical approval from the Oregon State University's Institutional Animal Care and Use Committee was obtained before the beginning of this research (# 4504).

2. Study Design

The present study was designed as a prospective double-blinded randomized crossover study, with subjects serving as their own control. Randomization of subjects and drug sequence was carried out by use of a modified Latin square so that each dog would receive tiletamine-zolazepam, alfaxalone, ketamine-diazepam, or propofol in four separate anesthetic episodes, with a wash out time of at least seven days to rule out any carryover effect. Overall, each dog was anesthetized four times (one per drug), every 7 days, two times per day (during phase I and phase III). No sedative compounds were administered at any point during this experiment to avoid the effects of these drugs on the cardiorespiratory system. Animals were excluded from the study if they were classified as $>$ ASA I upon pre-anesthetic physical examination.

3. Animals

Six purpose-bred adult healthy mixed-breed dogs, three intact females and three intact males, were enrolled in the study. Mean body weight \pm SD (Jennings & Davidson) were 22.1 ± 2.6 kg. Animal mean age was 14.6 ± 3 month. Dogs were housed in two large

pens in groups of three divided by gender. They were acclimated for one week before starting the trial. Physical exam, complete chemistry and cell blood count were performed on the day after acclimation was complete. Dogs were fed twice a day with commercially available dry food, and given water ad libitum. They were considered healthy and entered in the study. Before each anesthetic episode of the trial, the animals were weighed and a pre-anesthetic physical exam was performed by the same individual. All dogs were fasted twelve hours before the anesthetic trial to reduce the incidence of regurgitation and aspiration. Subject undergoing trial were separated from other dogs and conducted to the experiment area. Dogs undergoing trial was housed in a commercially available metal kennel with a clear front door to allow visual observation of the subject during recovery.

Once the anesthetic episode was completed, dogs were allowed to recover in the research area inside the same kennels used upon their arrival. A second physical exam was performed, catheter sites verified as not bleeding or swollen, and dogs were re-conducted to their housing facility. The morning after the anesthetic episode, the same veterinarian performed a second physical examination and the subject was transferred to the boarding facility.

At completion of the study, all dogs were disposed accordingly to Oregon State University's Animal Placement Policy.

4.4 Techniques

4.4.1 Arterial Blood Pressure Measurement

Direct arterial blood pressure monitoring was performed by connecting an arterial catheter to high-pressure tubing (non-compressible) attached to a blood pressure transducer and a multi parametric monitor. The transducer was zeroed and leveled at the level of the right atrium (reference point = greater trochanter of the dependent humerus) to ensure accuracy. Catheter potency was maintained with heparinized saline. All transducers were placed on the same holding mount which was leveled as previously described.

A square wave test was performed once the zeroing and the leveling process were completed to verify any under- and overdamping phenomenon by fast-flushing the high-pressure tubing connected to the arterial catheter. This process allows for identification of the presence of clot, air bubble, and kinking or disconnection of the noncompliant tubing.

Monitoring direct arterial blood pressure in veterinary medicine is perhaps only limited to specialty practice and academia due to the technical difficulties that this technique presents, as well as the relatively high cost of the monitoring system. However, values obtained via direct arterial blood pressure monitoring are of paramount importance for calculation of other hemodynamic parameters which are of interest in the present study.

Although complications such as hematoma, bleeding, and infection of the catheter site, as well as vascular complications such as ischemia, thrombosis, and pseudoaneurism of the vessel requiring surgical intervention are described in human medicine (Valentine et al. 2005; Lucet et al. 2010; Garg et al. 2013; O'Horo et al. 2014), this technique remains

a priceless tool in assessing patient cardiovascular, respiratory, and acid-base status in the clinical setting.

4.4.2 Cardiac Output Measurement

Thermodilution is currently the gold standard for comparison of other methods to measure cardiac output. This technique is employed in human medicine to evaluate fluid status, monitor cardiac output, manage right ventricular failure, and diagnose pulmonary hypertension (Lough 2015). After placement of an 8F introducer in the right jugular vein, a tipped pulmonary arterial catheter is floated into the pulmonary artery via jugular vein, right atrium, and right ventricle. Placement can be accomplished with the help of real-time fluoroscopy guidance, or by observing changes in pressure typical of the locations the tip of the catheter will be travelling through. A graphic representation of the aforementioned waveforms is shown in Figure 7. Pulmonary arterial catheters have a minimum of three ports and multiple lumens. All ports are color and shape coded to prevent misidentification. In its final positioning the proximal port is located in the right atrium, and the distal port is going to be located in the main trunk of the pulmonary artery along with a thermistor. The third port allows for inflation of the balloon positioned at the tip of the catheter to measure pulmonary arterial wedge pressure. The balloon inflates to a maximum of 1.5 ml and is used to measure pulmonary arterial wedge pressure. If complete wedging occurs with less volume, the tip of the pulmonary arterial catheter must be retracted and verified for wedging into smaller branches of the pulmonary artery. Proximal

and distal ports are connected to a zeroed and leveled pressure transducer. This technique for assessing cardiac output utilizes changes in blood temperature following injection of iced saline bolus of known temperature into the proximal port of the pulmonary arterial catheter (Weisel et al. 1975). In the right atrium, blood mixes with iced-saline and moves to the pulmonary artery. At least three 5 or 10 ml saline injections are performed to obtain accurate measurements. Values varying by more than 10% among others should be discarded. Retained values are then averaged. The averaging process minimizes inaccuracy generated by the presence of arrhythmias. The change in blood temperature is detected at the distal port of the pulmonary arterial catheter by the thermistor and data is plotted in a graph as temperature over time. The area under the curve displayed on the bedside monitor represents cardiac output (Figure 8). This method is based in the Stewart-Hamilton equation:

$$f) \quad \text{Cardiac Output} = \frac{V * (TB - TI)}{\int_0^{\infty} \Delta T(t) * dt}$$

where V indicates volume of injected cold saline, TB indicates blood temperature, and TI temperature of injected saline. The denominator is an integral of the temperature gradient (ΔT), where dt represents the variable of integration. The domain of the integral is $t = 0$ to $t = \infty$. On the cardiac output curve, temperature returns to baseline. This is only a prediction of the mathematical model used by the computer, since due to recirculation, blood temperature does not actually return to baseline (Grimm et al. 2015). A small area under the curve will be indicative of a high cardiac output, due to the fact that this is inversely proportional to $\int \Delta T dt$. Conversely, when cardiac output is low, the cold saline makes its transition to the pulmonary artery in a longer time, making the area under the

curve wider and therefore cardiac output will be larger (Figure 9). In the present study, the cardiac output computer (Mac-Lab TRAM 451 Marquette, GE Medical Systems, Chicago, IL) was calibrated to inject 5 ml of iced saline. It is important to calibrate the cardiac output computer because the use of incorrect volume or temperature of the injected can produce false readings (Tournadre et al. 1997).

Ideally, the same individual should perform all injections to ensure consistency in injection speed and waveform, and all injections should be performed at expiration (Lough 2015). The advantage of this technique is not only allowing accurate measurements of CO, but also for sampling of mixed-venous blood for gas analysis and co-oximetry. Oxygen saturation of mixed-venous blood ($S_{mv}O_2$) can be measured in mixed-venous blood to assess tissue perfusion and oxygenation. Only blood in the pulmonary artery can offer reliable information for this purpose, since blood coming from the cranial and the caudal vena cava, and the coronary sinuses reaches full mixing here. Because a “wedged” catheter can cause artificially elevated $S_{mv}O_2$ values due to absorption of oxygen from the surrounding alveoli, sampling of the mixed-venous blood was performed before inflation of the balloon of the pulmonary arterial catheter to measure pulmonary arterial wedge pressure. Deviation of $S_{mv}O_2$ values by 10% for more than 5 minutes should be considered significant of changes in oxygen delivery and perfusion (Lough 2015).

Although placement of pulmonary arterial catheter provides the clinician with accurate and important information, its use in the clinical setting has been progressively abandoned due to several studies showing few advantages compared to disadvantages in human intensive care (Connors et al. 1996; Harvey et al. 2005; Sakr et al. 2005). Insertion

of a pulmonary arterial catheter is devoid of risks. Transient arrhythmias, hematoma, arterial puncture, hemo- and pneumothorax, pain, bleeding, and air embolus have all been describes as complications associated with pulmonary arterial catheter placement (Lough 2015). In veterinary medicine, pulmonary arterial catheter has little clinical application, also due to the cost associated with this technique (Gunkel et al. 2004); pulmonary arterial catheter are also difficult to be maintained in the correct location in awake animals; furthermore, morphologic differences in veterinary species compared to humans may increase the incidence of erroneous readings (Muir et al. 1976; Dyson et al. 1984; 水野豊香 et al. 1994).

Other less invasive techniques to measure CO have been developed in the last two decades for their advantages of being more clinically applicable, more affordable, and less technically demanding. Some of these techniques include NICO[®], lithium thermodilution (PiCCO-TD), pulse contour analysis (PiCCOc), lithium dilution (LiDCO), pulse power analysis (PulseCO), and echocardiography/echo-Doppler. However, thermodilution technique to measure CO remains the gold standard for comparison of other techniques in human and veterinary medicine and it has been historically used in classic hemodynamic studies (Shih et al. 2011).

4.5 Phase I: Instrumentation

Prior to each experiment, calibration of the respiratory gas analyzer (Gas Module GE[®], Datascope Corp; Mahawah, NJ) used for this study was performed according to

manufacturer recommendation with a calibration gas mix (Airgas Specialty Gases Inc.; Lenexa, KS, USA).

Dogs were acclimated to the research area on each day of the trial for a period of two hours, during which a pre-anesthetic physical exam was performed, and HR, RR, temperature (T), capillary refill time (CRT), and mucous membrane color were recorded and ASA physical status assigned. A venous catheter (18 SWG 48 mm, BD, Franklin Lakes, NJ) was aseptically placed in the right saphenous vein. Subsequently, a face mask was presented to the dog undergoing experimentation and sealed to make the borders of the mask have full contact with the skin of the muzzle. The mask was connected through an F-Universal circuit (One Nexus Unilimb rebreathing circuit, MMS Sales Corporation, McAllen, TX, USA) to a circle system of an anesthesia machine (Excel 210 MRI Compatible, Ohmeda, Madison, WI) provided with mechanical ventilator. A calibrated vaporizer (Sevotech 5, Datex Ohmeda Division, Helsinki, Finland) was then set to deliver 7% sevoflurane (Sevoflo, Abbott, North Chicago, IL), and the oxygen flow rate set between 250 and 300 ml/kg/min. During this process, one investigator guaranteed mask adhesion to the dog's muzzle, while another was restrained it. Once muscle tone decreased, dogs were placed in left lateral recumbency on a fluoroscopy table, and mask maintained in place until palpebral reflex was absent. Endotracheal intubation was performed using a laryngoscope (WelchAllyn, Skaneateles Falls, NY), and a silicone endotracheal tube (11 and 12 mm OD, Surgivet, Dublin, OH). The endotracheal tube was connected to an adaptor provided with a sidestream expired gases sampling port (luer lock connection), attached to a sampling line connected to the respiratory gas analyzer. This monitor utilizes

a non-dispersive infrared technique to analyze inhalant anesthetic agents and carbon dioxide measuring the absorption of the gas sample at several wavelengths, while oxygen concentration is measured via a sensor using the paramagnetic principle. A Universal F breathing system was connected to a circle system to deliver carrier and anesthetic gases to the subject. Oxygen flow was decreased to 2 L/min and the vaporizer setting was set to 3%. A leak test to test the sealing of the endotracheal tube cuff with the trachea was conducted, and the amount of air necessary to seal the leak was recorded during this phase for every dog during each anesthetic episode. Mechanical ventilation (end point, = $35 < \text{EtCO}_2 > 45$ mmHg) was initiated to maintain a steady anesthetic plan during this phase. Pulse oximetry was used to provide information on heart rate and SpO₂ (Masimo, Irvine, CA). Three ECG gel pads (Heart Trace, Noida, India) were placed on the medial aspect on both front limbs, and one on the lateral aspect of the right pelvic limb. The pads were also taped to ensure stability during the upcoming phase II and III. Three ECG leads were connected and an ECG tracing in lead II was obtained on a multi-parametric monitor (Spectrum[®], Datascope Corp; Mahawah, NJ, USA). A blood pressure cuff (Trimline, WelchAllyn, Skaneateles Falls, NY) of about 40% of the circumference of the limb was placed on the right pelvic limb around the tarsus to measure arterial blood pressure by oscillometric technique. Temperature was monitored via esophageal probe placed at the level on the 11th rib and maintained via the use of a warm-air blowing device (Bair Hugger[®], Arizant Inc., Eden Prairie, MN, USA) and a blanket (Jorgensen Laboratories, Inc, Loveland, CO, USA) to cover the torso of the animal. At this point, two 22G x 2.5cm arterial catheters (BD, Franklin Lakes, NJ) were placed in the coccygeal artery and the right dorsal pedal artery after aseptic preparation. Lactated Ringer's Solution (Hospira, Lake Forest,

IL) was administered IV at a rate of 5 ml/kg/hr according to the 2013 AAHA/AAFP Fluid Therapy Guidelines (Davis et al. 2013). A 10 by 10 cm area including the right jugular groove and corresponding to the level of the second and fourth cervical vertebrae was clipped and aseptically prepped. Using sterile technique, an 8 French (F) introducer (Cook Medical, Bloomington, IN) was placed in the right jugular vein using a modified Seldinger's technique. Cefazolin (22 mg/kg, West-Ward Pharmaceuticals, Eatontown, NJ) was prophylactically administered IV. Once patency was insured for all catheters, the vaporizer was turned off and oxygen flow was maintained at 2 L/min. Catheters were covered with cohesive wrapping material (Co-flex, Andover, England) and subjects were moved onto a mattress pad and covered with a blanket for recovery. Criterion for extubation was the presence of two consecutive swallows with tongue movement.

4.6 Phase II: Recovery from phase I

The same operator throughout the study restrained the animals during recovery from phase I. Special attention during recovery was given to maintaining catheter position to allow proper functioning for phase III. Animals were allowed to stand only when they were making significant coordinated effort to do so. If the dogs were ataxic, ambulation was restricted. End point to start phase III were a) at least 30 minutes after extubation from phase I, b) ataxia was no longer present, and c) the dogs socially interacted with research personnel. During this phase, two invasive blood pressure transducers were placed on the same mount to be parallel and on the same plane and were calibrated with a mercury column manometer at two different scales, and zeroed at the level of the point of

the dog's dependent shoulder when in left lateral recumbency during phase III. This anatomical landmark is the reference point for zeroing at the level of the right atrium and the phlebostatic axis (Lough 2015). An ice bath was prepared to cool down 200 ml of sterile NaCl (0.9% for irrigation, Baxter Healthcare Corporation, Deerfield, IL) to a temperature of 1°C. Saline temperature allowed to stabilize in an ice bath for 30 minutes and measured continuously to ensure proper temperature at injection and measure cardiac output by thermodilution (Mac-Lab TRAM 451 Marquette, GE Medical Systems, Chicago, IL). The temperature probe of the cardiac output monitor was inserted in the iced bath, in contact with the stainless steel bowl containing the sterile saline.

4.7 Phase III: Measurements

Once criteria for starting phase III were met, dogs were placed in left lateral recumbency on a fluoroscopy table, gently restrained, and the fluoroscopy C-arm (OEC[®] 9800 Plus Super C-arm, GE Healthcare, Chicago, IL) was centered at the level of the 3rd right rib. Tiletamine-zolazepam is manufactured in a powder that needs reconstitution with 10 ml of NaCl 0.9% to obtain a solution with a concentration of 50 mg/ml of a 50:50 mixture. Tiletamine-zolazepam (Telazol[®], Zoetis, New York, NY), was reconstituted no more than 10 minutes before the end of phase II. K (Zetamine, VetOne, Boise, ID) and diazepam (Diazepam, Hospira, Lake Forest, IL) were drawn in different syringes and then mixed in one syringe. Alfaxalone (Jurox, Kansas City, MO) and propofol (Propofol, Abbot, North Chicago, IL) was drawn according to manufacturers' recommendation. Induction drug volume for each agent was separated in four syringes containing 25% of the total

dose calculated for induction of each animal. Syringe content was made unrecognizable by covering the barrel with cohesive bandage material.

Arterial and venous catheters were checked for patency. Two 122 cm long non-compliant tubing (Smiths Medical, Dublin, OH) filled with a column of HS were connected to the arterial blood pressure transducer (DTXPlus[®], BD Medical Systems, Sandy, UT, USA) and to the pulmonary artery transducer and their ports respectively connected to the arterial catheter and to the proximal port of the pulmonary arterial catheter. Arterial waveform was observed and verified for under- and overdamping. If underdamping occurred, another ml of heparinized saline was used to flush the catheter. Overdamping was verified with a square wave test (Lough 2015). Continuous flush of heparinized saline was administered at a rate of 3 ml/hr intra-arterially to prevent clotting of the dorsal pedal arterial catheter's lumen. A bag of Lactated Ringer's solution was connected to the saphenous venous catheter via infusion set (Interlink, Baxter, Deerfield, IL), and infused at 5 ml/kg/hr for the duration of the procedure. Three electrocardiography leads were connected to the ECG gel pads.

A test fluoroscopy image was performed to verify correct positioning. A 3 port-7F pulmonary arterial catheter (Edwards Lifescience, Irvine, CA) was flushed with sterile saline and floated into the pulmonary artery via fluoroscopy guidance, and via observed pressure changes while the catheter was advanced progressively through the cranial vena cava, right atrium, right ventricle, and finally pulmonary artery. The tip of the pulmonary arterial catheter was positioned to obtain a waveform compatible with correct positioning into the main trunk of the pulmonary artery to avoid "wedging" of the catheter

into smaller branches. A radiographic image (Figure 10) provide confirmation of the pulmonary arterial catheter positioning. The length of the pulmonary arterial catheter (110 cm) was believed adequate to provide placement of the proximal port in proximity of or into the right atrium due to waveform characteristics compatible with the location. After instrumentation, dogs were allowed to acclimate until their heart rate reached values similar to the ones recorded at the previous physical exam, and the dog appeared relaxed. At this point, pre-induction baseline measurements were taken in three consecutive repetitions in the following order: mean right atrial pressure, mean pulmonary arterial pressure, mean pulmonary arterial wedge pressure, cardiac output, heart rate, mean systolic arterial blood pressure, mean arterial blood pressure, mean diastolic arterial blood pressure, and respiratory rate. All measurements were performed in triplicate. Five ml of iced NaCl 0.9% were injected as a bolus into the proximal port of the pulmonary arterial catheter three to five times to measure cardiac output, and three values within 10% variation accepted and averaged for statistical analysis. If respiratory sinus arrhythmia was present, cold saline injections to measure cardiac output were performed at the beginning of inspiration and heart rate averaged for minute. The number of injections was recorded for each time point. Body temperature was measured with a rectal thermometer at each time point.

Baseline arterial and mixed-venous blood samples were also anaerobically drawn respectively from the coccygeal arterial catheter and from the distal port of the pulmonary arterial catheter. Three ml syringes were heparinized accordingly to previously described technique (Hopper 2005). A 1 ml and an 8 ml pre-sample were respectively drawn from the dorsal pedal artery and the pulmonary artery before sampling. This blood volume was then returned to the dog after sampling was complete. Acid-base variables measured were

arterial pH_a , PaO_2 , PaCO_2 , aHCO_3^- , glucose (GL_a), lactate (LAC_a), and base excess (BE_a). Acid-base variables measure for mixed-venous were pH_{mv} , PvO_2 , PmvCO_2 , mvHCO_3^- , glucose (GL_v), lactate (LAC_{mv}) and base excess (BE_{mv}). All blood gas measurements were corrected for temperature, FiO_2 , and barometric pressure. Total hemoglobin, SaO_2 , and SmvO_2 were measured via co-oximetry. Electrolytes measured in both arterial and mixed-venous samples were Na^+ , Cl^- , K^+ , Ca^{++} . Samples were immediately processed for blood gas analysis or stored in ice and measured for less than 10 minutes. A blood gas analyzer (RAPIDlab 1200 systems, Siemens, Munich, Germany) was used for processing blood samples; this blood gas analyzer utilizes potentiometry to measure pH; Severinghaus method for PCO_2 ; amperometric for PO_2 , lactate, and glucose; spectrophotometric for hemoglobin and SaO_2 (co-oximetry); Ion specific electrode for Na^+ , Cl^- , iCa^{++} , and K^+ . Packed cell volume and total plasma proteins were determined respectively by centrifugation and refractometry.

After collection of baseline data, successive increments (25% of the total dose) of one of the trial drugs was administered over 10 seconds until tracheal intubation was performed. The person performing tracheal intubation, the one assessing jaw tone, and the one administering the treatment were all blinded to the drug administered. A period of 15 seconds separated each 25% dose injections to minimize differences in administration rate between drugs, while maintaining endotracheal intubation as the end-point to induction. An additional 25% of the trial drug in use each day of the experiment was possible as rescue dose if intubation was not achievable with the full calculated dose (alfaxalone 4 mg/kg, ketamine-diazepam 7 and 0.3 mg/kg, propofol 6 mg/kg, tiletamine-zolazepam 5 mg/kg). Mean dose for each treatment was calculated based on the amount administered.

Hypoxemia was defined as a $\text{PaO}_2 < 80$ mmHg and apnea as the absence of inspiration greater than 30 seconds. Carbon dioxide absorber in the circle system was changed whenever the inspired fraction of CO_2 was higher than 2 mmHg.

A timer was used to dictate intervals between time points. The endotracheal tube was cuffed with the same amount of air recorded in phase I to avoid performing a leak test which would have lowered EtCO_2 and potentially reaches the apneic threshold. An F-Universal breathing circuit provided with sidestream adaptor for respiratory gas sampling and a 3 L reservoir rebreathing bag. Oxygen flow was set at 60 to 100 ml/kg/min, isoflurane vaporizer (Isotec 5[®], Datex Ohmeda Division, Helsinki, Finland, Isoflo[®], Abbott Animal Health, Abbott Park, IL, USA) was set to deliver 2 volume % via a circle system, and the adjustable pressure limiting valve was closed to allow filling of the rebreathing bag. If apnea was present and greater than 30 seconds, one breath every 30 seconds was administered until spontaneous respiration was restored. For the purpose of data collection, EtCO_2 during apnea was recorded as 0 mmHg. Once this was properly filled, adjustable pressure limiting valve valve was opened. SpO_2 , heart rate were measured with the same techniques previously described. Capnography and respiratory gas analysis was used to collect data on respiratory rate, EtCO_2 , end-tidal concentration of isoflurane (Et_{ISO}), as well as FiO_2 and the inspired fraction of oxygen (EtO_2). Once Et_{ISO} reached MAC values for canines was reached (Steffey & Howland Jr 1977), the vaporizer was adjusted to maintain a light surgical plan of anesthesia. The same sequence of data collection was followed to obtain values at post-induction, and at 10 minutes (10M), 20 minutes (20M), 40 minutes (40M), and 60 minutes (60M) after intubation. Throughout the procedure, body temperature was maintained with a warm-air blowing device and a blanket placed to cover the

subject's torso leaving the neck exposed. At the end of the trial, the introducer, pulmonary arterial catheter and arterial catheters were removed and the sites wrapped with 4 by 4 cm sterile gauze and cohesive bandaging material (Co-flex, Andover, England) to apply pressure. After collection of data at the 60M time point, cefazolin (22 mg/kg IV) was repeated. Fluids were discontinued and venous catheter was left in place covered with the same cohesive bandaging material previously used. Vaporizer and oxygen flow were turned off and dogs were moved to a kennel for recovery. Recovery time was defined as the time elapsed between the vaporizer was turned off and extubation. Criterion for extubation was the presence of two consecutive swallows with tongue movement. Each one of the tasks of this study was performed by the same individual over time (i.e. same person performed physical exams, physical restraint during phase I and II, intubation, and extubation). All investigators, except the one performing placement of catheters, were blind to the treatment administered to the subjects at all times during the experiment.

4.8 Phase IV: Recovery from Phase III

After the endotracheal tube was removed, the door of the kennel was closed and dogs were allowed to recover without physical restraint, and closely monitored by one of the investigators during the following hour to ensure that they were able to breathe, swallow, stand, and walk independently. A camera (GoPro, San Mateo, CA) was placed in front of the kennel to record videos of the recovery period (at least 30 minutes per recovery episode). A rescue dose of 1 μ g/kg of dexmedetomidine (Dexdomitor, Zoetis, Kalamazoo, MI) administered IV was used as a rescue for recoveries of poor quality (flailing for more

than 2 minutes, excitement that causes direct injury to the subject) if needed. After standing and becoming conscious of the surroundings, dogs were allowed to walk outside the research area on a leash placed around the torso. After at least 1.5 hours from conscious interaction with personnel, and only if catheterization sites were properly clotted and free from bleeding, the dogs were returned to the housing facility. Otherwise, they would be housed in the wards of the Oregon State University Veterinary Teaching Hospital. Senior students and staff in the hospital monitored them during the following night, and they returned to the housing facility the morning after.

Digital anesthetic record software (VetDAR, Dimple Hill Software LLC, Corvallis, OR) was used to record anesthetic data and provide comprehensive information about the events of the study. A separate data sheet was used to manually record cardiorespiratory values in triplicate for each time point during the study.

4.9 Post-hoc Calculated Parameters

Cardiac index, stroke volume, stroke volume index, pulmonary vascular resistance, systemic vascular resistance, arterial and mixed-venous oxygen content, oxygen delivery, oxygen consumption, and oxygen extraction ratio were calculated using standard equations reported in literature for dogs (Haskins et al. 2005).

4.10 Recovery Scores

Twenty-four videos of recoveries (one for each dog under each treatment) were recorded throughout the experiment. Videos were randomly assigned a number ranging from 1 to 24 using online randomization software (Random.org). Three evaluators blinded to treatment scored each recovery starting at extubation for a period of 15 minutes. Criteria for evaluation included struggling and excitement, paddling and flailing, vocalization, and use of rescue drugs needed for chemical restraint. Each observable was scored from 0 to 3 based on the criteria indicated in Table 4, to obtain scores ranging from 0 to 12 (lowest score being indicator of better quality of recovery). The recovery scoring system was modified from studies previously conducted in dogs (Jiménez et al. 2012; Maney et al. 2013). Sequence of video evaluation was randomized by the use of the same software used for subject and sequence randomization, and recoveries evaluated twice by each evaluator, for a total of six scores for each video. To further ensure anonymity, videos were scored by the three evaluators at least six months after the end of the experiment.

4.11 Statistical Analysis

Statistical analysis was performed using open access statistical software (R[®], 2014 version; Bell Laboratories, Murray Hill, NJ, USA). Although analysis of variance (ANOVA) models typically assume homogeneity of variances across groups, a Shapiro-Wilk test was used to test for normality of data. Parametric data are presented as mean \pm

SD. All hemodynamic, respiratory, and acid-base measures and calculated parameters under all treatments were analyzed with a repeated analysis of variance model (RM-ANOVA) for difference between and within time points accounting for the treatment received, and reported as mean \pm SE. The RM-ANOVA model was adjusted for subject, sequence of treatment as fixed factors to test the “drug” effect. The model for cardiovascular, respiratory, and acid-base parameters follows the following form:

$$g) \text{ Outcome variable} = \text{Intercept} + \text{Drug (factor)} + \text{Subject (factor)} + \text{Sequence (factor)} + \text{Time-Point (factor)}$$

An ANOVA was then performed to compare the indicated model and a model lacking the factor “drug”. For all tests, significance was standardly set at a p-values < 0.05 . If significance was found amongst groups for each time point, a post-hoc student-t between tiletamine-zolazepam and the other treatments was performed, and p-values corrected with a Bonferroni correction (p-values multiplied by 3) . For an arbitrary decision that does not affect the results of this study, alfaxalone was randomly set as the baseline to which the differences with the other induction protocol are compared to. Differences are presented as a positive or negative coefficient representing the variation from baseline (response under alfaxalone).

Recovery scores were tested for intra-rater and inter-rater consistency with Pearson’s correlation, and a paired t-test was used to test difference between the first and the second scorings for each rater. In all linear models, recovery time is modeled as a linear function of induction agent (factor), round of anesthetic episode (factor), subject (factor), and final concentration of Et_{ISO} (continuous) at the end of the trial before disconnecting the dogs from the breathing circuit. The recovery scores in the model also accounts for

recovery time and individual scorer. Difference in recovery time was tested with a paired t-test, while difference in recovery scores was tested by an ANOVA linear model as previously mentioned. Results for these comparisons are reported as difference from a reference group of categorical variable as follows: tiletamine-zolazepam (treatment), first round of evaluation, subject 1, and rater 1 (arbitrary decisions that do not affect the results of the analysis). Comparison of the two linear models used for recovery time and scores were plotted in a scatter plot to verify their relationship, whereas stripcharts were used to represent the distribution of recoveries from each induction agent, time, and average recovery score.

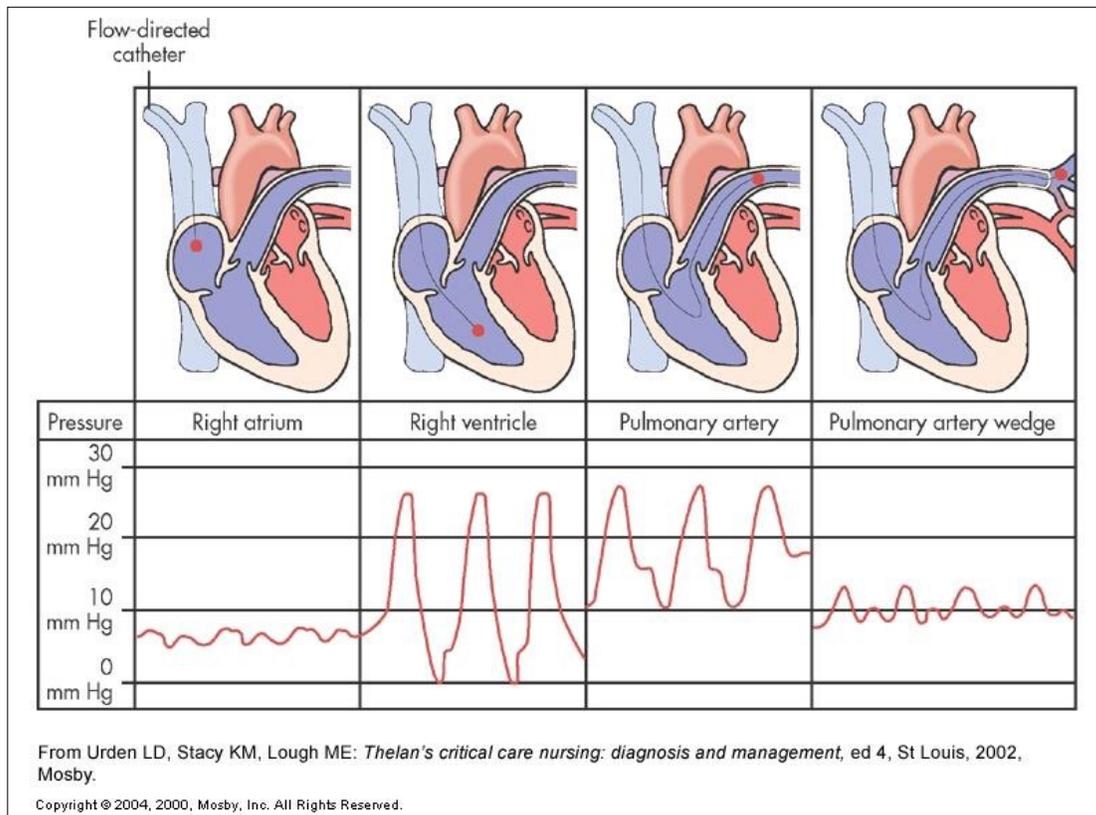


Figure 7. Characteristic pressure waveforms of right atrium, right ventricle, pulmonary artery, and wedged pulmonary artery encountered while advancing a pulmonary arterial catheter into the pulmonary artery. From (Urden et al. 2002).

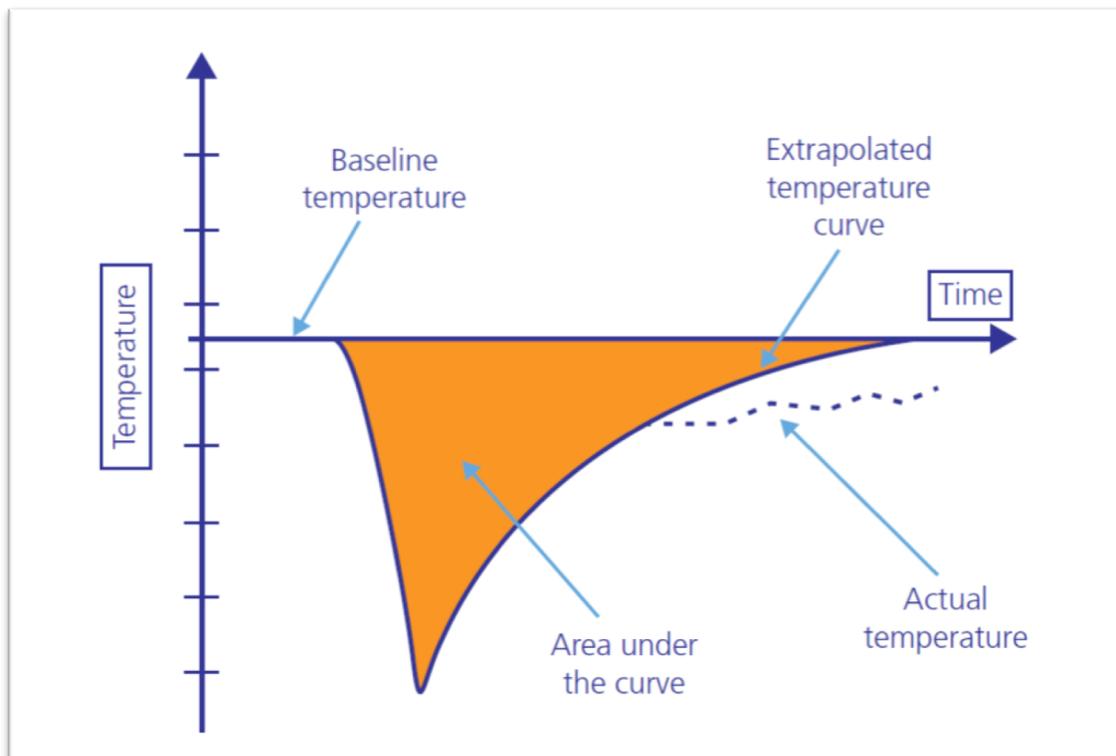


Figure 8. Cardiac output dilution curve by thermodilution technique. In orange the area under the curve (AUC). From (Grimm et al. 2015)

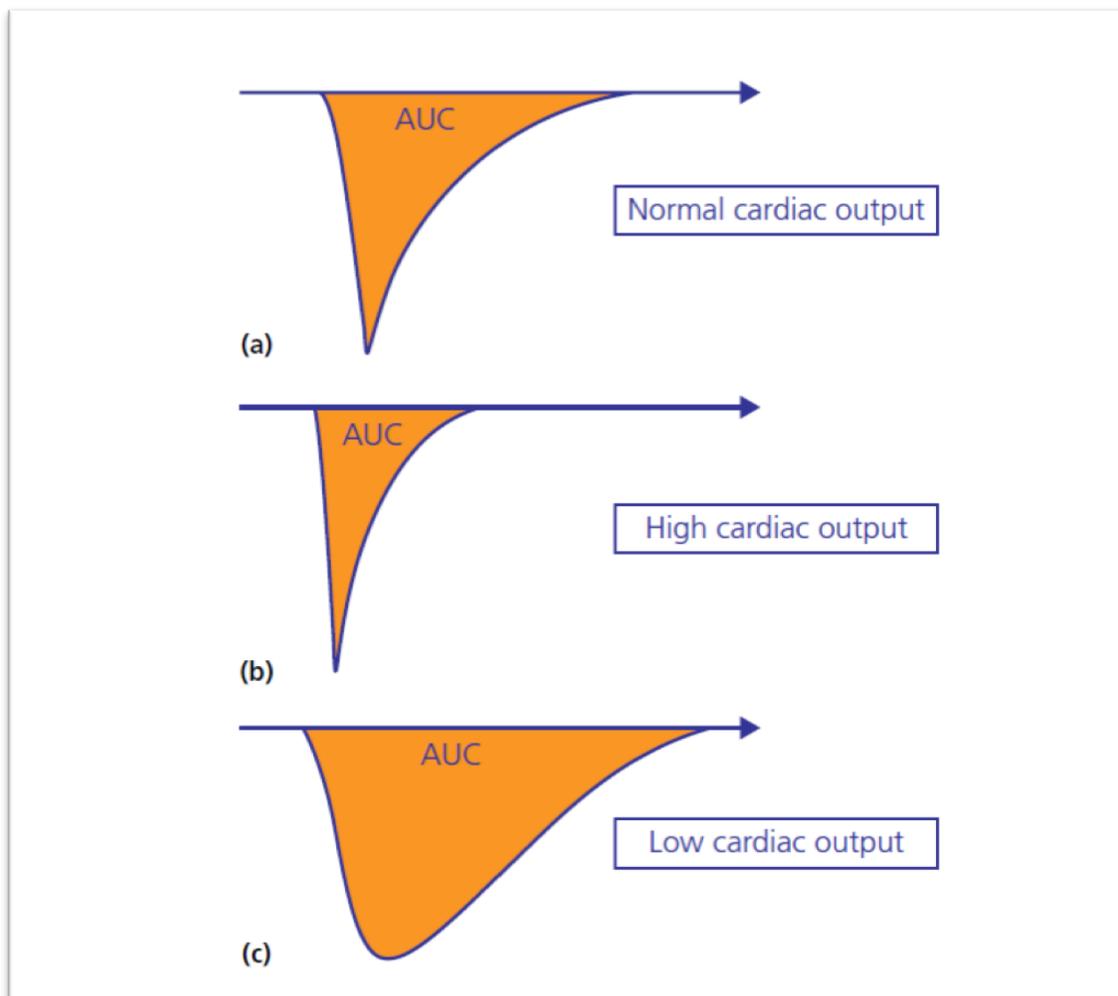


Figure 9. Cardiac output dilution curves. (a) represents a normal cardiac output, (b) a high cardiac output (small area under the curve), and (c) a low cardiac output (large area under the curve). From (Grimm et al. 2015)

Description	0	1	2	3
<i>Struggling/Excitement</i>	None	Transient, easily calmed	Prolonged, > 1 minute	Needs physical restraint
<i>Paddling/Flailing</i>	None	Transient, easily calmed	Prolonged, > 1 minute	Needs physical restraint
<i>Vocalization</i>	None	Minor	Intermittent	Persistent
<i>Rescue drugs needed</i>	No	NA	NA	Yes

Table 4. Criteria for scoring recoveries over a period of 15 minutes. Higher scores were indicative of poorer quality of recovery.



Figure 10. Fluoroscopic image of a pulmonary arterial catheter (PAC) in place before and during cardiac output measurements.

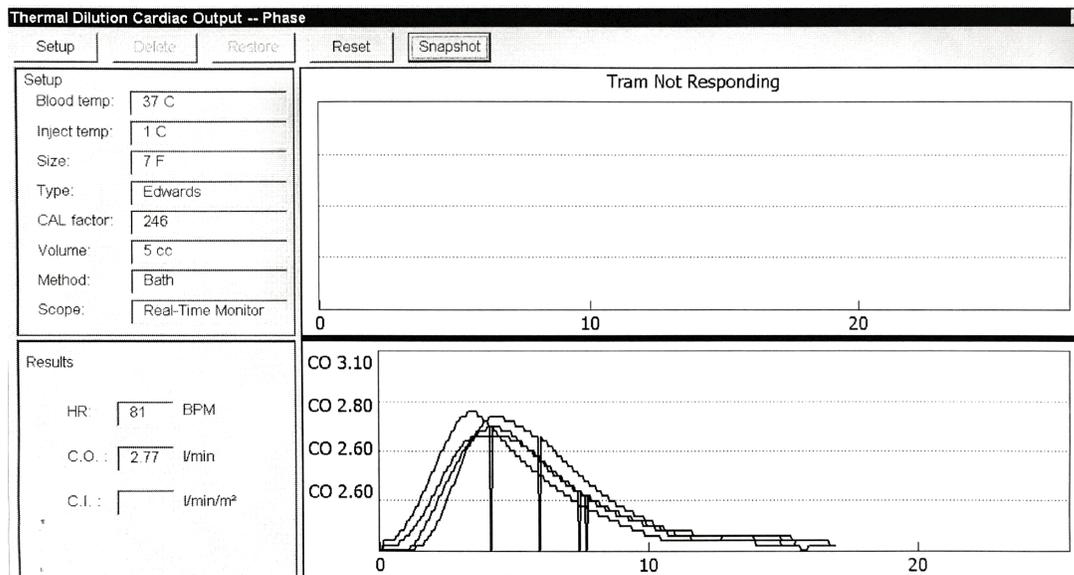


Figure 11. Sample cardiac output measurement performed during the study. Values with variation $> 10\%$ in absolute value were discarded and three accepted measurements averaged.

5. RESULTS

Doses used for induction were respectively 3.8 ± 0.7 mg/kg for tiletamine-zolazepam, 2.8 ± 0.3 mg for alfaxalone, 6.1 ± 0.9 mg/kg and 0.3 mg/kg for ketamine-diazepam, and 5.4 ± 1 mg/kg for propofol. All induction agents resulted in smooth and quickly achievable endotracheal intubation despite one induction under propofol that was prolonged and where a supplementation with the rescue dose was necessary to achieve intubation. Intubation was informally rated by a blind operator that performed this task throughout the study. Induction with alfaxalone had the best quality of induction producing no swallowing or coughing in any of the subjects. Two dogs in the tiletamine-zolazepam group and one of the ketamine-diazepam group had some involuntary tongue movements and one of them coughed once during intubation. One dog in the ketamine-diazepam group had marked coughing and one swallow, whereas propofol induction was overall smooth, except for one subject that showed marked jaw tone and swallowing during intubation and required a rescue dose of propofol to allow placement of the endotracheal tube. With the exception of this case, all cases except the aforementioned one, depth of anesthesia was judged to be adequate to perform tracheal intubation in all the dogs.

No significant difference was found within or among induction protocol on Et_{1SO} at any time point across treatments. Mean Et_{1SO} used in this study for 60 minutes was $1.14 \pm 0.32\%$. All subjects recovered from anesthesia uneventfully.

5.1. Cardiovascular Effects

Cardiovascular parameters are synthesized in Table 5 and their graphic representation is provided in Figures 13, 14, and 15. The cardiovascular parameter most affected by the induction protocol was heart rate. There was no significant difference among induction protocols at baseline, before anesthetic agent administration between treatment groups ($p=0.48$). Significant difference was found post-induction ($p=0.02$), and at M10 ($p=0.012$), M20 ($p=0.009$), and M40 ($p=0.047$). Propofol was the induction agent to have in average the lowest heart rate (-16.9 beats/minute), whereas ketamine-diazepam and tiletamine-zolazepam had respectively -9.9 and +5.2 beats/minute compared to alfaxalone. The averaged heart rate under alfaxalone was 107.7 ± 26.3 beat/minute. With tiletamine-zolazepam, an average increase in heart rate of 94.9% from baseline was observed, with an overtime return near baseline at the 60M. Dogs anesthetized with propofol showed a mild increase in heart rate by 23.2% in average, fully returning to baseline values at M20, and overall maintaining the lowest heart rate across treatments. Induction with A produced an increase in heart rate by 54.3% in average, maintaining in average + 20 beats/minute at M60. With ketamine-diazepam, heart rate increased by 74.7% in average, and a decrease in heart rate overtime that failed to return to baseline at M60. Heart rate at M60 was not significantly different ($p=0.073$) among treatments. Trends for these parameters are shown in Figure 13.

Systolic arterial blood pressure differed across treatments at baseline ($p=0.016$) and at M60 ($p=0.009$). In general, systolic, mean and diastolic arterial blood pressure decreased similarly after induction in all treatments. Parameters that did not differ at any of the time points amongst induction drugs used were cardiac output, cardiac index, systemic

vascular resistance, mean and diastolic arterial blood pressure. Cardiac output values are listed in table 5 along with other cardiovascular parameters. The tendency noted for cardiac output is to increase with tiletamine-zolazepam, alfaxalone, and ketamine-diazepam after induction, and then decrease overtime, whereas cardiac output decreased after induction with propofol (Figure 13). This phenomenon follows the same trend of heart rate. Stroke volume and stroke volume index were significantly different respectively at M40 ($p=0.013$) and M60 ($p=0.023$), and at baseline ($p=0.03$) and M40 ($p=0.037$). The overall trend common to all treatments was a fall in stroke volume at induction of anesthesia, followed by stable values across the anesthetic episode for all drugs. Tiletamine-zolazepam showed the lowest stroke volume and stroke volume index of all groups, while propofol the highest. Oxygen delivery was significantly different post-induction ($p=0.043$) and at M60 ($p=0.039$), with tiletamine-zolazepam showing the highest oxygen delivery post-induction (47.770 ± 9.719 ml/kg/min), followed by ketamine-diazepam (42.182 ± 8.739 ml/kg/min), alfaxalone (41.909 ± 6.316 ml/kg/min), and propofol (35.358 ± 6.848 ml/kg/min), and the lowest at M60. Oxygen consumption, oxygen extraction ratio, and $S_{mv}O_2$ were not different across induction agents at any of the time points. Oxygen consumption and oxygen extraction ratio followed the same trend in decreasing after induction and maintaining constant at a decreased level until M60.

Analysis on right atrial pressure with a linear model including subject, drug, sequence, and transducer, reported that significant “transducer” effect ($p=0.0186$) was present as a consequence of a change in blood pressure transducers deputed to this variable during the course of the study. None of the other measured variables was found significantly different. In general, right atrial pressure was higher at baseline, to then fall and

staying constant throughout the anesthetic episode. Although trends show ketamine-diazepam to maintain the highest right atrial pressure, these changes are not statistically significant ($p=0.008$) but need to be interpreted with care. Mean pulmonary arterial pressure was statistically different among induction drugs at M10 ($p=0.003$) and M20 ($p=0.049$), with the latter being borderline significant. Propofol maintained overall highest mean pulmonary arterial pressure among groups during the trial (+1.1 mmHg, $p=0.046$). Mean pulmonary arterial wedge pressure differed at baseline ($p=0.024$), M10 ($p=0.012$), M20 ($p=0.04$), and M40 ($p=0.016$), with propofol maintaining the highest (+1.46 mmHg), followed by ketamine-diazepam (+1.21 mmHg), and then tiletamine-zolazepam which produced the lowest (-0.8 mmHg, $p<0.001$).

Although systemic vascular resistance were not statistically different between treatments, its trend is worth noting. Alfaxalone, ketamine-diazepam, and tiletamine-zolazepam caused an equal decrease in systemic vascular resistance to the same level, while propofol caused a less great fall, which then increased to reach the same value at M60. Pulmonary vascular resistance were statistically significant ($p=0.007$) at M60 for comparison between treatments but had no significant coefficients, although an increase in pulmonary vascular resistance with propofol is easily recognizable when this is plotted against time.

5.2. Respiratory Effects

Some respiratory and acid-base parameters are calculated and tabulated in Table 6. Respiratory rate did not differ at any of the time points amongst induction drugs, although some agents showed a higher incidence of apnea compared to others. Post-induction apnea occurred in 20.8% of the subjects. After alfaxalone administration, 3 dogs (50%) were apneic for up to 60 seconds, whereas after propofol and tiletamine-zolazepam 1 of 6 dogs for each group experienced apnea (16.6%). Apnea was not noted after administration of ketamine-diazepam in any of the subjects. EtCO₂ differed significantly at M10 (p=0.007) and at M20 (p=0.008), although the highest average value seen among the two time points was 46.2 ± 1.9 mmHg, and this change did not correspond to an increased PaCO₂. Arterial partial pressure of oxygen and PmvO₂ were statistically insignificant. However, SaO₂ was significantly different at baseline measurements (p=0.014) across treatments. Arterial partial pressure of carbon dioxide increased after induction of anesthesia overtime although it was within normal limits. Propofol showed a stable trend after the initial increase in PaCO₂, while alfaxalone caused the highest peak to then decrease overtime and reach value comparable to propofol and ketamine-diazepam. Ketamine-diazepam and tiletamine-zolazepam followed the same trend until M40, where ketamine-diazepam maintained constant PaCO₂, whereas this increased with tiletamine-zolazepam at M60 and was the highest of the four induction regimen tested in this study.

5.3. Effects on Acid-base and Electrolytes

Some key acid-base parameters are synthesized in tables 7 and 8, and trends shown in Figures 16 and 17. Parameters that did not differ at any of the time points amongst induction drugs used in arterial and mixed-venous blood gas, electrolyte, and metabolite analysis were $C_{mv}O_2$, CaO_2 , $P_{mv}O_2$, PaO_2 , hemoglobin, Na^+ , Cl^- , Ca^{++} , glucose, and lactate. P-value for arterial Cl^- was borderline for significance ($p=0.048$) at M10. Serum K^+ in both arterial and mixed-venous blood was significantly different after induction ($p=0.07$ and 0.016 respectively), and significantly higher in the ketamine-diazepam ($+ 0.129$ mmol/L, $p=0.008$) and tiletamine-zolazepam ($+ 0.172$ mmol/L, $p=0.008$) groups compared to reference treatment (alfaxalone), although not increased from baseline. Serum potassium was decreased after induction with alfaxalone for then returning to levels similar to the other induction agents at M20, whereas this was overall higher with ketamine-diazepam and tiletamine-zolazepam compared to alfaxalone and propofol in both mixed-venous and arterial blood ($p=0.008$, $p=0.002$), although within normal limits. Arterial and mixed-venous pH were significantly different among treatments at M20, with a concomitant significance at the same time point for $PaCO_2$ ($p=0.03$), $P_{mv}CO_2$ ($p=0.04$), pH_{mv} ($p=0.015$), pH_a ($p=0.013$), and BE_{mv} ($p=0.012$). Mixed-venous base excess also differed at baseline ($p=0.034$) and M60 ($p=0.042$), although always remaining within normal limits and this significance can be considered borderline. Furthermore, ${}_{mv}HCO_3^-$ was significantly different among treatments at baseline, which is consistent with the concomitant significance of BE_{mv} in MV blood. BE was lowest with alfaxalone compared to other treatments ($p<0.001$), with overall values of -2.66 ± 1.29 mmol/L. Lactate was overall lowest with propofol with a coefficient compared to alfaxalone of -0.19 mmol/L, although

values were within physiologic limits (0.85 ± 0.3 mmol/L). ${}_a\text{HCO}_3^-$ was significantly different at baseline ($p=0.029$), whereas ${}_{mv}\text{HCO}_3^-$ differed at M60 (0.044), although average values were normal (22.2 ± 0.72 mmol/L in Art blood, 23.4 ± 0.77 mmol/L for MV blood). Overall, HCO_3^- slowly raised its concentration due to the presence of increased PmvCO_2 .

Total plasma proteins and packed cell volume decrease overtime during the experiment in all dogs, but maintaining acceptable values (4.8 ± 0.39 g/dL in arterial blood, and 5 ± 0.4 g/dL in mixed-venous blood, $\text{PCV} = 40.4 \pm 4.1\%$). Averaged mixed-venous hemoglobin for all groups was 13.7 ± 1.8 g/dL, and there was borderline significant difference across groups ($p=0.044$, alfaxalone reference point, ketamine-diazepam -0.07 g/dL, propofol -0.55 g/dL, and tiletamine-zolazepam -0.35 g/dL). Arterial oxygen content followed the same trend of hemoglobin in decreasing overtime. However, this change was not statistically significant.

5.4.Recovery

One recovery video was not usable due to technical difficulties during recording. Therefore, recovery data from one dog receiving ketamine-diazepam for induction are missing. Intra-rater correlations between the two scoring processes were the same for each of the raters (CDCC 0.77, RM 0.62, and TM 0.71), showing good consistency within evaluators. A paired t-test comparing recovery scores from the first and the second evaluation was performed and one evaluator's scores were significantly lower in the second round ($p<0.001$). However, this rater had the highest correlation (0.77) within ratings, therefore being very consistent in scoring the evaluation of videos 0.782 point on average

lower than scores in the evaluation. Intra-rater correlations for rater 2 and 3 were respectively 0.62 and 0.71.

Recovery times were 3.06 minutes shorter with propofol compared to tiletamine-zolazepam, although this difference is not statistically significant ($p=0.114$). Recovery from alfaxalone was 42 seconds in average shorter than tiletamine-zolazepam, and ketamine-diazepam was longer by 55 seconds. These differences were not significant. One dog enrolled in this study had significant longer recovery times on an average of 7.97 minutes ($p=0.012$) compared to the other dogs in this study.

Averaged recovery scores from the three raters were lower when propofol was used as induction agent by 1.1 point ($p=0.043$) compared to tiletamine-zolazepam, whereas comparison with alfaxalone and ketamine-diazepam was statistically insignificant (-0.84 , $p=0.12$), although ketamine-diazepam had higher scores compared to tiletamine-zolazepam ($+0.7$ point in average, $p=0.292$). Based on this analysis, subject, sequence of anesthetic episode, and Et_{ISO} have no effect on recovery scores, while the only predictor of shorter recovery, although borderline significant was the use of propofol as induction agent. However, when individual scores from single raters were included in the linear model instead of the averages, scores from propofol are very statistically significant compared to tiletamine-zolazepam ($p<0.001$), with an average score lower by 1.1 points. Alfaxalone also had significantly better recovery scores (-0.84 points, $p=0.008$), while ketamine-diazepam and tiletamine-zolazepam did not differ ($p=0.078$).

The same trend in recovery scores (Propofol < alfaxalone < tiletamine-zolazepam < ketamine-diazepam) can be seen in recovery time. Therefore, average recovery scores

were plotted against recovery time and clusters observed (Figure 18). Furthermore, a strip-chart shows the distribution of recovery time according to drug used for induction (Figure 19). It is evident from this chart how recoveries from 60 minutes of general anesthesia under isoflurane and induced with propofol have the most predictable recoveries in terms of time.

Parameter	Induction Agent	Baseline	Post-Induction	M10	M20	M40	M60
HR (beats/minute)	A	84.1 ± 12	129 ± 22.9 ^a	123 ± 23.9 ^a	115 ± 19.9 ^a	109.9 ± 13.8 ^a	104.3 ± 12.9
	KID	80.3 ± 21.2	140.7 ± 29.3 ^a	117.6 ± 20.5 ^a	106.9 ± 19.5 ^a	102.8 ± 14.3 ^a	104 ± 8
	P	90 ± 25.8	110.9 ± 20.5 ^a	98.4 ± 16 ^a	91.4 ± 15 ^a	92 ± 17.6 ^a	93.3 ± 15.8
	TZ	85.3 ± 27.1	166.9 ± 28.4 ^a	128 ± 18.5 ^a	115.9 ± 17.3 ^a	101.8 ± 15 ^a	104.3 ± 11.8
	A	3811.1 ± 728	4916.7 ± 920	4011.1 ± 402.6	3816.7 ± 423	3550 ± 612.4	3472.2 ± 536
	KID	4161.1 ± 1388.9	4566.7 ± 635.6	3933.3 ± 683.4	3627.8 ± 604.6	3316.7 ± 636.2	3388.9 ± 536.1
CO (ml/minute)	P	4505.5 ± 1456.5	4100 ± 1116.3	3788.9 ± 797.1	3516.7 ± 814.8	3444.4 ± 791.2	3461.1 ± 761.1
	TZ	4400 ± 1332.2	5027.8 ± 1288.8	4050 ± 891.1	3550 ± 790	3127.8 ± 546.3	3094 ± 484.2
	A	45.3 ± 6	38.2 ± 6.2	33.4 ± 5.2	33.5 ± 5.4	32.3 ± 4 ^a	33.5 ± 5.5 ^a
	KID	51.3 ± 7.3	33 ± 3.6	33.7 ± 4.3	34.2 ± 4	32.3 ± 4.2 ^a	32.5 ± 3.4 ^a
	P	49.7 ± 2.6	36.5 ± 3.6	38.4 ± 4.9	38.1 ± 3.8	37.2 ± 2.7 ^a	36.9 ± 4.1 ^a
	TZ	52.3 ± 7.4	30.2 ± 6.4	31.6 ± 4.9	30.6 ± 4.2	30.7 ± 2.5 ^a	29.7 ± 2.9 ^a
SV (ml/beat)	A	86.2 ± 6.6	77.4 ± 7.5	63.8 ± 5	63.2 ± 3.5	66 ± 17	68.9 ± 2.3
	KID	87 ± 11.7	74.8 ± 18.8	68.7 ± 6.8	64.2 ± 6.3	63.2 ± 3.8	68.6 ± 6
	P	86.9 ± 14.6	71.1 ± 17.2	64.3 ± 13.4	64.1 ± 13.7	61.2 ± 17.6	71.6 ± 12.5
	TZ	90.7 ± 9.5	76.1 ± 7.7	67.3 ± 8.9	62.3 ± 8.7	59.6 ± 8.2	61.8 ± 8.5
	A	35.8 ± 11.2	41.9 ± 6.3 ^a	34.9 ± 5	31.6 ± 3.4	28.5 ± 5	27.6 ± 3.9 ^a
	KID	35.6 ± 15.8	42.2 ± 8.7 ^a	34.8 ± 7.9	30.8 ± 7.3	26.6 ± 5.6	26.7 ± 4.2 ^a
MABP (mmHg)	P	41.5 ± 14.5	35.4 ± 6.8 ^a	31.4 ± 4.4	27.9 ± 3.3	26.3 ± 3	26.3 ± 2.3 ^a
	TZ	42.5 ± 15.6	47.7 ± 9.7	35.4 ± 6.4	30 ± 5.4	24.9 ± 3.4	24.1 ± 3 ^a
	A	6.1 ± 0.7	4.7 ± 1.5	1.1 ± 0.5	1.4 ± 0.7	1.4 ± 0.5	1.6 ± 0.7
	KID	6 ± 1.3	4 ± 3	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.4
	P	6.9 ± 1.8	2.7 ± 1.8	1.1 ± 0.8	1.4 ± 0.5	1.6 ± 0.5	1.7 ± 0.6
	TZ	5.7 ± 3.1	3.7 ± 2.1	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.3	1.4 ± 0.4
DO ₂ (ml/kg/min)	A	6.1 ± 0.7	4.7 ± 1.5	1.1 ± 0.5	1.4 ± 0.7	1.4 ± 0.5	1.6 ± 0.7
	KID	6 ± 1.3	4 ± 3	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.4
	P	6.9 ± 1.8	2.7 ± 1.8	1.1 ± 0.8	1.4 ± 0.5	1.6 ± 0.5	1.7 ± 0.6
	TZ	5.7 ± 3.1	3.7 ± 2.1	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.3	1.4 ± 0.4
	A	6.1 ± 0.7	4.7 ± 1.5	1.1 ± 0.5	1.4 ± 0.7	1.4 ± 0.5	1.6 ± 0.7
	KID	6 ± 1.3	4 ± 3	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.4
VO ₂ (ml/kg/minute)	P	6.9 ± 1.8	2.7 ± 1.8	1.1 ± 0.8	1.4 ± 0.5	1.6 ± 0.5	1.7 ± 0.6
	TZ	5.7 ± 3.1	3.7 ± 2.1	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.3	1.4 ± 0.4
	A	6.1 ± 0.7	4.7 ± 1.5	1.1 ± 0.5	1.4 ± 0.7	1.4 ± 0.5	1.6 ± 0.7
	KID	6 ± 1.3	4 ± 3	1.4 ± 0.5	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.4
	P	6.9 ± 1.8	2.7 ± 1.8	1.1 ± 0.8	1.4 ± 0.5	1.6 ± 0.5	1.7 ± 0.6
	TZ	5.7 ± 3.1	3.7 ± 2.1	1.3 ± 0.5	1.2 ± 0.5	1.3 ± 0.3	1.4 ± 0.4

Table 5. Mean \pm SD values for cardiovascular parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane $1.14 \pm 0.32\%$. HR = Heart rate; CO = Cardiac output; SV = Stroke volume; MABP = Mean arterial blood pressure; DO_2 = Oxygen delivery; VO_2 = Oxygen consumption. ^a indicates statistical significance across groups at time point ($p < 0.05$).

Parameter	Induction	Baseline	Post-Induction	M10	M20	M40	M60
O₂ER (%)	A	17.8 ± 4.2	11.8 ± 5.2	3.3 ± 1.7	4.5 ± 3	5.1 ± 2.9	6 ± 3
	KD	18.2 ± 4.2	10 ± 7.4	4.1 ± 1.1	4.6 ± 2.1	5.6 ± 2.1	6 ± 1.8
	P	17.8 ± 4.9	8.2 ± 6.1	3.8 ± 3	5.1 ± 2.6	6.4 ± 2.6	6.6 ± 2.7
	TZ	14 ± 8.5	7.4 ± 3.3	3.8 ± 1.9	4.2 ± 2.1	5.6 ± 1.7	6 ± 2.3
	A	80.9 ± 4.2	85.7 ± 6.7	96.4 ± 1.7	95.2 ± 3	94.6 ± 2.9	93.8 ± 3
	KD	81.7 ± 4.6	87.6 ± 8.1	95.7 ± 1	95.2 ± 2	94.2 ± 2	93.9 ± 1.7
SmvO₂ (%)	P	81.5 ± 4.9	90.4 ± 6.9	95.8 ± 2.7	94.6 ± 2.4	93.4 ± 2.5	93.1 ± 2.5
	TZ	85.1 ± 8.5	92.7 ± 3.2	96 ± 1.8	95.5 ± 2	94.2 ± 1.6	93.7 ± 2.2
	A	17.8 ± 3.5	4 ± 8	7 ± 4	8 ± 5	12 ± 7	13 ± 6
	KD	14 ± 3	9 ± 7	20 ± 13	17 ± 13	13 ± 6	17 ± 11
	P	17 ± 5	25 ± 36	28 ± 34	24 ± 36	25 ± 36	26 ± 35
	TZ	27 ± 16	11 ± 8	27 ± 16	14 ± 14	12 ± 8	14 ± 9
RR (breath/minute)	A		14 ± 22	46 ± 2 ^a	46 ± 2 ^a	45 ± 4	41 ± 10
	KD		32 ± 18	40 ± 5 ^a	38 ± 8 ^a	40 ± 6	41 ± 4
	P		36 ± 18	44 ± 4 ^a	43 ± 4 ^a	44 ± 2	43 ± 3
	TZ		31.3 ± 18	37 ± 6 ^a	42 ± 5 ^a	43 ± 3	42 ± 5
	A	4.7 ± 3.2 ^a	2.5 ± 2.8	1.7 ± 2.1 ^a	2.5 ± 3 ^a	2.5 ± 2.9 ^a	3.8 ± 4.6
	KD	9 ± 2 ^a	5.5 ± 1.6	6.2 ± 2 ^a	6.2 ± 1.3 ^a	6 ± 2.2 ^a	5.8 ± 1.7
PAWP (mmHg)	P	5.5 ± 3.2 ^a	5.3 ± 5.6	4.8 ± 4.9 ^a	4.7 ± 3.8 ^a	4.7 ± 3.8 ^a	5.3 ± 4.6
	TZ	6.5 ± 2.2 ^a	2.7 ± 3.2	2.8 ± 2.3 ^a	2.7 ± 3.4 ^a	2.3 ± 2.9 ^a	2 ± 3.1
	A	15.7 ± 2.2	15.3 ± 2.9	11.8 ± 1.5 ^a	11.7 ± 1.6 ^a	11.5 ± 2.7	12.8 ± 3.9
	KD	17.5 ± 3.6	17.5 ± 2.4	15.5 ± 2 ^a	14.3 ± 1.4 ^a	13.2 ± 1.7	13.3 ± 1.2
	P	16.8 ± 2.8	18.8 ± 6	13.7 ± 2.7 ^a	13.3 ± 3.4 ^a	12.2 ± 2.3	12.8 ± 3.1
	TZ	17.2 ± 3	15.8 ± 1.6	12.8 ± 1.7 ^a	12 ± 2.1 ^a	11 ± 1.5	11 ± 1.3
PAP (mmHg)	A		14 ± 22	46 ± 2 ^a	46 ± 2 ^a	45 ± 4	41 ± 10
	KD		32 ± 18	40 ± 5 ^a	38 ± 8 ^a	40 ± 6	41 ± 4
	P		36 ± 18	44 ± 4 ^a	43 ± 4 ^a	44 ± 2	43 ± 3
	TZ		31.3 ± 18	37 ± 6 ^a	42 ± 5 ^a	43 ± 3	42 ± 5
	A	4.7 ± 3.2 ^a	2.5 ± 2.8	1.7 ± 2.1 ^a	2.5 ± 3 ^a	2.5 ± 2.9 ^a	3.8 ± 4.6
	KD	9 ± 2 ^a	5.5 ± 1.6	6.2 ± 2 ^a	6.2 ± 1.3 ^a	6 ± 2.2 ^a	5.8 ± 1.7

Table 6. Mean \pm SD values for cardiorespiratory parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane $1.14 \pm 0.32\%$. O₂ER = Oxygen extraction ratio; S_{mv}O₂ = Oxygen saturation in mixed-venous blood; RR = Respiratory rate; PAWP = Pulmonary artery wedge pressure; PAP = Pulmonary artery pressure. ^a indicates statistical significance across groups at time point ($p < 0.05$).

Parameter	Induction	Baseline	Post-Induction	M10	M20	M40	M60
PaO ₂ (mmHg)	A	96.3 ± 5.4	219.1 ± 156.4	568.9 ± 18.3	576 ± 18.3	573.7 ± 29.9	568.4 ± 18.6
	KD	98.1 ± 5.9	351.8 ± 183.4	576.9 ± 21.7	585.8 ± 19.4	556.1 ± 18.8	570 ± 14.8
	P	103 ± 5.1	382.4 ± 190	541.7 ± 45	567.9 ± 36.6	571.3 ± 25.3	569.4 ± 13.2
	TZ	101.7 ± 7.7	385.8 ± 137.3	579.5 ± 26.6	580.3 ± 31.8	574.5 ± 33	574 ± 36.4
	A	7.419 ±	7.361 ± 0.031	7.334 ±	7.314 ±	7.340 ± 0.030	7.356 ±
	KD	7.420 ±	7.403 ± 0.074	7.378 ±	7.393 ± 0.062	7.369 ± 0.050	7.373 ±
pH	P	7.419 ±	7.356 ± 0.039	7.342 ±	7.342 ± 0.048	7.348 ± 0.045	7.355 ±
	TZ	7.430 ±	7.387 ± 0.056	7.373 ±	7.381 ± 0.062	7.341 ± 0.053	7.335 ±
	A	32.8 ± 1.3	39 ± 3.4	44.1 ± 2.7	47.6 ± 9.7 ^a	42.8 ± 3.5	40.2 ± 3.9
PaCO ₂ (mmHg)	KD	34.3 ± 0.8	36 ± 6	39.2 ± 7.4	37.9 ± 6.5 ^a	40.8 ± 5	39.2 ± 5.2
	P	33.4 ± 3	39.6 ± 1.7	42.8 ± 3.9	42.7 ± 5.3 ^a	42.2 ± 8.7	41.3 ± 8.2
	TZ	32.9 ± 1.2	38.2 ± 6.9	39.9 ± 5.2	39.2 ± 7.6 ^a	44.2 ± 6.8	45.9 ± 8.6
HCO ₃ ⁻ (mmol/L)	A	20.6 ± 0.58	21.4 ± 1.18	22.8 ± 0.61	23.3 ± 1.91	22.4 ± 0.79	21.9 ± 0.66 ^a
	KD	21.6 ± 0.87	21.6 ± 0.75	22.2 ± 1.25	22.3 ± 1.43	22.9 ± 1.27	22.1 ± 1.26 ^a
	P	21 ± 1.75	21.6 ± 1.67	22.5 ± 1.14	22.5 ± 1.13	22.5 ± 1.56	22.5 ± 1.40 ^a
	TZ	21.3 ± 0.85	22.1 ± 1.50	22.5 ± 0.89	22.4 ± 1.55	23.2 ± 0.87	23.6 ± 1.27 ^a
	A	-2.600 ±	-3.367 ± 1.277	-2.983 ±	-3.067 ±	-3.133 ± 0.950	-3.233 ±
	KD	-1.867 ±	-2.317 ± 1.526	-2.517 ±	-2.133 ±	-2.233 ± 1.617	-2.667 ±
BE (mmol/L)	P	-2.350 ± 1.47	-3.400 ± 2.141	-3.033 ±	-3.133 ±	-2.900 ± 1.516	-2.800 ±
	TZ	-1.933 ±	-2.367 ± 1.076	-2.483 ±	-2.467 ±	-2.650 ± 0.838	-2.350 ±
	A	0.932 ±	0.885 ± 0.259	0.825 ±	0.800 ± 0.282	0.877 ± 0.527	0.890 ±
LAC _a	KD	0.902 ±	0.972 ± 0.327	0.908 ±	0.922 ± 0.183	0.945 ± 0.229	0.973 ±
	P	0.733 ±	0.825 ± 0.337	0.675 ±	0.640 ± 0.220	0.613 ± 0.186	0.675 ±
	TZ	0.773 ±	0.855 ± 0.326	0.923 ±	0.947 ± 0.241	0.950 ± 0.221	0.972 ±

Table 7. Mean \pm SD values for acid-base parameters measured in six non-sedated dogs at baseline, and then after induction (PI) of anesthesia with alfaxalone (A), ketamine-diazepam (KD), propofol (P), or tiletamine-zolazepam (TZ) via intravenous injection, and at 10 (M10), 20 (M20), 40 (M40), and 60 (M60) minutes after induction and during maintenance on isoflurane $1.14 \pm 0.32\%$. PaO₂ = Partial pressure of arterial oxygen; PaCO₂ = Partial pressure of arterial carbon dioxide; a_pH = Arterial pH; aHCO₃⁻ = Arterial bicarbonate; a_{BE} = Arterial base excess; a_{LAC} = Arterial lactate. ^a indicates statistical significance across groups at time point (p<0.05).

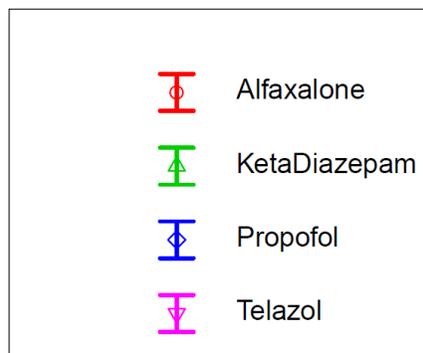


Figure 12. Keys for plot interpretation.

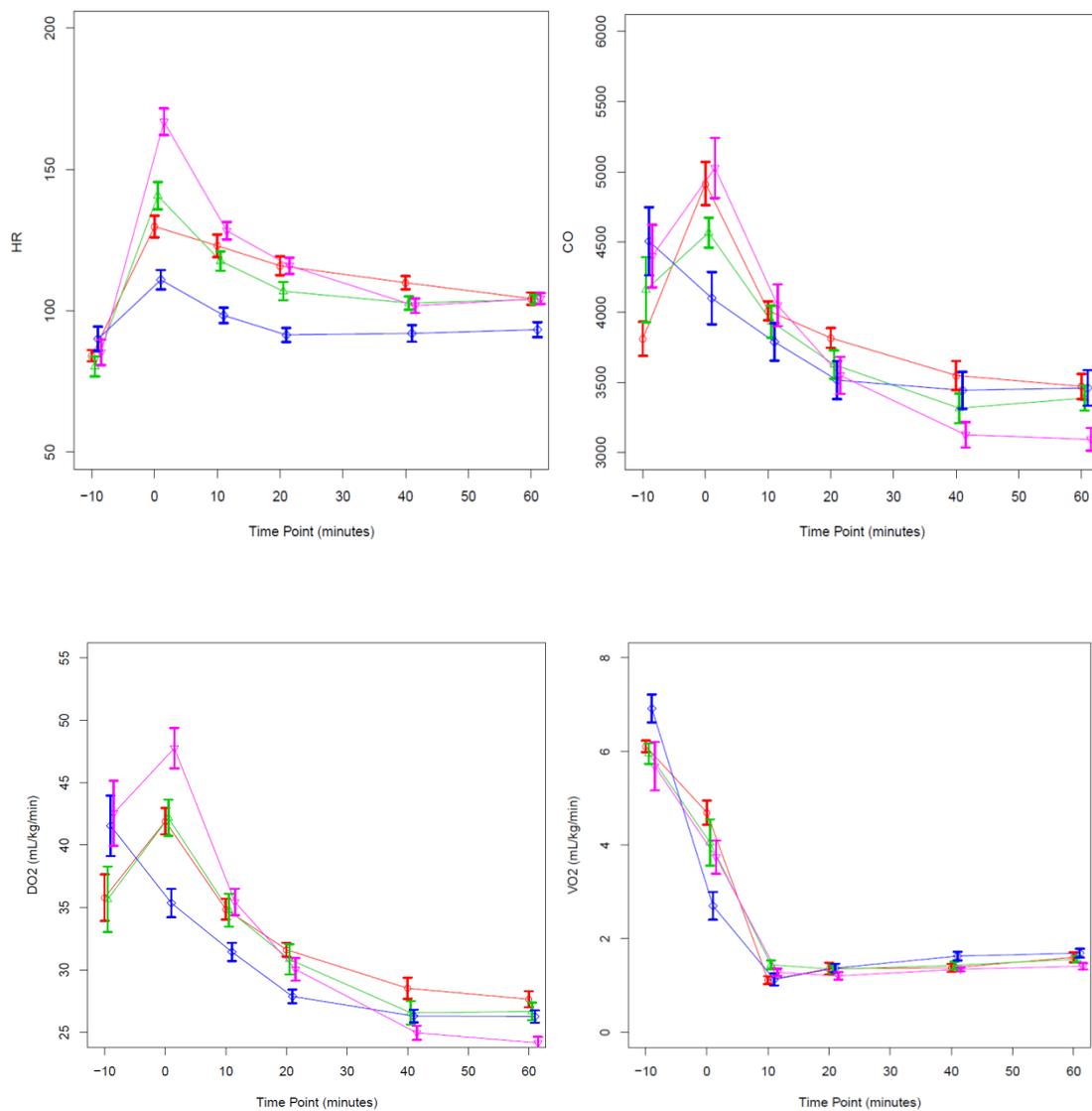


Figure 13. Plots showing trends of heart rate (HR), cardiac output (CO), oxygen delivery (DO₂), and oxygen consumption (VO₂) from baseline (-10) to 60 minutes post-induction with four different induction regimens.

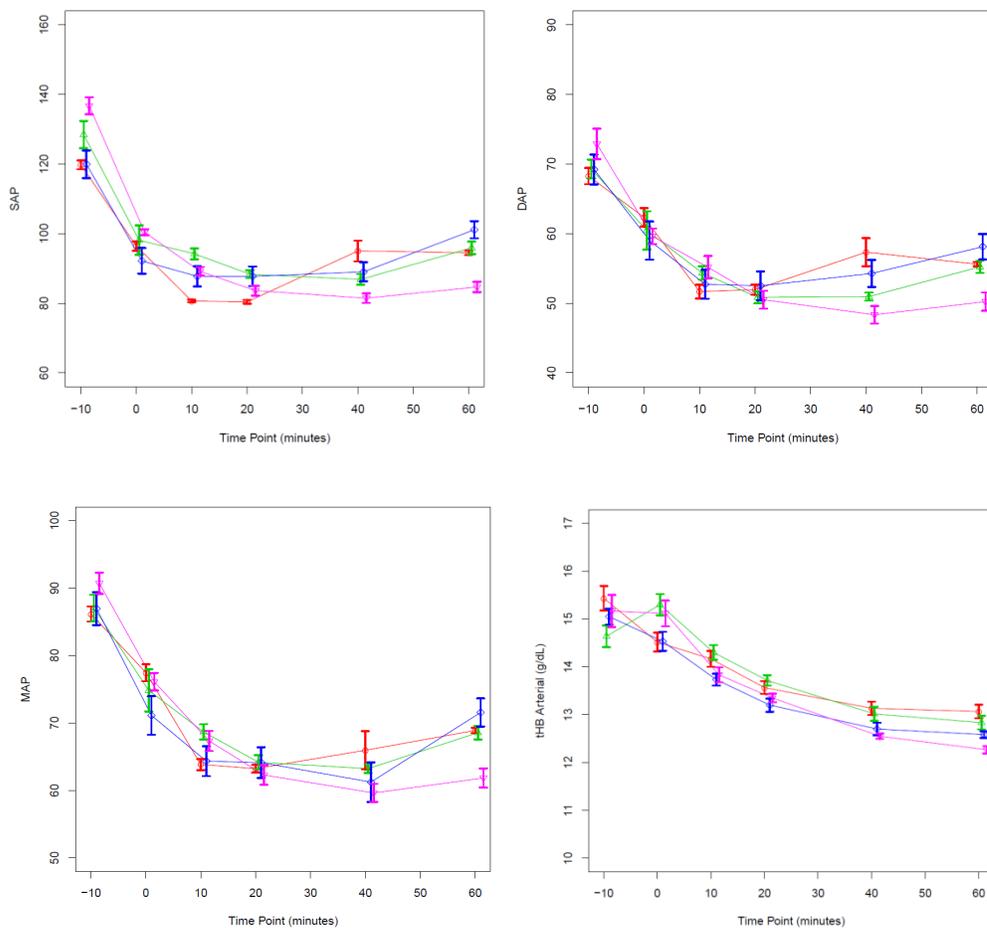


Figure 14. Plots showing trends of systolic arterial blood pressure (SABP), diastolic arterial blood pressure (DABP), mean arterial blood pressure (MABP), and total arterial Hb (Hb_a) from baseline (-10) to 60 minutes post-induction with four different induction regimens.

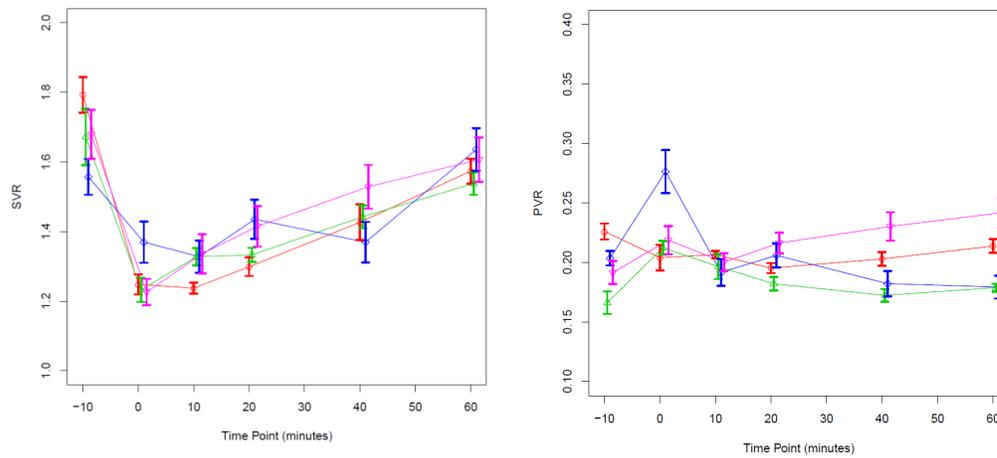


Figure 15. Plots showing trends of systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) from baseline (-10) to 60 minutes post-induction with four different induction regimens.

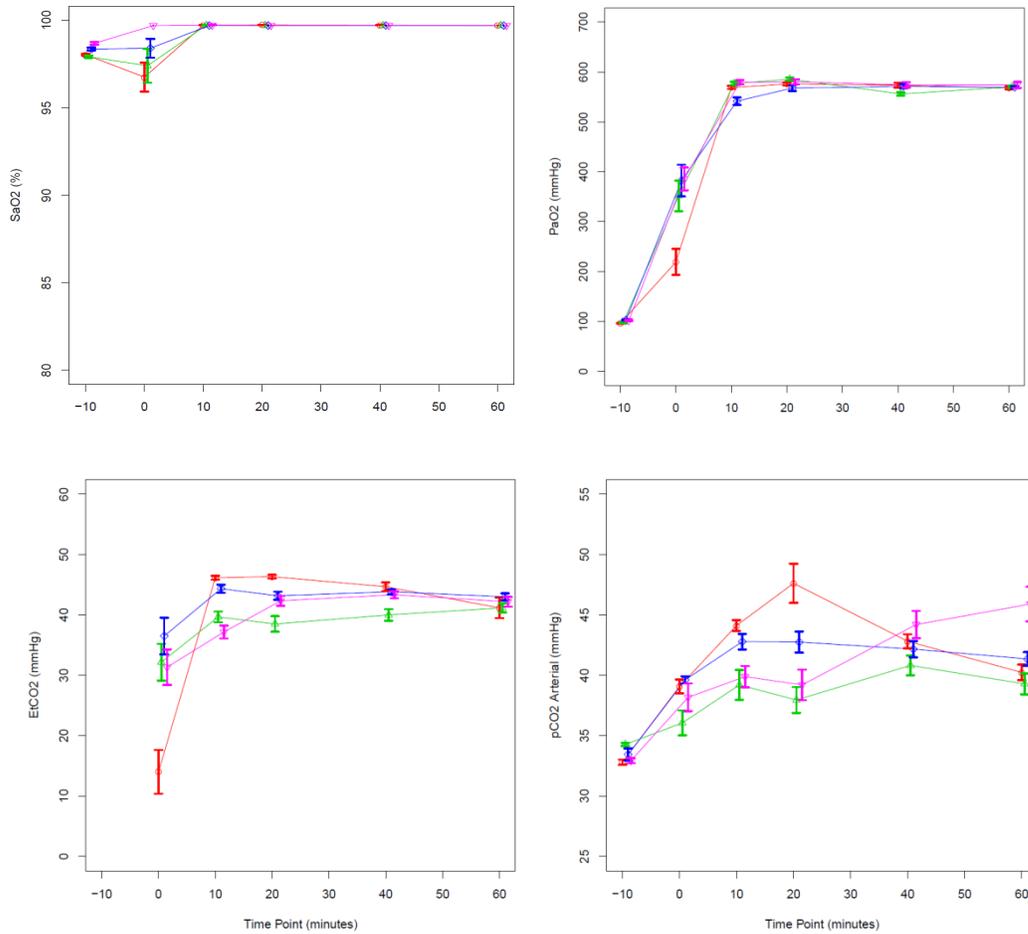


Figure 16. Plots showing trends of oxygen saturation of arterial blood (SaO₂), partial pressure of oxygen (PaO₂) and carbon dioxide (PaCO₂) in arterial blood, and end-tidal partial pressure of carbon dioxide (EtCO₂) from baseline (-10) to 60 minutes post-induction with four different induction regimens.

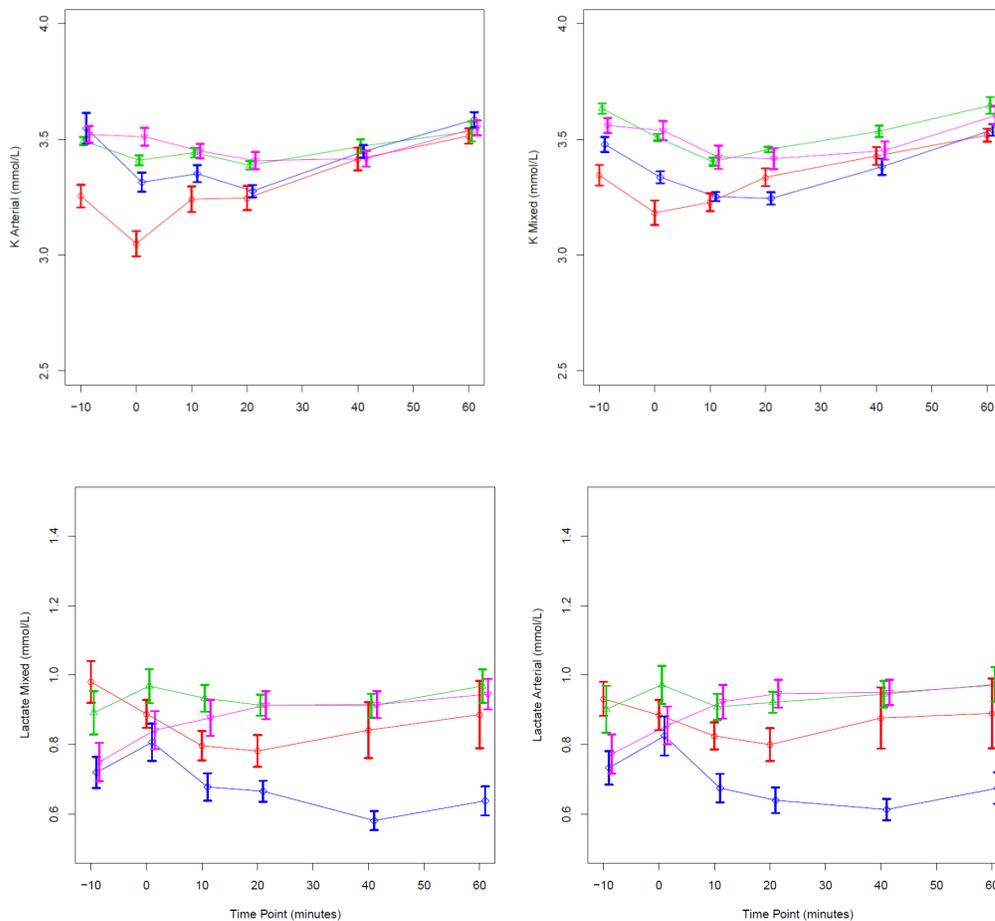


Figure 17. Plots showing trends of serum potassium of arterial (K^+ arterial) and mixed-venous (K^+ mixed) blood, and arterial and mixed venous concentrations of lactate from baseline (-10) to 60 minutes post-induction with four different induction regimens.

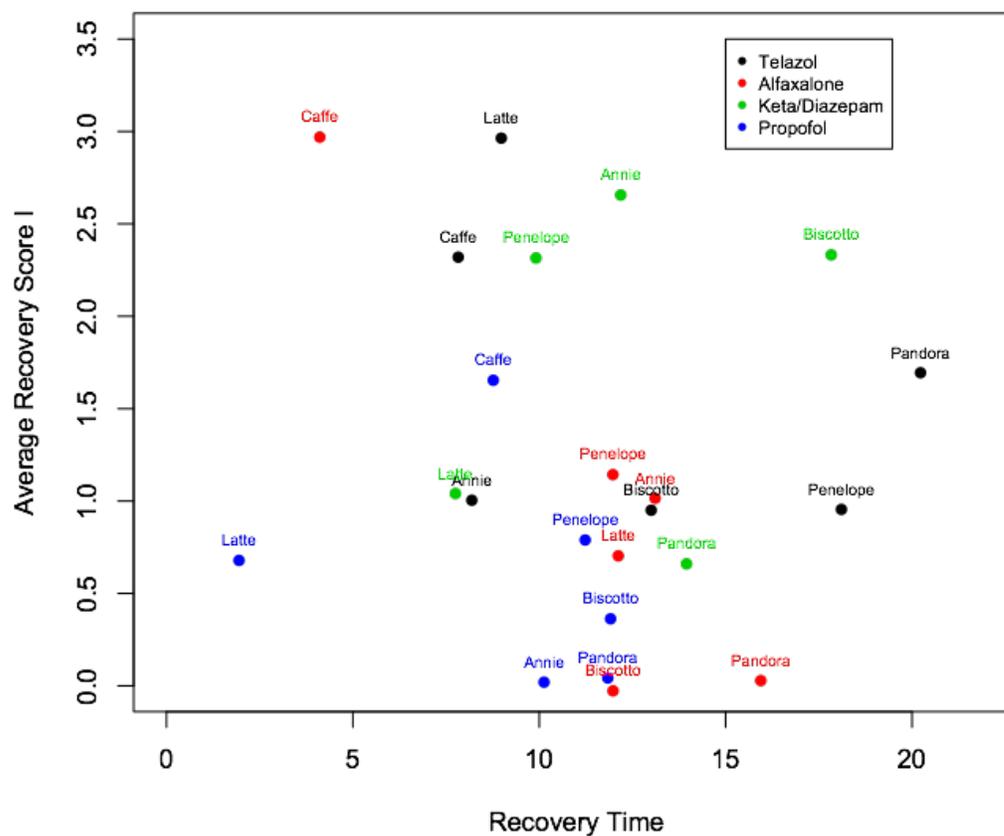


Figure 18. Plot showing the relationship between average recovery scores and recovery time for six dogs anesthetized in 24 episodes with four different induction regimens.

Lowest recovery scores are concentrated in a recovery time ranging between 10 and 16 minutes.

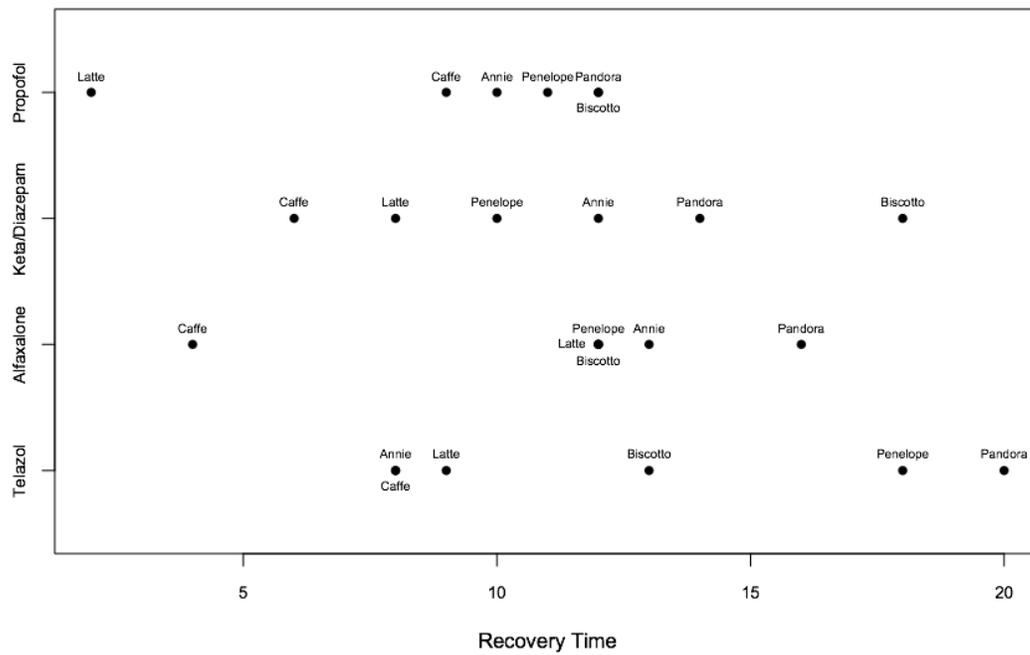


Figure 19. Stripchart showing distribution of recovery times according to drug administered for induction of anesthesia in 6 dogs maintained under anesthesia with isoflurane at MAC values.

6. DISCUSSION

The null hypotheses tested in this study were there is no significant difference in a) cardiovascular parameters with particular attention to oxygen delivery; b) respiratory parameters; c) acid-base status; d) recovery quality in dogs induced with tiletamine-zolazepam and alfaxalone, ketamine-diazepam, or propofol and maintained under general anesthesia for 60 minutes at MAC values of isoflurane.

Overall, all the induction agents tested in this trial provided satisfactory induction of anesthesia, adequate oxygen delivery and $SmvO_2$ values, indicating adequacy of global tissue perfusion, comparable performance on respiratory system and acid-base status. Recovery from anesthesia was uneventful in all groups, although significant difference between recovery quality and time was found.

Titration to desired effect is the standard used in veterinary medicine for induction of anesthesia to insure safety and minimize the risk of overdosage. Doses of induction agents used in the present study were consistent with doses for tiletamine-zolazepam (HELLYER et al. 1989), alfaxalone (Weaver & Raptopoulos 1990; Maney et al. 2013), ketamine-diazepam (HELLYER et al. 1991), propofol (Weaver & Raptopoulos 1990; Sams et al. 2008; Maney et al. 2013) available in the literature for non-sedated dogs. Although equipotency would be desirable in comparing “drug” effects on the cardiorespiratory system, this is only necessary in case of administration of a full dose in the absence of titration. In this study, induction protocols were administered to effect to the common end-point of endo-tracheal intubation, and doses needed to reach the end-point were consistent with other studies conducted in non-sedated animals. Intubation was smooth and uneventful in most cases, although three of the subjects anesthetized with dissociative

agents had spontaneous tongue movement, and one dog administered tiletamine-zolazepam had profuse salivation noted by a blinded observer. These effects have been described in the literature (Haskins et al. 1985b), and they are characteristic of the type of anesthetic used. The use of anticholinergic in premedication to reduce ptyalism has been proposed, although there are concerns on the potential additive effects of these drugs with the increase in sympathetic outflow produced by dissociative agents. Coughing is not a desirable event during intubation. In fact, it has been shown to increase systolic, intracranial, and intraocular pressures, and potentially cause regurgitation via stimulation of the larynx (Drenger & Pe'er 1987; Minogue et al. 2004). In this study, propofol and alfaxalone were superior in avoiding coughing and swallowing during intubation when administered with the technique used in this study compared to ketamine-diazepam and tiletamine-zolazepam. In one dog where anesthesia was induced with propofol, intubation was not achievable with 6 mg/kg administered over about a minute in increments of 25% every 15 seconds, and a rescue dose (1.5 mg/kg) had to be administered to achieve intubation. This subject had elevated heart rate and cardiac output at baseline. However, this was not statistically different ($p=0.483$, $p=0.34$), but it still may have influenced the propofol dose required for intubation.

The difficulty in assessing depth of anesthesia when inducing with dissociative agents resides in the fact that ocular reflexes, jaw tone/movements, pharyngeal, and laryngeal reflexes are preserved. In this experiment, attempting of intubation may have occurred too soon, in the case of dissociative agents (which have a slighter slower onset compared to propofol), resulting in coughing and jaw movements during intubation.

After induction, dogs were maintained under anesthesia with isoflurane at MAC as previously reported in the literature (Steffey & Howland Jr 1977) and there was no difference in Et_{ISO} across groups. The choice of maintaining a light plan of anesthesia at isoflurane MAC instead of direct assessment of subject's ocular reflexes and jaw tone was due to the fact that 50% of our induction regimens were dissociative agents. No noxious stimulus was applied to the dogs while performing phase III, therefore reducing the incidence of arousal from a light anesthetic plan. In conclusion, Et_{ISO} concentrations did not differ across groups, and therefore we believe that depth of anesthesia produced by MAC of isoflurane was appropriate for the purposes of this clinical trial.

Null hypothesis: tiletamine-zolazepam does not differ in cardiovascular parameters from other induction protocols

All induction protocols studied produced an initial increase in heart rate after induction of general anesthesia. Increased heart rate did not return to baseline by the end of the experiment (60M) with any of the induction regimens except with propofol, although this difference was not statistically significant ($p=0.073$). Furthermore, dogs induced with alfaxalone, ketamine-diazepam, and tiletamine-zolazepam had very similar heart rate at M60 (104.2 ± 0.15 beats/minutes). The increase in heart rate after induction with dissociative agents is largely reported in the literature (Haskins et al. 1986; HELLYER et al. 1989). Sympathetic nervous system outflow increases, while norepinephrine reuptake is inhibited causing increase levels of circulating catecholamine and stimulating the sinus and the sinoatrial nodes (Traber et al. 1970). The direct mechanism for which alfaxalone increases heart rate after administration is known, although it has been speculated that this phenomenon may be due to a baroreceptor response (Muir et al. 2008). The

stimulatory effect on heart rate observed in this study may be beneficial in clinical practice for subjects that exhibit high vagal tone before induction and bradycardia. Furthermore, absence of sedation may have contributed to such dramatic increase in heart rate and oxygen delivery, although cardiac output and cardiac index were not significantly different across treatments.

Oxygen delivery followed the same trend of heart rate for all induction protocols except for propofol, where despite a slight increase in heart rate, cardiac output was diminished along with systemic vascular resistance, suggesting that preload and contractility may have been the most affected determinants of oxygen delivery by this induction agent compared to others. tiletamine-zolazepam maintained the highest oxygen delivery at M10, whereas alfaxalone had the overall highest oxygen delivery overtime, with M60 being significant for tiletamine-zolazepam producing the lowest oxygen delivery (24.14 ± 2.96 ml/kg/min, $p=0.039$). This finding is clinically important for the anesthetist that may choose tiletamine-zolazepam over ketamine-diazepam, propofol, and alfaxalone for anesthetic procedure of short duration (<20 minutes) due to best oxygen delivery performance in this timeframe, while for procedure of longer duration alfaxalone is an effective alternative to propofol to maintained better oxygen delivery between 20 and 60 minutes after induction.

Tachycardia is normally accompanied by a compensatory decrease in stroke volume because diastolic filling time is reduced, and less blood volume is accommodated in the heart chambers. However, sinus tachycardia can also decrease diastolic relaxation where coronary perfusion occurs, therefore having potential for cardiac arrhythmias due to hypoperfusion if the myocardium. In our cohort of healthy dogs, we noticed that sinus

tachycardia induced by tiletamine-zolazepam and ketamine-diazepam did not produce cardiac arrhythmias, although extrapolation of this information to critically ill patients may result in different outcome. Heart rate trended back to baseline values overtime, although compensation of stroke volume to heart rate decrease did not occur. This event explains the decrease oxygen delivery and cardiac output seen with tiletamine-zolazepam and ketamine-diazepam on the final time points of this experiment. Being cardiac output dependent on stroke volume and heart rate, if one fails to compensate changes in the other, the result is overall decrease in cardiac output, which will ultimately affect oxygen delivery as well. This phenomenon may be the result of myocardial depression induced by ketamine unmasked by the offset of sympathetic stimulation, which by M20 seemed to be in the process of decline. Oxygen consumption and oxygen extraction ratio followed the same trend in decreasing after induction of general anesthesia, and slightly increase overtime until the end of the experiment. Both parameters fell into normal values for anesthetized dogs (Haskins et al. 1986; Haskins & Patz 1990). The highest (but not significant) oxygen extraction ration during anesthesia occurred at induction with alfaxalone ($10 \pm 7.2\%$), but it was not statistically significant. Values for $SmvO_2$ were at all-time points, for each treatment higher than 70%, indicating adequacy of global perfusion. In fact, this mark point is used along with lactate, cardiac output, oxygen delivery, and stroke volume variation in the anesthesiology and intensive care departments in goal-directed resuscitation therapy (Lough 2015).

Several reports and studies have document the negative inotropic and chronotropic effect of propofol (Goodchild & Serrao 1989; Short & Bufalari 1999; Henao-Guerrero & Riccó 2014). In the present study propofol induced a mild increase in heart rate post-

induction that quickly disappeared and produced the lowest heart rate of all the investigated induction protocols. In a study conducted on dogs premedicated with fentanyl, propofol was more likely to produce -7.7 beats/minute compared to alfaxalone. This result is consistent with our finding on heart rate trends. Alfaxalone has been reported to increase heart rate after induction (Amengual et al. 2013), although the evidence of a consistent increase in heart rate produced by alfaxalone is weak (Chiu et al. 2016). However, our results show that alfaxalone caused an increase in heart rate post-induction that lasted overtime until the end of the experiment. This characteristic of alfaxalone may be responsible for the overall best oxygen delivery maintained overtime compared to the other induction protocol included in the present study. This is an important consideration for the clinician, who may choose to avoid such drug in the case of a patient presenting with bradycardia preceding the anesthetic episode, and where tiletamine-zolazepam, ketamine-diazepam, or alfaxalone seem to produce beneficial increases in heart rate in the peri-induction period.

Although arterial blood pressure was not significantly different between treatments, a pattern in reduction of systolic, mean, and diastolic blood pressures joined all induction protocols, and was consistent with systemic vascular resistance trends. Besides the change in systemic vascular resistance post-induction, was not significantly different across treatments, meaning that all the induction protocols investigated produced equal decrease in systemic vascular resistance. This common feature may be due to a) direct effects of induction drugs on vasomotor tone, preload, and contractility, or/and to b) vasodilatory and negative inotropic effects produced by isoflurane, even at MAC values (Steffey & Howland Jr 1977). In any case, increase overtime in arterial blood pressure

occurs, although not completely efficient in returning arterial blood pressure to baseline. This event could be ascribed to the IV administration of lactated Ringer's solution during the experiment as described by Muir et al, which could have increased preload over time, although the infusion rate used in their study was twice as much as the one used in the present study (10 ml/kg) (Muir III et al. 2011). Findings from the aforementioned study on hemoglobin concentration and packed cell volume are consistent with the trend encountered in our cohort of dogs, which suffered from a time-dependent decrease in packed cell volume and hemoglobin concentration in both arterial and mixed-venous blood, which was ascribed to hemodilution in the presence of no fluid loss by neither evaporation nor conduction. Similarly, mean arterial blood pressure increased overtime during infusion of lactated Ringer's solution under isoflurane anesthesia but changes were not statistically significant.

Cardiac output and cardiac index were not significantly different among induction protocols at any time point. This finding may be surprising at first, although an attentive analysis of various factor affecting these variables can be provided; even in the presence of initial sympathetic stimulation observed with ketamine-diazepam and tiletamine-zolazepam, these drugs are known to have negative inotropic effects. In addition to these cardiodepressant effects, vasodilation from isoflurane administration may have "flattened" features of each individual regimen, masking significance. However, the intent of this study design was to collect data from a reproduction of common clinical situations, where these induction agents are used in couple with inhalant anesthesia for maintenance. Despite this, oxygen delivery was increased and best maintained for the first 20 minutes of the anesthetic episode by tiletamine-zolazepam, ketamine-diazepam, and alfaxalone, in

order of efficacy. A significant oxygen delivery in the face of a non-significant difference in cardiac output leads the investigator to suspect that increased arterial oxygen content provided by high FiO_2 may have caused it. This emphasized the importance of providing gas mixtures enriched in oxygen to allow physiologic compensation (with limitations) for decreased cardiac output encountered during induction and maintenance of general anesthesia.

Systemic vascular resistance represents left ventricular afterload. In a study conducted in non-premedicated dogs with residual isoflurane anesthesia induced with tiletamine-zolazepam, systemic vascular resistance decreased after induction, and the authors hypothesized that this finding may have been a direct vasodilatory effect of tiletamine-zolazepam, a change in vasomotor tone, or a residual vasodilatory effect from isoflurane (HELLYER et al. 1989). This findings support our observations made in the present study. Systemic vascular resistance was far from being different across treatments, probably due to isoflurane contribution to a direct effect of induction protocol. Systemic vascular resistance is calculated by subtracting right atrial pressure from mean arterial blood pressure and dividing this value by cardiac index (Haskins et al. 2005). Since statistical analysis revealed that different pressure transducer for part of the experiment on right atrial pressure readings, interpretation of systemic vascular resistance from the present study should be attempted carefully.

Pulmonary vascular resistance represent right ventricular afterload, and it has been reported to increase after ketamine injection. A case-report in the literature describes the occurrence of pulmonary edema and cardiac dysfunction caused by induction with ketamine-diazepam, due to the transient pulmonary hypertension caused by ketamine after

induction (Boutureira et al. 2007). None of the dogs induced with any of the protocols suffered from side effects or consequences from the anesthetic protocols used in this study, and pulmonary vascular resistance were not significantly different across treatments, except for M60 where they were higher with alfaxalone and tiletamine-zolazepam, and decreased with ketamine-diazepam and propofol ($p=0.007$). The interpretation of this data is challenging because it represents a single point of significance without a trend to be contextualized with. Perhaps, a lighter plan of general anesthesia due to offset of injectable drugs in the presence of a constant Et_{ISO} may explain this event.

Null hypothesis: tiletamine-zolazepam does not differ in respiratory effects from other induction protocols

Although apneustic pattern has been noticed in dogs and cats anesthetized with ketamine (Calderwood et al. 1971), this characteristic breathing pattern did not occur in our cohort of dogs. Respiratory rate in this study was not significant due to the high standard deviation in the propofol group, although significant incidence of apnea has been noticed after administration of alfaxalone (50% prevalence), while tiletamine-zolazepam and propofol caused apnea in 16.6% of dogs. No apnea was encountered after ketamine-diazepam administration, confirming its low potential to cause respiratory depression at clinical doses. $EtCO_2$ and $PaCO_2$ were significantly increased at M20 with alfaxalone showing mild respiratory acidosis ($a_pH = 7.314$, $PaCO_2 = 47.6$ mmHg) compared to tiletamine-zolazepam, propofol, and ketamine-diazepam. alfaxalone also was the slowest agent to reach physiologic PaO_2 on FiO_2 of 1, suggesting some degree of ventilation/perfusion mismatch during the first phase of anesthesia, and perhaps related to the apneic episodes

seen with its use. Arterial oxygen content, $CmvO_2$, and $PmvO_2$ did not differ across treatments and were within normal limits at all times (Haskins et al. 2005). At doses used in this study, tiletamine-zolazepam provides good respiratory performance comparable to propofol, and better than alfaxalone.

Null hypothesis: tiletamine-zolazepam does not differ in acid-base status from other induction protocols

Acid-base changes observed in this study mostly reflect mild respiratory acidosis associated with induction and maintenance of general anesthesia. Significant alterations in pH were associated with significant changes in $PaCO_2$, which reflects the respiratory component of the acidosis. Most of the measured parameters were expected to be normal since compensatory mechanisms for acute respiratory acidosis do not start before one hour from instauration of the disturbance. The borderline significant p-value for tiletamine-zolazepam at M60 on $aHCO_3^-$ reflects a non-significant increase in $PaCO_2$ at the same time point for tiletamine-zolazepam, which is not matched by significant difference in mixed-venous bicarbonate. No significant changes in bicarbonate were found in a study conducted in dogs induced with tiletamine-zolazepam and let recover (Savvas et al. 2005). In this study, base excess did not vary overtime because activation of metabolic compensatory mechanisms did not have enough time to occur. Mixed-venous base excess was statistically significant at baseline, M20, and M60. This significance reflects differences across treatments and it is of difficult explanation because bicarbonate levels stayed fairly constant throughout the anesthetic episode.

Potassium levels were lower at baseline and post-induction with alfaxalone, although only the latter was statistically significant for both arterial and mixed-venous blood.

Overall, tiletamine-zolazepam and ketamine-diazepam significantly maintained average K^+ levels higher than alfaxalone by respectively +0.172 mEq/L and + 0.129 mEq/L in arterial blood ($p=0.008$), and by +0.132 and +0.128 mEq/L ($p=0.002$) across the anesthetic episode. A clarification in this case is needed; serum potassium was never outside the normal range (3.7-5.0 mEq/L). The fact that it is reported to be higher is because it was most common that dissociative agents had the highest serum potassium of all treatments, and not because it increased to break the upper limit of the reference range. It is unlikely that lactated Ringer's solution infusion caused this change because it has been shown to have no effect on blood electrolyte composition for short term procedures (Muir III et al. 2011). Ketamine anesthesia has been associated with decreased serum potassium in humans and monkeys (Bali & Dundee 1974; Kim et al. 2005). This finding does not have a robust literature behind, although it has been linked to membrane-stabilization by induction agents used. Acidemia shifts ketamine from the intracellular to the extracellular space; however, very mild respiratory acidosis was present with dissociative agents, and surely of less importance compared to the one produced by alfaxalone.

Lactate levels were never higher than 2.5 mmol/L which has been adopted as the cutoff value for mild global hypoperfusion in dogs, therefore indicating excellent global perfusion across all treatments. tiletamine-zolazepam maintained excellent acid-base status and oxygenation with mild respiratory acidosis being the most common derangement.

Null hypothesis: tiletamine-zolazepam does not differ in recovery quality and time from other induction protocols

Significant difference was found in recovery scores based on induction agent used via a linear model for scores from individual raters. Propofol was strongly significant for

having an average of 1.1 points of recovery score less than other induction protocols, providing best recovery quality, followed by alfaxalone, tiletamine-zolazepam and ketamine-diazepam. There was no significant difference in recovery scores between dissociative agents. Recoveries with propofol were also shorter (3 minutes compared to tiletamine-zolazepam), and ketamine-diazepam had the longest recovery time (+55 seconds in average from tiletamine-zolazepam). This results likely reflect the pharmacokinetic properties of the induction drugs included in the study, but also their different nature and mechanisms of action. Visual analysis of the scatterplot shows a cluster of positive recovery scores between minute 10 and 16 from extubation, which means that best recoveries take place in that window. The agents that have the highest distribution in that area are propofol and alfaxalone, confirming the results of the linear model. These findings are coherent with the existing literature on recovery quality with propofol, ketamine-diazepam, tiletamine-zolazepam, and alfaxalone (Haskins et al. 1986; HELLYER et al. 1989; HELLYER et al. 1991; Short & Bufalari 1999; Jiménez et al. 2012).

A significant transducer effect exists for right atrial pressure measurements due to a change in pressure transducer due to technical difficulties. Values of right atrial pressure differed significantly between transducers and therefore they were not interpreted after statistical analysis confirmed significance. Other minor limitations of the present study include the lack of spirometry in the data collection which would have provided more complete information on the effects of these induction agents on alveolar ventilation, and the fact that standardization of the administration technique for these agents may have penalized agents with a slower onset of action (alfaxalone, ketamine-diazepam, tileta-

mine-zolazepam) compared to propofol which exhibits a shorter onset with maximum intensity of induction reached sooner than other agents. However, the purpose of the study was to reproduce clinical situations commonly encountered in daily veterinary practice, and titration to effect is a popular technique amongst clinicians. One video of a recovery from ketamine-diazepam was unusable and data from this recovery could not be used in the statistical analysis. Although results from recovery scores could have been affected by this missing data, strong statistical significance was found between ketamine-diazepam and the other induction protocols used in this study.

7. CONCLUSION

Overall, all the induction agents tested in this trial provided satisfactory and uneventful induction of anesthesia, adequate oxygen delivery, and oxygen saturation of mixed-venous blood values, indicating adequacy of global tissue perfusion. The most affected cardiovascular parameter by induction agent was heart rate, with tiletamine-zolazepam, ketamine-diazepam, and alfaxalone producing a substantial increase in heart rate. Tiletamine-zolazepam produced the best oxygen delivery among groups in the first 20 minutes of the anesthetic episode, while alfaxalone had superior oxygen delivery throughout the end of the anesthetic episode. Dissociative agents and propofol had superior respiratory and acid-base performance compared to alfaxalone, given the administration technique used in this study. Recovery from anesthesia was uneventful in all groups, although propofol produced best quality of recovery among the tested drugs.

8. BIBLIOGRAPHY

Aarnes TK, Bednarski RM, Lerche P et al. (2009) Effect of intravenous administration of lactated Ringer's solution or hetastarch for the treatment of isoflurane-induced hypotension in dogs. *Am J Vet Res* 70, 1345-1353.

ABDUL-RASOOL IH, CHAMBERLAIN JH, SWAN PC et al. (1987) Cardiorespiratory and metabolic effects of dopamine and dobutamine infusions in dogs. *Critical care medicine* 15, 1044-1050.

Abrahamsen EJ (2009) Chemical Restraint, Anesthesia, and Analgesia for Camelids. *Veterinary Clinics of North America: Food Animal Practice* 25, 455-494.

Allen SE, Holm JL (2008) Lactate: physiology and clinical utility. *Journal of Veterinary Emergency and Critical Care* 18, 123-132.

Ambros B, Duke-Novakovski T, Pasloske KS (2008) Comparison of the anesthetic efficacy and cardiopulmonary effects of continuous rate infusions of alfaxalone-2-hydroxypropyl-beta-cyclodextrin and propofol in dogs. *Am J Vet Res* 69, 1391-1398.

Amengual M, Flaherty D, Auckburally A et al. (2013) An evaluation of anaesthetic induction in healthy dogs using rapid intravenous injection of propofol or alfaxalone. *Veterinary anaesthesia and analgesia* 40, 115-123.

Andaluz A, Felez-Ocana N, Santos L et al. (2012) The effects on cardio-respiratory and acid-base variables of the anaesthetic alfaxalone in a 2-hydroxypropyl- β -cyclodextrin (HPCD) formulation in sheep. *The Veterinary Journal* 191, 389-392.

Appel E, Dudziak R, Palm D et al. (1979) Sympathoneuronal and sympathoadrenal activation during ketamine anesthesia. *European journal of clinical pharmacology* 16, 91-95.

Arndt JO, Mikat M, Parasher C (1984) Fentanyl's analgesic, respiratory, and cardiovascular actions in relation to dose and plasma concentration in unanesthetized dogs. *Anesthesiology* 61, 355-361.

Arnold RC, Shapiro NI, Jones AE et al. (2009) Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock* 32, 35-39.

Arrijoja-Dechert A (2002) *Compendium of Veterinary Products*, CD edition. Port Huron, MI: North American Compendiums. Inc.

Atchison SR, Durant P, Yaksh TL (1986) Cardiorespiratory effects and kinetics of intrathecally injected D-Ala²-D-Leu⁵-enkephalin and morphine in unanesthetized dogs. *Anesthesiology* 65, 609-616.

Bali I, Dundee J (1974) Immediate changes in plasma potassium, sodium and chloride induced by intravenous induction agents. *British journal of anaesthesia* 46, 929-933.

Bednarski R, Muir 3rd W (1990) Ventricular arrhythmogenic dose of epinephrine in dogs and cats anesthetized with tiletamine/zolazepam and halothane. *American journal of veterinary research* 51, 1468-1470.

Bennett R, Fancy S, Walsh C et al. (2008) Comparison of sevoflurane and isoflurane in dogs anaesthetised for clinical surgical or diagnostic procedures. *Journal of Small Animal Practice* 49, 392-397.

Bennett R, Orton E, Tucker A et al. (1989) Cardiopulmonary changes in conscious dogs with induced progressive pneumothorax. *American journal of veterinary research* 50, 280-284.

Boutureira J, Trim CM, Cornell KK (2007) Acute pulmonary edema after diazepam–ketamine in a dog. *Veterinary anaesthesia and analgesia* 34, 371-376.

Brashers V, McCance K (2010) Structure and function of the cardiovascular and lymphatic systems. *Pathophysiology: The Biologic Basis for Disease in Adults and Children* 6th ed Maryland Heights, MO: Mosby Elsevier, 1091-1141.

Broadbelt D, Hammond R, Tuminaro D et al. (2006) Risk factors for anaesthetic-related death in referred dogs. *Veterinary record* 158, 563.

Broadbelt D, Pfeiffer D, Young L et al. (2007) Risk factors for anaesthetic-related death in cats: results from the confidential enquiry into perioperative small animal fatalities (CEPSAF)†. *British journal of anaesthesia* 99, 617-623.

Broadbelt DC (2006) The confidential enquiry into perioperative small animal fatalities. Royal Veterinary College, University of London.

Broadbelt DC, Blissitt KJ, Hammond RA et al. (2008) The risk of death: the confidential enquiry into perioperative small animal fatalities. *Veterinary anaesthesia and analgesia* 35, 365-373.

Brüssel T, Theissen JL, Vigfusson G et al. (1989) Hemodynamic and cardiodynamic effects of propofol and etomidate: negative inotropic properties of propofol. *Anesthesia & Analgesia* 69, 35-40.

Buback JL, Boothe HW, Carroll GL et al. (1996) Comparison of three methods for relief of pain after ear canal ablation in dogs. *Vet Surg* 25, 380-385.

BVSC GH (1998) Evaluation of age as a risk factor for perianesthetic morbidity and mortality in the dog. *Journal of Veterinary Emergency and Critical Care* 8, 222-236.

Calderwood H, Klide A, Cohn B et al. (1971) Cardiorespiratory effects of tiletamine in cats. *Amer J Vet Res.*

Carroll G, Hartsfield S, Hambleton R (1997) Anesthetic effects of tiletamine-zolazepam, alone or in combination with butorphanol, in goats. *Journal of the American Veterinary Medical Association* 211, 593-597.

Casoni D, Spadavecchia C, Wampfler B et al. (2015) Clinical and pharmacokinetic evaluation of S-ketamine for intravenous general anaesthesia in horses undergoing field castration. *Acta Vet Scand* 57, 21.

Chen T-L, Huang F, Lin S et al. (1989) Hemodynamic response to ketamine and diazepam in dogs with acute cardiac tamponade. *Ma zui xue za zhi= Anaesthesiologica Sinica* 27, 19-25.

Chiu K, Robson S, Devi J et al. (2016) The cardiopulmonary effects and quality of anesthesia after induction with alfaxalone in 2-hydroxypropyl- β -cyclodextrin in dogs and cats: a systematic review. *Journal of Veterinary Pharmacology and Therapeutics.*

Clarke K, Hall L (1990) A survey of anaesthesia in small animal practice: AVA/BSAVA report. *Veterinary anaesthesia and analgesia* 17, 4-10.

Clarke KW, Trim CM (2013) *Veterinary anaesthesia*. Elsevier Health Sciences.

Clerbaux T, Gustin P, Detry B et al. (1993) Comparative study of the oxyhaemoglobin dissociation curve of four mammals: man, dog, horse and cattle. *Comparative Biochemistry and Physiology Part A: Physiology* 106, 687-694.

Connors AF, Speroff T, Dawson NV et al. (1996) The effectiveness of right heart catheterization in the initial care of critically III patients. *Jama* 276, 889-897.

Cox R, Peterson L, Detweiler D (1976) Comparison of arterial hemodynamics in the mongrel dog and the racing greyhound. *American Journal of Physiology--Legacy Content* 230, 211-218.

Cuvelliez S, Rosseel G, Blais D et al. (1995) [Intravenous anesthesia in the horse: comparison of xylazine-ketamine and xylazine-tiletamine-zolazepam combinations]. *The Canadian veterinary journal La revue veterinaire canadienne* 36, 613-618.

Davies C (1991) Excitatory phenomena following the use of propofol in dogs. *Veterinary anaesthesia and analgesia* 18, 48-51.

Davis H, Jensen T, Johnson A et al. (2013) 2013 AAHA/AAFP Fluid Therapy Guidelines for Dogs and Cats*. *Journal of the American Animal Hospital Association* 49, 149-159.

Diaz F, Bianco J, Bello A et al. (1976) Effects of ketamine on canine cardiovascular function. *British journal of anaesthesia* 48, 941-946.

DiBartola SP (2011) *Fluid, Electrolyte, and Acid-Base Disorders in Small Animal Practice*. Elsevier Health Sciences.

Donaldson L, McGrath C, Tracy C (1989) TESTING LOW-DOSES OF INTRAVENOUS TELAZOL IN CANINE PRACTICE. *Veterinary medicine* 84, 1202-1207.

Donati A, Loggi S, Preiser J-C et al. (2007) Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. *CHEST Journal* 132, 1817-1824.

Dowdy EG, Kaya K (1968) Studies of the mechanism of cardiovascular responses to CI-581. *The Journal of the American Society of Anesthesiologists* 29, 931-942.

Drenger B, Pe'er J (1987) Attenuation of ocular and systemic responses to tracheal intubation by intravenous lignocaine. *British journal of ophthalmology* 71, 546-548.

Dyson D, Maxie M, Schnurr D (1998) Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. *Journal of the American Animal Hospital Association* 34, 325-335.

Dyson D, McDonnell W, Horne J (1984) Accuracy of thermodilution measurement of cardiac output in low flows applicable to feline and small canine patients. *Canadian Journal of Comparative Medicine* 48, 425.

Enouri SS, Kerr CL, McDonell WN et al. (2008) Cardiopulmonary effects of anesthetic induction with thiopental, propofol, or a combination of ketamine hydrochloride and diazepam in dogs sedated with a combination of medetomidine and hydromorphone. *American journal of veterinary research* 69, 586-595.

Estes K, Brewster M, Webb A et al. (1990) A non-surfactant formulation for alfaxalone based on an amorphous cyclodextrin: Activity studies in rats and dogs. *International journal of pharmaceutics* 65, 101-107.

Feigl EO, D'Alecy LG (1972) Normal arterial blood pH, oxygen, and carbon dioxide tensions in unanesthetized dogs. *Journal of Applied Physiology* 32, 152-153.

Ferchichi S, Troncy E, Guillot M et al. (2013) Excitement in dogs recovering from alfaxalone anaesthesia: is the absent drug blamed in error? *Veterinary anaesthesia and analgesia* 40, 655-656.

Ferré PJ, Pasloske K, Whittam T et al. (2006) Plasma pharmacokinetics of alfaxalone in dogs after an intravenous bolus of Alfaxan-CD RTU. *Veterinary anaesthesia and analgesia* 33, 229-236.

Ferreira JP, Dzikit TB, Zeiler GE et al. (2015) Anaesthetic induction and recovery characteristics of a diazepam-ketamine combination compared with propofol in dogs. *J S Afr Vet Assoc* 86, 1258.

Floriano BP, Wagatsuma JT, Ferreira JZ et al. (2016) Effects on indicators of tissue perfusion in dogs anesthetized with isoflurane at two multiples of the minimum alveolar concentration. *American journal of veterinary research* 77, 24-31.

Gallagher EJ, Rodriguez K, Touger M (1997) Agreement between peripheral venous and arterial lactate levels. *Annals of emergency medicine* 29, 479-483.

Garcia PS, Kolesky SE, Jenkins A (2010) General anesthetic actions on GABAA receptors. *Current neuropharmacology* 8, 2-9.

Garg K, Howell BW, Saltzberg SS et al. (2013) Open surgical management of complications from indwelling radial artery catheters. *Journal of vascular surgery* 58, 1325-1330.

Gaynor JS, Dunlop CI, Wagner AE et al. (1999) Complications and mortality associated with anesthesia in dogs and cats. *Journal of the American Animal Hospital Association* 35, 13-17.

Ghurashi M, Seri H, Bakheit A et al. (2009) Evaluation of ketamine/diazepam anaesthesia for performing surgery in desert goats under field condition. *Australian Journal of Basic and Applied Sciences* 3, 455-459.

Gil L, Redondo JI (2013) Canine anaesthetic death in Spain: a multicentre prospective cohort study of 2012 cases. *Veterinary anaesthesia and analgesia* 40, e57-e67.

GOLDBERG AH, KEANE PW, Phear W (1970) Effects of ketamine on contractile performance and excitability of isolated heart muscle. *Journal of Pharmacology and Experimental Therapeutics* 175, 388-394.

Gómez-Villamandos RJ, Martínez C, Navarrete R et al. (2013) Romifidine and low doses of tiletamine-zolazepam in dogs. *Veterinary anaesthesia and analgesia* 40, e40-e47.

Goodchild C, Serrao J (1989) Cardiovascular effects of propofol in the anaesthetized dog. *British journal of anaesthesia* 63, 87-92.

Green C, Knight J, Precious S et al. (1981) Ketamine alone and combined with diazepam or xylazine in laboratory animals: a 10 year experience. *Laboratory Animals* 15, 163-170.

Grimm KA, Lamont LA, Tranquilli WJ et al. (2015) *Veterinary Anesthesia and Analgesia*. John Wiley & Sons.

Gunkel CI, Valverde A, Morey TE et al. (2004) Comparison of non-invasive cardiac output measurement by partial carbon dioxide rebreathing with the lithium dilution method in anesthetized dogs. *Journal of Veterinary Emergency and Critical Care* 14, 187-195.

Guyton A, Hall J (2006) Transport of oxygen and carbon dioxide in blood and tissue fluids. Textbook of medical physiology.

Hall JE, Guyton AC (2011) Textbook of medical physiology. Saunders London.

Harvey S, Harrison DA, Singer M et al. (2005) Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet* 366, 472-477.

Hasiuk MM, Forde N, Cooke A et al. (2014) A comparison of alfaxalone and propofol on intraocular pressure in healthy dogs. *Veterinary ophthalmology* 17, 411-416.

Haskins S, Farver T, Patz J (1985a) Ketamine in dogs. *American journal of veterinary research* 46, 1855-1860.

Haskins S, Pascoe PJ, Ilkiw JE et al. (2005) Reference cardiopulmonary values in normal dogs. *Comparative medicine* 55, 156-161.

Haskins SC, Farver TB, Patz JD (1985b) Ketamine in dogs. *Am J Vet Res* 46, 1855-1860.

Haskins SC, Farver TB, Patz JD (1986) Cardiovascular changes in dogs given diazepam and diazepam-ketamine. *Am J Vet Res* 47, 795-798.

Haskins SC, Patz JD (1990) Ketamine in hypovolemic dogs. *Crit Care Med* 18, 625-629.

HELLYER P, MUIR WW, HUBBELL JA et al. (1989) Cardiorespiratory Effects of the Intravenous Administration of Tiletamine-Zolazepam to Dogs. *Veterinary Surgery* 18, 160-165.

HELLYER P, WILLIAM III W, HUBBELL JA et al. (1988) Cardiorespiratory Effects of the Intravenous Administration of Tiletamine-zolazepam to Cats. *Veterinary Surgery* 17, 105-110.

HELLYER PW, FREEMAN LC, HUBBELL JA (1991) Induction of Anesthesia with Diazepam-Ketamine and Midazolam-Ketamine in Greyhounds. *Veterinary Surgery* 20, 143-147.

Henao-Guerrero N, Riccó CH (2014) Comparison of the cardiorespiratory effects of a combination of ketamine and propofol, propofol alone, or a combination of ketamine and diazepam before and after induction of anesthesia in dogs sedated with acepromazine and oxymorphone. *Am J Vet Res* 75, 231-239.

Hirshman C, McCullough R, Cohen P et al. (1977) Depression of hypoxic ventilatory response by halothane, enflurane and isoflurane in dogs. *British journal of anaesthesia* 49, 957-963.

Hofmeister EH, Mosunic CB, Torres BT et al. (2006) Effects of ketamine, diazepam, and their combination on intraocular pressures in clinically normal dogs. *American journal of veterinary research* 67, 1136-1139.

Holm J, Håkanson E, Vánky F et al. (2011) Mixed venous oxygen saturation predicts short-and long-term outcome after coronary artery bypass grafting surgery: a retrospective cohort analysis. *British journal of anaesthesia*, 116.

Holm J, Håkanson RE, Vánky F et al. (2010) Mixed venous oxygen saturation is a prognostic marker after surgery for aortic stenosis. *Acta anaesthesiologica Scandinavica* 54, 589-595.

Hughes D (2000) Lactate measurement: diagnostic, therapeutic, and prognostic implications. *KIRKS CURRENT VETERINARY THERAPY* 13, 112-115.

Hughes D (2006) Interpretation of lactate—What's it? What can We do with it. In: *Proceedings of North America Veterinary Conference*.

Hughes D, Rozanski E, Shofer F et al. (1999) Effect of sampling site, repeated sampling, pH, and PCO₂ on plasma lactate concentration in healthy dogs. *American journal of veterinary research* 60, 521-524.

Ilkiw J, Davis P, Church D (1989) Hematologic, biochemical, blood-gas, and acid-base values in greyhounds before and after exercise. *American journal of veterinary research* 50, 583-586.

Ilkiw JE (1992) Other potentially useful new injectable anesthetic agents. *The Veterinary clinics of North America Small animal practice* 22, 281-289.

Ilkiw JE, Rose R, Martin I (1991) A Comparison of Simultaneously Collected Arterial, Mixed Venous, Jugular Venous and Cephalic Venous Blood Samples in the Assessment of Blood-Gas and Acid-Base Status in the Dog. *Journal of Veterinary Internal Medicine* 5, 294-298.

Jang H-S, KWON Y-S, LEE M-G et al. (2004) The effect of tiletamine/zolazepam (Zoletile) combination with xylazine or medetomidine on electroencephalograms in dogs. *Journal of Veterinary Medical Science* 66, 501-507.

Jang M, Park S, Son Wg et al. (2015) Effect of tiletamine–zolazepam on the intraocular pressure of the dog. *Veterinary ophthalmology* 18, 481-484.

Jaspar N, Mazzarelli M, Tessier C et al. (1983) Effect of ketamine on control of breathing in cats. *Journal of Applied Physiology* 55, 851-859.

Jennings D, Davidson J (1984) Acid-base and ventilatory adaptation in conscious dogs during chronic hypercapnia. *Respiration physiology* 58, 377-393.

Jiménez CP, Mathis A, Mora SS et al. (2012) Evaluation of the quality of the recovery after administration of propofol or alfaxalone for induction of anaesthesia in dogs anaesthetized for magnetic resonance imaging. *Veterinary anaesthesia and analgesia* 39, 151-159.

Johnston G, Eastment J, Taylor P et al. (2004) Is isoflurane safer than halothane in equine anaesthesia? Results from a prospective multicentre randomised controlled trial. *Equine veterinary journal* 36, 64-71.

Jones DJ, Stehling LC, Zauder HL (1979) Cardiovascular responses to diazepam and midazolam maleate in the dog. *Anesthesiology* 51, 430-434.

Kamibayashi T, Hayashi Y, Sumikawa K et al. (1991) Enhancement by propofol of epinephrine-induced arrhythmias in dogs. *Anesthesiology* 75, 1035-1040.

Kandel G, Aberman A (1983) Mixed venous oxygen saturation: Its role in the assessment of the critically ill patient. *Archives of internal medicine* 143, 1400.

Karagiannis MH, Reniker AN, Kerl ME et al. (2006) Lactate measurement as an indicator of perfusion. *Compendium* 28, 287-298.

Kasnitz P, Druger GL, Yorra F et al. (1976) Mixed venous oxygen tension and hyperlactatemia: survival in severe cardiopulmonary disease. *Jama* 236, 570-574.

Kawakubo A, Fujigaki T, Uresino H et al. (1999) Comparative effects of etomidate, ketamine, propofol, and fentanyl on myocardial contractility in dogs. *Journal of anaesthesia* 13, 77-82.

Keates H, Whittam T (2012) Effect of intravenous dose escalation with alfaxalone and propofol on occurrence of apnoea in the dog. *Research in veterinary science* 93, 904-906.

Keating S, Kerr C, McDonnell W et al. (2016) Effects of acepromazine or dexmedetomidine on fentanyl disposition in dogs during recovery from isoflurane anesthesia. *Veterinary anaesthesia and analgesia* 43, 35-43.

Kim CY, Lee HS, Han SC et al. (2005) Hematological and serum biochemical values in cynomolgus monkeys anesthetized with ketamine hydrochloride. *Journal of medical primatology* 34, 96-100.

Klöppel H, Leece EA (2011) Comparison of ketamine and alfaxalone for induction and maintenance of anaesthesia in ponies undergoing castration. *Vet Anaesth Analg* 38, 37-43.

Klotz U, Antonin K, Bieck P (1976) Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. *Journal of Pharmacology and Experimental Therapeutics* 199, 67-73.

Ko J, Nicklin C, Melendaz M et al. (1998) Effects of a microdose of medetomidine on diazepam-ketamine induced anesthesia in dogs. *Journal of the American Veterinary Medical Association* 213, 215-219.

Ko JC, Berman AG (2010) Anesthesia in shelter medicine. *Top Companion Anim Med* 25, 92-97.

Kovalcuka L, Birgele E, Bandere D et al. (2013) The effects of ketamine hydrochloride and diazepam on the intraocular pressure and pupil diameter of the dog's eye. *Veterinary ophthalmology* 16, 29-34.

Kreisberg RA (1980) Lactate homeostasis and lactic acidosis. *Ann Intern Med* 92, 227-237.

Krimins RA, Ko JC, Weil AB et al. (2012a) Evaluation of anesthetic, analgesic, and cardiorespiratory effects in dogs after intramuscular administration of dexmedetomidine–butorphanol–tiletamine–zolazepam or dexmedetomidine–tramadol–ketamine drug combinations. *American journal of veterinary research* 73, 1707-1714.

Krimins RA, Ko JC, Weil AB et al. (2012b) Hemodynamic effects in dogs after intramuscular administration of a combination of dexmedetomidine–butorphanol–tiletamine–zolazepam or dexmedetomidine–butorphanol–ketamine. *Am J Vet Res* 73, 1363-1370.

Kudnig ST, Mama K (2002) Perioperative fluid therapy. *Journal of the American Veterinary Medical Association* 221, 1112-1121.

Kwak KH, Lee C, Lee S et al. (2010) Emergence agitation/delirium: we still don't know. *Korean J Anesthesiol* 59, 104-110.

Lagutchik MS, Ogilvie GK, Hackett TB et al. (1998) Increased lactate concentrations in III and injured dogs. *Journal of Veterinary Emergency and Critical Care* 8, 117-127.

Lagutchik MS, Ogilvie GK, Wingfield WE et al. (1996) Lactate Kinetics in veterinary Critical Care: A Review. *Journal of Veterinary Emergency and Critical Care* 6, 81-95.

Laing S, Paul V, Murison P (2009) The effects of nitrous oxide on recovery from isoflurane anaesthesia in dogs. *Journal of Small Animal Practice* 50, 82-86.

Lepouse C, Lautner C, Liu L et al. (2006) Emergence delirium in adults in the post-anaesthesia care unit. *British journal of anaesthesia* 96, 747-753.

Lerche P, Nolan A, Reid J (2000) Comparative study of propofol or propofol. *The Veterinary record* 146, 571-574.

Lin H, Thurmon J, Benson G et al. (1993a) Review: Telazol—a review of its pharmacology and use in veterinary medicine. *Journal of Veterinary Pharmacology and Therapeutics* 16, 383-418.

Lin H, Thurmon J, Benson G et al. (1989) The Hemodynamic Response of Calves to Tiletamine-Zolazepam Anesthesia. *Veterinary Surgery* 18, 328-334.

Lin H, Tyler J, Wallace S et al. (1993b) Telazol and xylazine anesthesia in sheep. *The Cornell veterinarian* 83, 117-124.

Lopez LA, Hofmeister EH, Pavez JC et al. (2009) Comparison of recovery from anesthesia with isoflurane, sevoflurane, or desflurane in healthy dogs. *American journal of veterinary research* 70, 1339-1344.

Lough ME (2015) *Hemodynamic Monitoring: Evolving Technologies and Clinical Practice*. Elsevier Health Sciences.

Love EJ, Holt PE, Murison PJ (2007) Recovery characteristics following maintenance of anaesthesia with sevoflurane or isoflurane in dogs premedicated with acepromazine. *Vet Rec* 161, 217-221.

Lucet J-C, Bouadma L, Zahar J-R et al. (2010) Infectious risk associated with arterial catheters compared with central venous catheters*. *Critical care medicine* 38, 1030-1035.

MACDONALD R (1977) Red cell 2, 3-diphosphoglycerate and oxygen affinity. *Anaesthesia* 32, 544-553.

Maddern K, Adams VJ, Hill NA et al. (2010) Alfaxalone induction dose following administration of medetomidine and butorphanol in the dog. *Veterinary anaesthesia and analgesia* 37, 7-13.

Magilligan DJ, Teasdall R, Eisingminger R et al. (1987) Mixed venous oxygen saturation as a predictor of cardiac output in the postoperative cardiac surgical patient. *The Annals of thoracic surgery* 44, 260-262.

Maney JK, Shepard MK, Braun C et al. (2013) A comparison of cardiopulmonary and anesthetic effects of an induction dose of alfaxalone or propofol in dogs. *Veterinary anaesthesia and analgesia* 40, 237-244.

Martinez-Taboada F, Leece EA (2014) Comparison of propofol with ketofol, a propofol-ketamine admixture, for induction of anaesthesia in healthy dogs. *Veterinary anaesthesia and analgesia* 41, 575-582.

Massolo A, Sforzi A, Lovari S (2003) Chemical immobilization of crested porcupines with tiletamine HCl and zolazepam HCl (Zoletil®) under field conditions. *Journal of wildlife diseases* 39, 727-731.

Mathias DW, Clifford PS, Klopfenstein H (1988) Mixed venous blood gases are superior to arterial blood gases in assessing acid-base status and oxygenation during acute cardiac tamponade in dogs. *Journal of Clinical Investigation* 82, 833.

Mauderly JL (1974) Influence of sex and age on the pulmonary function of the unanesthetized beagle dog. *Journal of gerontology* 29, 282-289.

McCallum JB, Stekiel TA, Bosnjak ZJ et al. (1993) Does Isoflurane Alter Mesenteric Venous Capacitance in the Intact Rabbit? *Anesthesia & Analgesia* 76, 1095-1105.

McLellan S, Walsh T (2004) Oxygen delivery and haemoglobin. *Continuing Education in Anaesthesia, Critical Care & Pain* 4, 123-126.

Michou JN, Leece EA, Brearley JC (2012) Comparison of pain on injection during induction of anaesthesia with alfaxalone and two formulations of propofol in dogs. *Veterinary anaesthesia and analgesia* 39, 275-281.

Middleton D, Ilkiw J, Watson A (1982) Physiological effects of thiopentone, ketamine and CT 1341 in cats. *Research in veterinary science* 32, 157-162.

Middleton P, Kelly A, Brown J et al. (2006) Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emergency medicine journal* 23, 622-624.

Miller RD, Eriksson LI, Fleisher LA et al. (2014) *Miller's anesthesia*. Elsevier Health Sciences.

Minogue SC, Ralph J, Lampa MJ (2004) Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. *Anesthesia & Analgesia* 99, 1253-1257.

Mizock BA, Falk JL (1992) Lactic acidosis in critical illness. *Critical care medicine* 20, 80-93.

Moore J, Owen RaR, Lumsden J (1976) Clinical evaluation of blood lactate levels in equine colic. *Equine veterinary journal* 8, 49-54.

Moreland A, Glaser C (1985) Evaluation of ketamine, ketamine-xylazine and ketamine-diazepam anesthesia in the ferret. *Laboratory animal science* 35, 287-290.

Morgan D, Legge K (1989) Clinical evaluation of propofol as an intravenous anaesthetic agent in cats and dogs. *The Veterinary record* 124, 31-33.

Morita K, Kawashima Y, Irita K et al. (2001) [Perioperative mortality and morbidity in 1999 with a special reference to age in 466 certified training hospitals of Japanese Society of Anesthesiologists--report of Committee on Operating Room Safety of Japanese Society of Anesthesiologists]. *Masui The Japanese journal of anesthesiology* 50, 909-921.

Muggenburg BA, Mauderly J (1974) Cardiopulmonary function of awake, sedated, and anesthetized beagle dogs. *Journal of Applied Physiology* 37, 152-157.

Muir 3rd W, Gadawski J (1998) Respiratory depression and apnea induced by propofol in dogs. *American journal of veterinary research* 59, 157-161.

Muir III WW, Hubbell JA (2008) *Equine anesthesia: monitoring and emergency therapy*. Elsevier Health Sciences.

Muir III WW, Kijawornrat A, Ueyama Y et al. (2011) Effects of intravenous administration of lactated Ringer's solution on hematologic, serum biochemical, rheological, hemodynamic, and renal measurements in healthy isoflurane-anesthetized dogs. *Journal of the American Veterinary Medical Association* 239, 630-637.

Muir W, Lerche P, Wiese A et al. (2008) Cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in dogs. *Veterinary anaesthesia and analgesia* 35, 451-462.

Muir W, Skarda R, Milne D (1976) Estimation of cardiac output in the horse by thermodilution techniques. *American journal of veterinary research* 37, 697-700.

Muir WW (2010) NMDA receptor antagonists and pain: ketamine. *Veterinary Clinics of North America: Equine Practice* 26, 565-578.

Nelson DP, Beyer C, Samsel RW et al. (1987) Pathological supply dependence of O₂ uptake during bacteremia in dogs. *Journal of Applied Physiology* 63, 1487-1492.

O'Hagan B, Pasloske K, McKinnon C et al. (2012) Clinical evaluation of alfaxalone as an anaesthetic induction agent in dogs less than 12 weeks of age. *Australian veterinary journal* 90, 346-350.

O'Horo JC, Maki DG, Krupp AE et al. (2014) Arterial Catheters as a Source of Bloodstream Infection: A Systematic Review and Meta-Analysis*. *Critical care medicine* 42, 1334-1339.

Okushima S, Vettorato E, Corletto F (2015) Chronotropic effect of propofol or alfaxalone following fentanyl administration in healthy dogs. *Veterinary anaesthesia and analgesia* 42, 88-92.

Pablo LS, Bailey JE (1999) Etomidate and telazol. *Veterinary Clinics of North America: Small Animal Practice* 29, 779-792.

Pagel PS, Hettrick DA, Kersten JR et al. (1998) Cardiovascular effects of propofol in dogs with dilated cardiomyopathy. *The Journal of the American Society of Anesthesiologists* 88, 180-189.

Pagel PS, Kampine JP, Schmeling WT et al. (1991) Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. *Anesthesiology* 74, 1103-1114.

Pagel PS, Kampine JP, Schmeling WT et al. (1992) Ketamine depresses myocardial contractility as evaluated by the preload recruitable stroke work relationship in chronically instrumented dogs with autonomic nervous system blockade. *Anesthesiology* 76, 564-572.

Pagel PS, Warltier DC (1993) Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs. *Anesthesiology* 78, 100-108.

Parsons C, Gibbens H, Magnago T et al. (1988) At which 'sigma' site are the spinal actions of ketamine mediated? *Neuroscience letters* 85, 322-328.

Pasloske K, Sauer B, Perkins N et al. (2009) Plasma pharmacokinetics of alfaxalone in both premedicated and unpremedicated Greyhound dogs after single, intravenous administration of Alfaxan® at a clinical dose. *Journal of Veterinary Pharmacology and Therapeutics* 32, 510-513.

Pavlin EG, Hornbein TF (1986) Anesthesia and the control of ventilation. *Comprehensive Physiology*.

Perz S, Uhlig T, Kohl M et al. (2011) Low and "supranormal" central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study. *Intensive care medicine* 37, 52-59.

Pölonen P, Ruokonen E, Hippeläinen M et al. (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesthesia & Analgesia* 90, 1052-1059.

Porter JM, Ivatury RR (1998) In search of the optimal end points of resuscitation in trauma patients: a review. *The Journal of trauma* 44, 908-914.

Psatha E, Alibhai HI, Jimenez-Lozano A et al. (2011) Clinical efficacy and cardiorespiratory effects of alfaxalone, or diazepam/fentanyl for induction of anaesthesia in dogs that are a poor anaesthetic risk. *Veterinary anaesthesia and analgesia* 38, 24-36.

Pypendop B, Verstegen J (1999) Cardiorespiratory effects of a combination of medetomidine, midazolam, and butorphanol in dogs. *American journal of veterinary research* 60, 1148-1154.

Quandt J, Robinson E, Rivers W et al. (1998) Cardiorespiratory and anesthetic effects of propofol and thiopental in dogs. *American journal of veterinary research* 59, 1137-1143.

Redondo J, Rubio M, Soler G et al. (2007) Normal values and incidence of cardiorespiratory complications in dogs during general anaesthesia. A review of 1281 cases. *Journal of Veterinary Medicine Series A* 54, 470-477.

Reeves RB, Park J, Lapennas GN et al. (1982) Oxygen affinity and Bohr coefficients of dog blood. *Journal of Applied Physiology* 53, 87-95.

Reich DL, Silvey G (1989) Ketamine: an update on the first twenty-five years of clinical experience. *Canadian Journal of Anaesthesia* 36, 186-197.

Reynolds BS, Geffré A, Bourges-Abella NH et al. (2012) Effects of intravenous, low-dose ketamine-diazepam sedation on the results of hematologic, plasma biochemical, and coagulation analyses in cats. *J Am Vet Med Assoc* 240, 287-293.

Robinson R, Borer-Weir K (2013) A dose titration study into the effects of diazepam or midazolam on the propofol dose requirements for induction of general anaesthesia in client owned dogs, premedicated with methadone and acepromazine. *Veterinary anaesthesia and analgesia* 40, 455-463.

Rodríguez JM, Muñoz-Rascón P, Navarrete-Calvo R et al. (2012) Comparison of the cardiopulmonary parameters after induction of anaesthesia with alphaxalone or etomidate in dogs. *Veterinary anaesthesia and analgesia* 39, 357-365.

Rose R, Carter J (1979) Some physiological and biochemical effects of acetazolamide in the dog. *Journal of Veterinary Pharmacology and Therapeutics* 2, 215-221.

Sakr Y, Vincent J-L, Reinhart K et al. (2005) Use of the pulmonary artery catheter is not associated with worse outcome in the ICU. *CHEST Journal* 128, 2722-2731.

Sams L, Braun C, Allman D et al. (2008) A comparison of the effects of propofol and etomidate on the induction of anesthesia and on cardiopulmonary parameters in dogs. *Veterinary anaesthesia and analgesia* 35, 488-494.

Samsel RW, Nelson DP, Sanders WM et al. (1988) Effect of endotoxin on systemic and skeletal muscle O₂ extraction. *Journal of Applied Physiology* 65, 1377-1382.

Savvas I, Plevraki K, Raptopoulos D et al. (2005) Blood gas and acid–base status during tiletamine/zolazepam anaesthesia in dogs. *Veterinary anaesthesia and analgesia* 32, 94-100.

Schwieger IM, Szlam F, Hug Jr CC (1991) The pharmacokinetics and pharmacodynamics of ketamine in dogs anesthetized with enflurane. *Journal of pharmacokinetics and biopharmaceutics* 19, 145-156.

Seliskar A, Nemec A, Roskar T et al. (2007) Total intravenous anaesthesia with propofol or propofol/ketamine in spontaneously breathing dogs premedicated with medetomidine. *Vet Rec* 160, 85-91.

Shih A, Maisenbacher HW, Bandt C et al. (2011) Assessment of cardiac output measurement in dogs by transpulmonary pulse contour analysis. *J Vet Emerg Crit Care (San Antonio)* 21, 321-327.

Short CE (1987) Principles and practice of veterinary anesthesia. Williams & Wilkins.

Short CE, Bufalari A (1999) Propofol anesthesia. *Veterinary Clinics of North America: Small Animal Practice* 29, 747-778.

Steffey E, Howland Jr D (1977) Isoflurane potency in the dog and cat. *American journal of veterinary research* 38, 1833-1836.

Suarez MA, Dziki BT, Stegmann FG et al. (2012) Comparison of alfaxalone and propofol administered as total intravenous anaesthesia for ovariohysterectomy in dogs. *Veterinary anaesthesia and analgesia* 39, 236-244.

Sweitzer RA, Ghneim GS, Gardner IA et al. (1997) Immobilization and physiological parameters associated with chemical restraint of wild pigs with Telazol® and xylazine hydrochloride. *Journal of wildlife diseases* 33, 198-205.

Thurmon JC, Tranquilli WJ, Grimm KA et al. (2007) Lumb and Jones' Veterinary Anesthesia and Analgesia. Blackwell.

To QG Cardiopulmonary Care.

Toda H, Nakamura K, Hatano Y et al. (1992) Halothane and isoflurane inhibit endothelium-dependent relaxation elicited by acetylcholine. *Anesthesia & Analgesia* 75, 198-203.

Toffaletti JG (1991) Blood lactate: biochemistry, laboratory methods, and clinical interpretation. *Critical reviews in clinical laboratory sciences* 28, 253-268.

Tournadre J, Chassard D, Muchada R (1997) Overestimation of low cardiac output measured by thermodilution. *British journal of anaesthesia* 79, 514-516.

Traber D, Wilson R, Priano L (1970) A detailed study of the cardiopulmonary response to ketamine and its blockade by atropine. *Southern medical journal* 63, 1077-1081.

Tuchschildt J, Oblitas D, Fried JC (1991) Oxygen consumption in sepsis and septic shock. *Critical care medicine* 19, 664-671.

Urden LD, Stacy KM, Lough ME et al. (2002) *Thelan's critical care nursing: Diagnosis and management*. Mosby Inc.

Vachon P, Dupras J, Prout R et al. (1999) EEG recordings in anesthetized rabbits: comparison of ketamine-midazolam and telazol with or without xylazine. *Journal of the American Association for Laboratory Animal Science* 38, 57-61.

Valentine RJ, Modrall JG, Clagett GP (2005) Hand ischemia after radial artery cannulation. *Journal of the American College of Surgeons* 201, 18-22.

van Beest P, Wietasch G, Scheeren T et al. (2011) Clinical review: use of venous oxygen saturations as a goal-a yet unfinished puzzle. *Crit Care* 15, 232-240.

Van der Linden P, Schmartz D, De Groote F et al. (1998) Critical haemoglobin concentration in anaesthetized dogs: comparison of two plasma substitutes. *Br J Anaesth* 81, 556-562.

Van der Linden P, Schmartz D, Gilbert E et al. (2000) Effects of propofol, etomidate, and pentobarbital on critical oxygen delivery. *Crit Care Med* 28, 2492-2499.

van Foreest A (1991) [The application of tiletamine/zolazepam (Zoletil) anesthesia in dental treatments in dogs]. *Tijdschrift voor diergeneeskunde* 116, 1063-1066.

Vigani A, Shih AC, Buckley GJ et al. (2011) Cardiopulmonary effects of a new inspiratory impedance threshold device in acute hemorrhagic shock in dogs. *J Vet Emerg Crit Care (San Antonio)* 21, 618-624.

Waller J, Kaplan J, Bauman D et al. (1982) Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery. *Anesthesia & Analgesia* 61, 676-679.

Warne LN, Beths T, Whittam T et al. (2015) A review of the pharmacology and clinical application of alfaxalone in cats. *The Veterinary Journal* 203, 141-148.

Watney G, Pablo L (1992) Median effective dosage of propofol for induction of anesthesia in dogs. *American journal of veterinary research* 53, 2320-2322.

Weaver B, Raptopoulos D (1990) Induction of anaesthesia in dogs and cats with propofol. *The Veterinary record* 126, 617-620.

Weil M (2005) Defining hemodynamic instability. In: *Functional Hemodynamic Monitoring*. Springer. pp. 9-17.

Weisel RD, Berger RL, Hechtman HB (1975) Measurement of cardiac output by thermodilution. *New England Journal of Medicine* 292, 682-684.

Weiskopf RB, Townsley MI, Riordan KK et al. (1981) Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia. *Anesthesia & Analgesia* 60, 481-491.

White KL, Shelton K, Taylor PM (2001) Comparison of diazepam–ketamine and thiopentone for induction of anaesthesia in healthy dogs. *Veterinary anaesthesia and analgesia* 28, 42-48.

Wilson RP, Zagon IS, Larach DR et al. (1993) Cardiovascular and respiratory effects of tiletamine-zolazepam. *Pharmacology Biochemistry and Behavior* 44, 1-8.

Wise W (1973) Normal arterial blood gases and chemical components in the un-anesthetized dog. *Journal of Applied Physiology* 35, 427-429.

Wong DH, Jenkins LC (1974) An experimental study of the mechanism of action of ketamine on the central nervous system. *Canadian Anaesthetists' Society Journal* 21, 57-67.

水野豊香, 間弘子, 原秀昭 et al. (1994) Comparison of methods of cardiac output measurements determined by dye dilution, pulsed Doppler echocardiography and thermodilution in horses. *Journal of Veterinary Medical Science* 56, 1-5.

9. APPENDIX

9.1 Abbreviations

[HCO₃⁻]; Serum Bicarbonate Concentration

10M; 10 minutes post-induction

2,3-DPG; 2,3-Bisphosphoglyceric Acid

20M; 20 minutes post-induction

40M; 40 minutes post-induction

60M; 60 minutes post-induction

_aHCO₃⁻; Arterial Serum Bicarbonate

A-HPCD; Alfaxalone in 2-hydroxypropyl-beta-cyclodextrin

ANOVA: Analysis of Variance

ARD; Acid Reflux Disease

ASA; American Society of Anesthesiologists

A_{tot}; Serum Weak Acid Total Concentration

ATP; Adenosine Triphosphate

BE_a; Base Excess of Arterial Blood

BE_{mv}; Base Excess of Mixed-Venous Blood

BMI; Body Mass Index

Ca⁺⁺; Calcium

CAD; Coronary Artery Disease

CaO₂; Arterial Oxygen Content

CI; Cardiac Index

Cl⁻; Chloride

CmvO₂; Mixed-Venous Oxygen Content

CO; Cardiac Output

CO₂; Carbon Dioxide

COPD; Chronic Obstructive Pulmonary Disease

CVA; Cerebral Vascular Accident

CvO₂; Venous Oxygen Content

CVP; Central Venous Pressure

DABP; Diastolic Arterial Blood Pressure

DIC; Disseminated Intravascular Coagulation

DM; Diabetes Mellitus

DO₂; Oxygen Delivery

ECG; Electrocardiography

ESRD; End-Stage Renal Disease

EtCO₂; End-tidal Partial Pressure of Carbon Dioxide

Et_{ISO}; End-tidal Concentration of Isoflurane

EtO₂; End-tidal Fraction of Oxygen

FiO₂; Inspired Fraction of Oxygen

GABA; Gamma-Amino-Butyric Acid

GABA_A; Gamma-Amino-Butyric Acid Type A Receptor

GL_a; Arterial Glucose

GL_{mv}; Mixed-Venous Glucose

Hb; Hemoglobin

HCO₃⁻; Bicarbonate

HPCD; 2-hydroxypropyl-beta-cyclodextrin

HR; Heart Rate

HTN; Hypertension

iCa⁺⁺; Ionized Calcium

IM; Intramuscular

IV; Intravenous

K⁺; Potassium

KD; Ketamine-Diazepam

LAC_a; Arterial Lactate

LAC_{mv}; Mixed-Venous Lactate

MABP; Mean Arterial Blood Pressure

MDABP; Mean Diastolic Arterial Blood Pressure

MI; Myocardial Infarction

MPAP; Mean Pulmonary Arterial Pressure

MPAWP; Mean Pulmonary Arterial Wedge Pressure

MRAP; Mean Right Atrial Pressure

MSABP; Mean Systolic Arterial Blood Pressure

MV; Mixed-Venous

_{mv}HCO₃⁻; Mixed-Venous Serum Bicarbonate

Na⁺; Sodium

NaCl; Sodium Chloride

NICO; Non-Invasive Cardiac Output

NMDA; N-methyl-D-aspartate

O_2ER ; Oxygen Extraction Ratio

OD; Outer Diameter

P_ACO_2 ; Alveolar Partial Pressure of Carbon Dioxide

P_aCO_2 ; Arterial Partial Pressure of Carbon Dioxide

P_AO_2 ; Alveolar Partial Pressure of Oxygen

PaO_2 ; Partial Pressure of Oxygen in Arterial Blood

PAP; Pulmonary Arterial Pressure

PAWP; Pulmonary Arterial Wedge Pressure

PCA; Post-Conceptual Age

PCO_2 ; Partial Pressure of Carbon Dioxide

PCV; Packed Cell Volume

pH_a ; Arterial pH

pH_{mv} ; Mixed-Venous pH

PiCCO_c; Pulse Contour Analysis

PiCCO-TD; Transpulmonary Thermodilution

P_{mvCO_2} ; Mixed-Venous Partial Pressure of Carbon Dioxide

P_{mvO_2} ; Mixed-Venous Partial Pressure of Oxygen

PO_2 ; Partial Pressure of Oxygen

PS; Physical Status

PulseCO; Pulse Power Analysis

$PvCO_2$; Venous Partial Pressure of Carbon Dioxide

PvO_2 ; Venous Partial Pressure of Oxygen

PVR; Pulmonary Vascular Resistance

RM-ANOVA; Repeated Measures Analysis of Variance

SABP; Systolic Arterial Blood Pressure

SaO₂; Oxygen Saturation of Arterial Blood

SD; Standard Deviations

SID; Strong Ion Difference

SmvO₂; Oxygen Saturation of Mixed-Venous Blood

SO₂; Oxygen Saturation

SpO₂; Peripheral Capillary Oxygen Saturation

SV; Stroke Volume

SVI; Stroke Volume Index

SVR; Systemic Vascular Resistance

SVRI; Systemic Vascular Resistance Index

TIA; Transient Ischemic Attack

TPP; Total Plasma Protein Concentration

TZ; Tiletamine-Zolazepam

V/Q; Ventilation/Perfusion

VO₂; Oxygen Consumption