Anesthetic and Cardio-pulmonary Effects of Propofol or Alfaxalone with or without Midazolam Co-Induction in Fentanyl Sedated Dogs

by

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A Thesis

presented to

The University of Guelph

In partial fulfilment of requirements

for the degree of

Doctor of Veterinary Science

in

Clinical Studies

Guelph, Ontario, Canada

ABSTRACT

Anesthetic and Cardio-pulmonary Effects of Propofol or Alfaxalone with or without Midazolam Co-Induction in Fentanyl Sedated Dogs For Diagnostic Imaging

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This thesis describes a prospective, randomized, incomplete Latin-square crossover, blind trial to investigate the effects of midazolam (M) as a co-induction agent in dogs induced and maintained with propofol (P) or alfaxalone (A) for diagnostic imaging. The quality of induction and recovery, induction and maintenance dose requirements for P or A, ease of maintenance using total intravenous anesthesia (TIVA), and cardio-pulmonary effects were determined in ten dogs assigned to P-S: P with saline (S); A-S: A with S; P-M: P with M; A-M: A with M. Fentanyl (7 μg kg^{-1}, IV) was administered 10 minutes prior to an IV bolus of P (1 mg kg^{-1}) or A (0.5 mg kg^{-1}) followed by M (0.3 mg kg^{-1}, IV) or S and additional boluses of P or A for intubation, followed by P or A TIVA during imaging.

The induction quality was significantly better in A-M versus A-S, P-M versus P-S, and A-M versus P-S. The induction dose was significantly lower in P-M versus P-S, and A-M versus A-S. The TIVA rate with P-M was significantly lower than P-S but similar between A-M and A-S. Sedation, extubation and recovery quality, and TIVA duration were similar between treatments. Time to standing was significantly longer for A than P, but was similar within A or P treatments.

After induction, heart rate (HR) was significantly higher in A-M than A-S and P-S. During imaging, HR of A-S and A-M were significantly higher than P-S. Before recovery, HR of A-M was significantly higher than P-S. Systolic blood pressure of A-S was

significantly higher than A-M and P-M. There was no significant treatment difference for mean or diastolic blood pressure, cardiac index (CI), respiratory rate, occurrence of apnea, end-tidal CO_2, and blood gas values. However, CI and HR significantly decreased after imaging compared to other phases.

Midazolam improved the quality and reduced the required dose for both P and A induction, and reduced TIVA rate of P. There was no significant cardiopulmonary difference identified between treatments despite co-induction with M. The decrease in CI and HR after imaging warrants close monitoring during recovery.

ACKNOWLEDGEMENTS

First, I would like to thank my dad, mom, brother and two sisters who support me unconditionally for the past 30 years.

Second, I would like to thank Drs. Melissa Sinclair, Alex Valverde, Conny Mosley and Craig Mosley for their clinical and academic mentoring. Special thank to my supervisor Dr. Sinclair who made the whole residency/DVSc training possible for me and Dr. Sawyer who encouraged and assisted me to apply in the first place.

Third, I would like to thank my resident mates Andrea, Alicia and Rodrigo for helping each other out whenever needed and learned from each other.

Fourth, I would like to thank all the veterinarians and technicians in OVC especially anesthesia section: Emily, Lucy, Cindy, Andrea, Ines, Rob, Megan, Nick, Jen, Shirley for their patience and kindness.

Fifth, I would like to thank my neighbors and resident mates Miranda, Gonzalo and Rames whose presence made last three years more fun and pleasant.

Last, I would like to thank everyone I meet along the way of my life. I am who I am because of all of you.

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DECLARATION OF WORK PERFORMED

The authors' contribution is as follow:

PenTing Liao: Data collection, statistical analysis and manuscript preparation; **Melissa Sinclair**: Study design and funding application, data collection, video scoring of recovery and manuscript review and revision; **Alexander Valverde**: Data collection, video scoring of recovery and manuscript review and revision; **Conny Mosley**: Manuscript review, video scoring of recovery and revision; **Heather Chalmers**: Manuscript review and revision; **Shawn Mackenzie**: Data collection and manuscript review and revision; **Brad Hanna**: Manuscript review and revision.

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CHAPTER 1: GENERAL LITERATURE REVIEW

INTRODUCTION AND OBJECTIVES

General anesthesia is defined as a reversible, controlled, and drug-induced unconsciousness which is not arousable by noxious stimulation (Tranquilli et al. 2007). There are three main phases of general anesthesia: the induction phase, from consciousness to unconsciousness to facilitate endotracheal intubation; the maintenance phase, requiring a consistent surgical or diagnostic procedural depth with appropriate muscle relaxation and analgesia without movement; and the recovery phase, with return to consciousness and awareness. The induction of general anesthesia is commonly accomplished with a primary injectable induction agent (such as propofol or alfaxalone) alone or in combination with co-induction agents such as a benzodiazepine, lidocaine, or an opioid bolus.

Supplementary or co-induction agents are used with the primary injectable anesthetic agent to promote a smooth induction to unconsciousness and endotracheal intubation and to minimize the dose of the primary anesthetic induction agent, potentially reducing negative cardiovascular effects. The main co-induction agents reported in veterinary medicine are fentanyl, diazepam, midazolam, lidocaine, and low-dose ketamine. Data is available from both human and veterinary research describing the possible injectable dose reduction with co-induction agents, and includes both positive and negative findings (Short et al. 1992; Anderson & Robb 1998; Braun et al. 2007; Robinson & Borer-Weir 2013; Sanchez et al. 2013). In veterinary medicine, the ability to demonstrate a dose reduction of the primary induction agent is influenced by the order of administration of the co-induction agent relative to the primary injectable induction agent, especially with benzodiazepines (Sanchez et al. 2013) as well as the assessment methods of the study. Other reported factors impacting the benefits of these supplementary agents in dogs

include the dose, interval and speed of injection of the induction and co-induction agent, and the sedation level of the dog prior to induction (Covey-Crump & Murison 2008; Robinson & Borer-Weir 2013; Sanchez et al. 2013). The research to date in dogs suggests that a dose of midazolam of 0.2-0.4 mg kg^{-1}, intravenous (IV), is ideal after an initial IV bolus of propofol (Robinson & Borer-Weir 2013). The potential dose reduction, induction quality, and ease of endotracheal intubation in dogs given midazolam and alfaxalone as co-induction agents have not been investigated.

For propofol, the overall cardiovascular effects and benefit of combining the injectable anesthetic with the co-induction agent remains controversial in dogs (Anderson & Robb 1998; Jones et al. 2002; Goel et al. 2008; Hopkins et al. 2013). To the authors' knowledge, scientific studies investigating advanced cardiovascular and respiratory measurements during the induction phase and endotracheal intubation in fentanyl pre-medicated dogs induced with either propofol or alfaxalone, with or without midazolam co-induction, are not available. In addition, the ease of maintenance, cardio-pulmonary effects, and recovery characteristics during diagnostic imaging between propofol and alfaxalone have not been fully compared, especially with midazolam co-induction.

The purpose of this research is to investigate the cardio-pulmonary effects, induction dose reduction, quality during the induction phase, total intravenous anesthesia (TIVA) maintenance dose, and recovery characteristics with propofol or alfaxalone, with or without midazolam co-induction, in fentanyl sedated dogs. During the induction phase, total propofol or alfaxalone dose requirements, number of additional injectable doses, induction quality scoring, heart rate (HR), respiratory rate (RR), arterial blood pressure (ABP), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), oxygen saturation percentage

(SPO_2), and end-tidal carbon dioxide ($ETCO_2$) will be compared between treatments prior to mechanical ventilation. Maintenance quality, cardiovascular stability during propofol or alfaxalone TIVA during mechanical ventilation, and recovery characteristics during MRI or CT diagnostic imaging with or without intra-intervertebral disc injection will also be compared for propofol and alfaxalone.

STUDY GOALS AND STATEMENT OF HYPOTHESIS

This study will focus on three main goals: 1) to investigate the dose reduction of propofol and of alfaxalone for endotracheal intubation with and without midazolam co-administration in fentanyl sedated dogs; 2) to investigate the cardio-pulmonary effects of induction with propofol alone and with alfaxalone alone and when each is combined with midazolam in fentanyl sedated dogs; and 3) to investigate and compare the cardiovascular effects, maintenance quality, and recovery characteristics between alfaxalone and propofol TIVA with or without midazolam co-induction during MRI or CT diagnostic imaging.

The hypotheses are as follows:

With or without co-induction with midazolam (0.3 mg kg^{-1}, IV) after an initial bolus of propofol or alfaxalone in fentanyl sedated dogs:

1) There is no difference in the total dose of the induction agent required for endotracheal intubation
2) There is no difference in the induction quality and the requirements for additional injectable boluses to allow for endotracheal intubation
3) There is no difference in the cardio-pulmonary effects and maintenance quality during induction and TIVA during MRI or CT examination.
4) There is no difference in the extubation and recovery characteristics.

LITERATURE REVIEW

PRE-ANESTHETIC SEDATION

Pre-anesthetic sedation is important prior to induction of anesthesia to reduce the anxiousness and stress of the patient, provide pre-emptive analgesia for surgery, help minimize the amount of the injectable anesthetic agent required to induce unconsciousness, and also reduce the injectable or inhalant requirements during the maintenance phase of anesthesia (Grimm et al. 2015).

Opioids are commonly used sedatives in cardiovascularly compromised patients because of their high margin of safety, having minimal cardiopulmonary depression while providing excellent analgesia (Tranquilli et al. 2007). The first documented medical use of opium traces back to 2100 BC on the Sumerian clay tablet (Norn et al. 2005). Nevertheless, it wasn't until 1806 that morphine was isolated, followed by the development of other pure alkaloids and eventual wide spread use in the middle of nineteenth century (Norn et al. 2005).

There are three well-recognized opioid receptors μ (mu), κ (kappa), and δ (delta). According to the ligand receptor interaction, opioids can be classified into full agonists, partial agonists, and antagonists to any one of the opioid receptors, or as agonist/antagonists that interact with more than one receptor. Fentanyl is a pure mu-agonist with rapid onset, short duration, and a wide margin of safety. Despite individual variability, it is typically given at 5-10 μg kg^{-1}, IV, as a bolus in canines for sedation and analgesia (Kamata et al. 2012; Kukanich & Clark 2012).

The pharmacokinetic profile of fentanyl following IV administration has been reported in multiple scientific studies. Interestingly, one study demonstrated that fentanyl possesses a dose-independent pharmacokinetic profile after single intravenous doses from 2.5-640 μg kg^{-1} (Murphy et al. 1983). In general, other anesthetic agents have minimal influence on fentanyl's

pharmacokinetic profile. The impact of acepromazine (0.05 mg kg^{-1}, IV) compared to dexmedetomidine (2.5 μg kg^{-1}, IV), administered in the recovery period have both been assessed after 120 minutes of isoflurane general anesthesia with a constant rate infusion (CRI) of fentanyl (5 μg kg^{-1} hr^{-1}). This showed that acepromazine, but not dexmedetomidine, slightly increased fentanyl's clearance (128%) with minimal influence on plasma concentration compared to saline treatment, when the CRI of fentanyl was continued for 60 minutes after isoflurane discontinuation (Keating et al. 2015). In this study, systemic clearance of fentanyl ranged from 27.3-37.7 mL kg^{-1} min^{-1} and central and peripheral volume of distribution ranged from 0.69-0.81 L kg^{-1} to 3.17-4.17 L kg^{-1} (Keating et al. 2015). The reported elimination half-life, clearance, and volume of distribution of fentanyl in anesthetized dogs ranges from 2.4-3.4 hours, 32.6-58.9 mL kg^{-1} min^{-1} and 7.7-10.2 L kg^{-1} (Murphy et al. 1979; Lin et al. 1981) and in conscious dogs ranges from 0.75-6 hours, 20-77.9 mL kg^{-1} min^{-1} and 4.7-10.7 L kg^{-1} (Kyles et al. 1996; Sano et al. 2006; Little et al. 2008; KuKanich & Hubin 2010). However, the short duration of action seen with fentanyl clinically is the result of rapid redistribution and lowering of plasma concentration. Hence, elimination half-life is not a good indicator for actual drug duration if a low loading dose has been administered. Due to its high lipophilicity, fentanyl crosses the blood brain barrier with ease, with concentrations within the cerebrospinal fluid and brain tissue peaking within 2-10 minutes (Hug & Murphy 1979) and 10-15 minutes (Ainslie et al. 1979), respectively, after IV administration.

Fentanyl has an incredibly high therapeutic index. No mortalities resulted when 13 dogs were experimentally injected with 38.2 mg kg^{-1}, IV (Bailey et al. 1987). However, these dogs showed signs of sedation, such as ataxia and recumbency, and progressed to being non responsive to tail-clamping for a variable duration. This safety is likely related to the fact that

fentanyl has minimal negative effects on the cardiovascular system (Kukanich & Clark 2012). At a dose of 15 μg kg^{-1}, IV, fentanyl significantly reduces heart rate, however, cardiac index (CI; normalized cardiac output by body weight or surface area) and blood pressure are not significantly altered in dogs (Salmenpera et al. 1994). Cardiac output and blood pressure decreased moderately when fentanyl 50 μg kg^{-1}, IV, was administered during enflurane anesthesia (Hirsch et al. 1993). In another study, unsedated research dogs receiving a cumulative dose of fentanyl of 27.5 μg kg^{-1}, IV, over 15 minutes showed a mild increase in blood pressure (Arndt et al. 1984). In contrast to what has been demonstrated in people, fentanyl has a dose-dependent but minimal respiratory depressive effect at clinical doses in conscious dogs (Grimm et al. 2005). Moreover, the respiratory depression evident shows a ceiling effect, with only mild to moderate increases in arterial carbon dioxide observed at up to a hundred times the clinical dose in dogs (Bailey et al. 1987). These favorable characteristics of fentanyl make it a suitable and popular pre-medicant in cardiovascularly compromised patients.

In one study, fentanyl has been used as a co-induction agent in dogs. The dogs were given a bolus of fentanyl at 2 μg kg^{-1}, IV, prior to propofol induction to investigate the dose reduction of propofol (Covey-Crump & Murison 2008). This resulted in a dose reduction in propofol and overall improved induction characteristics when compared to midazolam administration prior to propofol. The use of opioids as co-induction agents is more common in people and has been demonstrated with fentanyl and alfentanil (Short et al. 1992). Fentanyl was selected to sedate the dogs in our study because of its cardiovascular stability and common use for pre-medication in sick clinical cases.

INJECTABLE INDUCTION AGENTS

Small animal practices in North America and Europe typically induce unconsciousness with injectable anesthetic agents intravenously. Propofol and alfaxalone are two common and readily available injectable induction agents, which are licensed for use in dogs and cats in South Africa, Australia, Canada, the United States, and Europe.

ALFAXALONE

The first described anesthetic use of steroids, especially pregnane and androstane, date back to 1941 (Selye 1941). Over time, many different compounds have been developed and studied for potential clinical application. Among these, Althesin^{TM} the human product or Saffan^{TM} the veterinary product, which contained 9 mg mL^{-1} alfaxalone and 3mg mL^{-1} alfadolone, formulated in Cremophor EL, had been extensively used in both humans and animals clinically. Alfaxalone is the active anesthetic of this combination. Cremophor EL was used as a non-ionic detergent to dissolve alfaxalone and combined with an additional steroid, alfadolone acetate, to further enhance the solubility of alfaxalone in the Cremophor EL vehicle. However Cremophor EL typically caused histamine release that resulted in allergic reactions resembling anaphylactic shock, including hypotension, bronchospasm, cardiovascular collapse, urticaria and erythema in humans and dogs, and also caused hyperaemia and edema in the pinnae and forepaws in 70% of cats (Child et al. 1971; Dodman 1980). These adverse effects, most importantly hypotension and even death in people, eventually lead to withdrawal of these products from the market in most countries.

Alfaxalone, is now formulated with 2-hydroxypropyl-beta-cyclodextrin and does not cause histamine-mediated allergic reactions. It was introduced to the Canadian market in 2008

and is licensed as an intravenous induction agent in dogs and cats at a dose of 2-3 mg kg^{-1} in dogs and 5 mg kg^{-1} in cats. It is not licensed for intramuscular (IM) use in Canada, as it is in Australia and New Zealand.

Physical and chemical properties

Alfaxalone is a clear, colorless, aqueous solution in a multi-use clear 10 mL vial. Since the vial does not contain preservative, any remaining drug should be discarded within 24 hours after opening and first use. However the company has suggested that alfaxalone may be stored at 4 °C for up to 7 days after it is opened (Jurox Pty Ltd, Australia). Nevertheless, Strachan et al, 2008, demonstrated exponential growth of Escherichia coli 24 hours after inoculation of two common environmental bacteria, Staphylococcus aureus and Escherichia coli, with alfaxalone on agar plate at 37°C (Strachan et al. 2008). Hence, caution should be exercised when keeping the opened alfaxalone vial for longer than the company recommends.

The alfaxalone formulation is composed of 1% alfaxalone, less than 10% 2-hydroxypropyl-beta-cyclodextrin, less than 1% non-hazardous ingredient and water to a 100% solution. Alfaxalone has a specific gravity of 1.02-1.03. a pH of 6.5-7.0, and is stable for 36 months after manufacturing.

The chemical structure is 3 alpha-hydroxy, 5 alpha-pregnane 11,20 dione. From persistent screening and testing of analogues over decades, scientists have discovered that oxygenation at each end of the steroid molecule is necessary for anesthetic activity (Sear 1996). However, substitutions at the other sites decreases anesthetic potency (Kumar et al. 1993). Also, the 3 alpha-hydroxyl shows a higher potency over the 3 beta-hydroxyl group (Sear 1996).

Pharmacology

Central nervous system effects

The exact mechanism of action of injectable anesthetics to induce general anesthesia remains under great debate. Many theories have been developed and examined such as an interaction with membrane lipid bilayers or membrane-bound proteins. However, controversial aspects of membrane lipid bilayer and voltage-gated ion channel interactions have resulted in the general conclusion that ligand-gated ion channels are the major sites of action (Pleuvry 2004). Among numerous ligand-gated ion channels, post-synaptic gamma-aminobutyric acid type A ($GABA_A$) receptor is the common site of action shared by many anesthetics including neurosteroids (Akk et al. 2007). Potentiation of both phasic (transient) and tonic (persistent) transmission by neurosteroids to decrease neuronal excitability has been suggested (Akk et al. 2007). Neurosteroids augment phasic transmission by prolonging the inhibitory current without a change in peak amplitude (Harrison et al. 1987). Moreover, through either direct activation or potentiation of GABA effects on extra-synaptic site receptors, neurosteroids increase tonic transmission (Stell et al. 2003; Shu et al. 2004).

Althesin™ has been shown to decrease cerebral metabolic rate and lower intracranial pressure in spontaneously breathing people with normal or high intracranial pressure, either induced by ketamine or trauma (Sari et al. 1976; Ekhart et al. 1979; Bullock et al. 1986). Also, it has been found that the decrease in intracranial pressure is reversible without a dangerous rebound in pressure in humans (Zattoni et al. 1980). These benefits, with minimal negative cardiovascular effects, have resulted in Althesin™ being recommended over barbiturates in patients with intracranial hypertension (Bullock et al. 1986).

A reduction in intracranial pressure following administration of Althesin™ was also observed in healthy cats (Baldy-Moulinier & Besset-Lehmann 1975). However, in this study the cerebral vasculature remained responsive to arterial carbon dioxide levels and hypercapnia diminished the reduction in intracranial pressure from Althesin™ (Baldy-Moulinier & Besset-Lehmann 1975; Baldy-Moulinier et al. 1975). Unlike the reports in people and cats, TIVA with Althesin™ did not alter cerebral blood flow or intracranial pressure in healthy dogs (Cohen et al. 1973). To the author's knowledge, no scientific data regarding the effects of alfaxalone on the cerebral vasculature have been published for dogs and cats. However, since the active ingredient in Althesin™ is alfaxalone, it is likely that the described effects on the central nervous system and neurologic outcomes apply.

Cardiovascular effects (see Table 1)

Alfaxalone causes a dose-dependent minimal to moderate reduction in systemic vascular resistance (SVR) and mean arterial pressure (MAP), and minimal to mild increases in heart rate (HR) and CI, in both sedated and unsedated healthy dogs, at clinically relevant induction doses (l.5-4.15 mg kg^{-1}, IV) (Ambros et al. 2008; Muir et al. 2008; Rodriguez et al. 2012; Amengual et al. 2013; Maney et al. 2013). Nevertheless, supra-clinical doses (20 mg kg^{-1}) can result in moderate decreases in SVR (2657 to 1781 dynes sec^{-1} cm^{-5}; 67%), MAP (123 to 65 mmHg; 52%), and CI (246 to 190 mL kg^{-1} $minute^{-1}$; 77%), despite minimal effects on HR (unchanged at 128-131 beats $minute^{-1}$) (Muir et al. 2008).

In general, alfaxalone causes a similar decrease in MAP when compared to propofol for anesthetic induction, although MAP remains within the normal range (Ambros et al. 2008; Amengual et al. 2013; Maney et al. 2013). However, in one study the results trended toward

higher HR and CI and lower SVR with alfaxalone than propofol despite of no statistical significant difference in acepromazine and hydromorphone sedated dogs (Ambros et al. 2008). Increases in HR following administration of alfaxalone have been reported in dogs sedated with fentanyl (Okushima et al. 2015), acepromazine with meperidine (Amengual et al. 2013), and unsedated dogs (Maney et al. 2013). These results indicate that the baroreceptor reflex might be better preserved by alfaxalone than propofol. However, further studies are required to assess the repeatability of this result and potential significance for cardiovascular effects.

Etomidate has been shown to cause minimal cardiovascular effects including in hypovolemic dogs (Pascoe et al. 1992). Alfaxalone resulted in similar cardiovascular effects after induction to those of etomidate in unsedated healthy research dogs (Rodriguez et al. 2012). This included an increase in HR and CI and decrease in SVR caused by alfaxalone that was significantly different from baseline. The ability of this study to demonstrate significant changes following alfaloxone administration is possibly due to the use of unsedated healthy research dogs and the use of a higher dose than in other studies where alfaxalone was compared to propofol without significant differences being found (Rodriguez et al. 2012).

In compromised dogs (American Society of Anesthesiologists classification system [ASA] three to five; Three: severe systemic disease, Four: severe systemic disease constantly threat to life, Five: moribund patients not expected to survive 24 hours with or without operation), induction with alfaxalone resulted in similar MAP and higher HR than dogs induced with a combination of fentanyl-diazepam, a commonly used safe combination for this type of patients (Psatha et al. 2011). Therefore alfaxalone is a suitable alternative to fentanyl-diazepam.

Overall, when considering the cardiovascular effects induction with, alfaxalone is at least equivalent to propofol, etomidate and diazepam/fentanyl in healthy dogs. However, more studies

are needed in clinically compromised dogs to completely assess the cardio-pulmonary profiles, as in healthy dogs the cardio-pulmonary parameters remained within acceptable range despite minor differences between induction agents.

Respiratory effects

Alfaxalone has been shown to induce dose-dependent respiratory depression ranging from a reduction in respiratory rate and minute volume to complete apnea at various doses ranging from 2 to 40 mg kg^{-1}, IV, in dogs 8 months to 10 years old (Muir et al. 2008; Keates & Whittem 2012). Nevertheless, the tidal volume has been shown to remain stable with as high as 6 and 20 mg kg^{-1} bolus injections, IV (Muir et al. 2008). With use of a smaller clinical dose of 2 mg kg^{-1}, IV, a shorter and lower degree of apnea was noted in adult dogs than was observed at doses of 6 and 20 mg kg-1 (Muir et al. 2008). In dogs under 12 weeks of age, alfaxalone administration at 1.7 ± 0.3 mg kg^{-1}, IV, at the rate of 2 mg $second^{-1}$ resulted in apnea in 1 of the 25 dogs (O'Hagan et al. 2012). These results demonstrate that alfaxalone has a wide margin of respiratory safety in healthy dogs of various ages, especially at clinically relevant doses.

Various studies have compared the respiratory effects between propofol and alfaxalone. Doses of 1, 2, 5, 10 and 20 times the clinical doses of propofol (6.5 mg kg^{-1}, IV) and alfaxalone (2 mg kg^{-1}, IV) were compared for bolus injection inducing apnea in 6 dogs and alfaxalone did not cause apnea in all dogs until 10 times the clinical dose was administered, whereas propofol caused apnea in 2 of 6 dogs at 5 times the clinical dose (Keates & Whittem 2012). However, other researchers did not report differences in respiratory function between propofol and alfaxalone (Ambros et al. 2008; Amengual et al. 2013; Maney et al. 2013). For example, acepromazine 0.03 mg kg^{-1} and meperidine 3 mg kg^{-1} given 30 minutes prior to administration of

3 mg kg^{-1} propofol or 1.5 mg kg^{-1} alfaxalone, as rapid bolus injections, IV, in 6 sedated dogs breathing spontaneously (FiO_2=1) resulted in similar numbers of apneic dogs and similar degree of increase in arterial carbon dioxide tensions between the groups (Amengual et al. 2013). Unsedated dogs breathing spontaneously (FiO_2=0.21) given propofol or alfaxalone to effect until endotracheal intubation was achieved did not demonstrate apnea (Maney et al. 2013). Furthermore, there were no differences between propofol or alfaxalone groups for blood pH, base excess, and end-tidal and arterial carbon dioxide tensions, but the alveolar-arterial oxygen tension gradient increased as a result of a decrease in arterial oxygen tension in both group (Maney et al. 2013). In another study, providing an FiO_2=1 in sedated dogs breathing spontaneously, no differences in percentage of apnea (1 out of 6), shunt fraction or alveolar dead-space were noted between propofol and alfaxalone (Ambros et al. 2008).

When compared to etomidate, alfaxalone demonstrates a similar degree of limited respiratory depression in terms of the end-tidal and arterial carbon dioxide tensions and arterial oxygen tension in healthy unsedated dogs (Rodriguez et al. 2012). A similar post-induction respiratory rate is shown between diazepam/fentanyl and alfaxalone in clinically compromised dogs (ASA 3-5) (Psatha et al. 2011).

In conclusion, alfaxalone exhibits similar, or possibly reduced, respiratory depression in healthy dogs whether sedated or not compared to propofol and etomidate. Alfaxalone, even in compromised patients, may not compromise respiratory function significantly. Additional research in compromised canine patients is warranted in clinical cases to fully define the respiratory effects when combined with other anesthetic and analgesic agents.

Induction dosage and quality (see Table 2)

The induction IV dose of alfaxalone in unsedated and sedated healthy dogs ranges from 2 to 4.15 mg kg^{-1} and 0.5 to 1.9 mg kg^{-1}, respectively. Even without premedication, the quality of induction with alfaxalone is repored as good to smooth (Muir et al. 2008; Rodriguez et al. 2012; Maney et al. 2013). The quality of induction has been found to be comparable to propofol (Ambros et al. 2008; Suarez et al. 2012; Amengual et al. 2013; Maney et al. 2013) and etomidate (Rodriguez et al. 2012). Reported side effects in dogs include excitement, paddling or muscle twitching (Maddern et al. 2010; Amengual et al. 2013; Maney et al. 2013). Pre-medication is recommended by the manufacturer (Jurox Pty Ltd, Australia) within the product monograph to prevent excitement and rough recoveries in dogs. Because alfaxalone is rapidly re-distributed, the company recommends an initial dose of 2-3 mg kg^{-1} in dogs to prevent arousal during the induction phase and/or transfer to maintenance phase. Clinically, with appropriate sedation, these higher doses may not be required, especially if a co-induction agent is also administered.

PROPOFOL

Physical and chemical properties

The development of propofol dates back to the 1970s. The chemical structure of propofol is 2,6-di-isopropylphenol, which is in oil form and insoluble in aqueous solvents at room temperature. It was formulated with Cremorphor EL initially, however, the anaphylactoid side effects and pain during injection of Cremorphor EL led to the development of a new formulation containing 1% propofol, 10% soybean oil, 2.25% glycerol, 1.2% purified egg phosphatide, which results in a preparation with a pH of around 7, and a milky white appearance (Short & Bufalari 1999). It is not light sensitive and is stable at room temperature (Miller 2005). However, there is

no preservative in the formulation, hence, all remaining drug should be discarded 6 hours after opening and first use (Tranquilli et al. 2007).

Pharmacology

Central nervous system effects

Propofol primarily acts on $GABA_A$ receptors, as well as $alpha_2$-adrenoreceptors, N-methyl-D-aspartate (NMDA) receptors, and glycine receptors (Miller 2005). Recognized CNS effects of propofol in dogs include a decrease in cerebral oxygen consumption and cerebral blood flow, a decrease in intracranial pressure, and preservation of autoregulation of arterial carbon dioxide tensions until high doses are administered (Artru et al. 1992) or conditions of hypoxia are present (Haberer et al. 1993).

Cardiovascular effects

Like alfaxalone, propofol has negative cardiovascular effects in animals and people. When compared to etomidate for induction, propofol causes lower MAP despite a higher HR (Sams et al. 2008). Dose-dependent suppression of preload, contractility and lusitropy have been shown with propofol (Puttick et al. 1992). Despite this, no direct suppression of cardiac contractility is reported in dogs until supraclinical plasma concentrations (more than 7μg mL^{-1}) are achieved (0.4 mg kg^{-1} min^{-1}), which suggests indirect myocardial depression through a central effect (Ismail et al. 1992; Belo et al. 1994; Kawakubo et al. 1999). Also, there is evidence suggesting that the current adjuvants (intrafat) within propofol cause vasoconstriction at relatively low concentration but vasodilation at relatively high concentration in isolated dog arteries (Nakamura et al. 1992). The underlying vasodilation mechanism of the adjuvants has

been related to nitric oxide pathway stimulation (Doursout et al. 2002) and either direct (Goodchild & Serrao 1989; Nakamura et al. 1992) or indirect effects (Robinson et al. 1997) of propofol. These effects, in combination with the fact that the baroreceptor reflex sensitivity is reset by propofol (Whitwam et al. 2000), result in a decrease in arterial blood pressure when propofol is used for anesthetic induction. Moreover, depression of the global cardiovascular effects from propofol induction have been reported in acutely hypovolemic dogs and it was not recommended for these cases (Ilkiw et al. 1992). Hence, titrating propofol to effect to the anesthetic depth required is important to minimize these negative cardiovascular effects.

Respiratory effects

Propofol has well documented respiratory depression and commonly results in post-induction apnea and cyanosis (Muir & Gadawski 1998). The apnea is both rate- and dose-dependent (Muir & Gadawski 1998). However, there is evidence to support an association between both rapid (Muir & Gadawski 1998) or slow (Murison 2001) injection with post-induction apnea. Hypoventilation, or elevated arterial carbon dioxide ($PaCO_{2)}$, is also common after propofol injection (Ambros et al. 2008). As outlined above, comparisons between propofol and alfaxalone have varying results. Propofol has been shown to have more respiratory depressive effects compared to alfaxalone (Keates & Whittem 2012), or similar mild respiratory effects (Ambros et al. 2008; Amengual et al. 2013; Maney et al. 2013). When compared to etomidate for induction, propofol causes a higher degree of respiratory depression that results in higher $PaCO_2$ and lower PaO_2 (Sams et al. 2008), but similar effects to thiopental (Redondo-Garcia et al. 1999).

Induction dosage and quality

The induction dose of propofol in dogs ranges from 2.6 to 5.5 mg kg^{-1} (Plumb 2011). The appropriate induction dose depends largely on the level of sedation in the animals achieved with premedication, the alertness and health status of the animal, and the injection rate (Amengual et al. 2013). At low doses, 0.5-1 mg kg^{-1}, IV, propofol has sedative effects (Yoon et al. 2002). Even though the induction quality of propofol in dogs is generally reported as satisfactory, excitement, dystonia, involuntary muscle contractions, paddling, opisthotonus and hyperextension have been reported (Davies & Hall 1991; Robertson et al. 1992; Smedile et al. 1996; Mitek et al. 2013) and clinically significant (Hall & Chambers 1987; Duke 1995). A recent retrospective study that excluded those cases with inadequate analgesia and/or depth of anesthesia by administration of an IV bolus of fentanyl or propofol showed a lower incidence of adverse neurological effects (6 out of 492;1.2%) (Cattai et al. 2015). These side effects are postulated to be due to antagonism of inhibitory glycine receptors at the subcortical level and imbalance between inhibitory dopamine receptors and excitatory cholinergic receptors in the basal ganglia especially during rapid change of the concentration in the brain (San-juan et al. 2010). In humans, electroencephalography has been performed during and after the abnormal activity and showed a lack of typical seizure patterns in most patients suggesting that the observed effects are seizure-like phenomenon (SLP) instead of a true seizure (San-juan et al. 2010). Appropriate sedation is thought to reduce the incidence of SLP in dogs and cats as was noted in a personal observation (Duke 1995) But in a retrospective study comparing SLP activity between dogs premedicated with methadone with or without acepromazine and non-premedicated dogs, the reported SLP prevalence was higher in premedicated dogs (1 out of 58; 1.72%) compared to non-premedicated dogs (5 out of 432; 1.15 %) (Cattai et al. 2015).

Therefore there is currently insufficient evidence to support the clinical impression that premedication may reduce SLP activity in dogs undergoing propofol induction and/or TIVA. Further studies are needed regarding the effects of different premedications on the incidence of adverse effects associated with propofol administration.

THE USE OF CO-INDUCTION AGENTS

Advantages

The main reasons for using a co-induction agent with an injectable anesthetic agent are to smooth the overall induction process enabling endotracheal intubation without swallowing or coughing, minimize the negative side effects of the primary induction agent (cardiovascular and respiratory), minimize the dose of injectable drug administered and thereby lower the overall cost, and promote a smoother transfer to the maintenance phase of anesthesia. The main advantages of using different types of drugs together during the induction of anesthesia in cardiovascularly compromised or critical patients are the lowered dose of the primary anesthetic induction agent, ease of endotracheal intubation and enhancement of both cardiorespiratory stability and muscle relaxation (Whitwam 1995). Common co-induction agents used in dogs are lidocaine, diazepam or midazolam and ketamine. Fentanyl, 2 $\mu g\ kg^{-1}$, IV, over 30 seconds, 2 minutes before propofol has been used in one canine study as a co-induction drug, after acepromazine and morphine sedation, and showed a 18% dose reduction (Covey-Crump & Murison 2008). However, opioids are more commonly used in the premedication and maintenance phases of anesthesia than as co-induction agents in veterinary medicine to date.

Results vary in the literature depending on the agent, dosage, induction technique (CRI or boluses), order of administration (before or after the induction agent), speed of injection of the

co-induction, and the primary induction agent used. For example, when used as a co-induction with propofol, an 18% propofol dose reduction and improved induction quality was demonstrated with fentanyl 2 μg kg^{-1}, IV, but not midazolam 0.25 mg kg^{-1}, IV, (Covey-Crump & Murrison 2008); whereas other investigations have demonstrated a dose reduction with diazepam or midazolam (0.2 or 0.5 mg kg^{-1}) used with propofol as the primary induction agent (Robinson & Borer-Weir 2013; Sanchez et al. 2013).

Disadvantages

The disadvantages of using a co-induction agent are potential excitement, the additional step of administering the co-induction agent, added cost of the co-induction agent, the necessary individual drug pharmacological knowledge, and potential drug interactions. Patient excitement is especially problematic for benzodiazepines, and may result in a higher dose of the induction agent. Proper use of co-induction agents requires training, skill and appropriate depth assessment to prevent excessive anesthetic depth and overdose. Proper monitoring with close assessment is key for patients undergoing co-induction.

Drugs commonly used as co-induction agents

Benzodiazepines

Benzodiazepines act primarily on the $GABA_A$ enhancing the binding between receptor and neurotransmitter and hence increasing the frequency of receptor opening (Tranquilli et al. 2007). However, since benzodiazepines do not possess intrinsic agonist activity, there is a ceiling to the sedative effect achieved even when a high dose is given (Saari et al. 2011).

In people, benzodiazepines cause greater sedation and even unconsciousness, however, on their own, benzodiazepines are not profound sedatives in dogs and cats. Moreover, excitement may appear due to "disinhibition" when given as a sole agent in healthy dogs (Haskins et al. 1986; Court & Greenblatt 1992). In people, the benzodiazepine may be given 30 minutes prior to the primary induction agent (Short et al. 1992). Due to these differences, benzodiazepines have been primarily investigated as co-induction agents in veterinary medicine with timing close to the primary induction agent (immediately before or after).

Current veterinary literature shows conflicting results in dogs regarding the dose reduction when benzodiazepines are used as co-induction agents with propofol. No reports are available for the use of benzodiazepines with alfaxalone in dogs but co-induction with midazolam showed dose reduction of alfaxalone in goats (Dzikiti et al. 2014). In earlier studies, a diazepam, 0.4 mg kg^{-1}, IV bolus, given 45 seconds prior to propofol titrated to effect, provided a 36% dose reduction of propofol (Ko et al. 2006) but this dose reduction was not seen when a dose of diazepam of 0.2 or 0.25 mg kg^{-1}, IV, bolus was given 45 seconds or two minutes prior to propofol (Ko et al. 2006; Braun et al. 2007). In contrast, when given after 1 mg kg^{-1} propofol, IV over 15-45 seconds, diazepam showed no dose reduction from 0.2 to 0.5 mg kg^{-1}, IV bolus (Robinson & Borer-Weir 2013). The different results in these investigations could be attributed to sedation level of the dogs, dose of diazepam, order of administration (before or after the initial bolus of propofol), speed of diazepam administration (bolus-slow injection over 30 seconds), and initial dose and rate of propofol administration.

The canine literature using midazolam as a co-induction agent also demonstrates conflicting results, likely related to those factors listed above. However, the results with midazolam are typically favorable. Midazolam, 0.25 mg kg^{-1}, given IV over 30 seconds two

minutes prior to propofol induction, did not cause dose reduction but resulted in excitement in 21 of 22 (95%) dogs, despite prior IM sedation with acepromazine (0.025 mg kg^{-1}) and morphine (0.25 mg kg^{-1}) 30 minutes before induction (Covey-Crump & Murison 2008). Administration of midazolam, 0.25 mg kg^{-1}, given IV over 1 minute, 30 seconds prior to 1 mg kg^{-1} propofol, demonstrated a 47 % dose reduction with excitement in 5 of 11 (45%) dogs previously sedated IM with acepromazine (0.02 mg kg^{-1}) and morphine (0.4 mg kg^{-1}) 30 minutes before induction (Sanchez et al. 2013). In another study, this same dose of midazolam (midazolam, 0.25 mg kg^{-1}, IV) given over 15 seconds, immediately prior to propofol, showed a 18% dose reduction and excitement in 5 of 9 (55%) dogs that were sedated IM with acepromazine (0.025 mg kg^{-1}) and morphine (0.25 mg kg^{-1}) 30 minutes before induction (Hopkins et al. 2013). The lower incidence of excitement in these latter studies is likely attributed to a shorter time delay between the administration of the midazolam and propofol. Reports also indicate that when midazolam is given after propofol, at 1 mg kg^{-1}, IV, a consistent significant dose reduction (38-66%) and lower excitement percentage (12-18%) is seen (Robinson & Borer-Weir 2013; Sanchez et al. 2013).

Considering the results of these studies, it appears that when choosing diazepam as a co-induction agent, a higher dose (0.4 mg kg^{-1}, IV) administered before propofol is most likely to cause a dose reduction of propofol. These findings coincide with the slower onset and lower potency characteristics of diazepam when compared to midazolam. When using midazolam as a co-induction agent, the timing between midazolam and propofol administration and speed of midazolam administration are the two main factors related to the demonstration of excitement and dose reduction with propofol. Nevertheless, midazolam still demonstrates the most promising performance when used as a co-induction agent with propofol and potentially with other injectable anesthetics. Due to these more consistent findings in the literature, midazolam

was chosen in our studies.

The actual mechanism of benzodiazepines to promote dose reduction and allow for a smoother induction is still unclear. Synergism and additive effects with the primary induction agent are most likely. In vitro research shows that benzodiazepines act like potentiators through changing gating equilibrium of $GABA_A$ receptors to different kinds of allosteric agonists (Li et al. 2013).

Midazolam is a benzodiazepine that contains a fused imidazole ring, which has a pH-dependent ring-opening phenomenon. The formulation is in aqueous form and is light sensitive. It is not irritating and is well absorbed via intramuscular injection. Midazolam is primarily metabolized in the liver and excreted through the kidneys. The lipophilicity of midazolam is higher than diazepam (Tranquilli et al. 2007) and the affinity to the $GABA_A$ receptor is double (Mohler & Okada 1977). Also, midazolam has shown higher potency than diazepam in humans (Reves et al. 1978; Buhrer et al. 1990) and dogs regarding to the elevation of the threshold of lidocaine-induced seizure in dogs (Horikawa et al. 1990). However, because of lower intrinsic potency of benzodiazepines in dogs compared to humans and similar anesthetic dose used clinically, further study is needed regarding to anesthetic potency between midazolam and diazepam in dogs. The pharmacokinetic profile of midazolam has been reported in number of studies. In conscious dogs: the volume of distribution in steady state after 0.2 mg kg^{-1}, IV, ranged from 0.68 ± 0.33 L kg^{-1} (Schwartz et al. 2013); the volume of distribution using area method after 0.2 – 0.5 mg kg^{-1}, IV, ranged from 1.10 ± 0.56 – 3.00 ± 0.90 L kg^{-1} (Court & Greenblatt 1992; Schwartz et al. 2013); the clearance after 0.2 – 0.5 mg kg^{-1}, IV, 10.1 ±1.9 – 27 ± 3 mL min^{-1} kg^{-1} (Court & Greenblatt 1992; Schwartz et al. 2013); the elimination half life after 0.2 – 0.5 mg kg^{-1}, IV, ranged from 63.3 ± 28.5 – 121 ± 6 minutes (Court & Greenblatt 1992;

Schwartz et al. 2013). In enflurane anesthetized dogs given midazolam 2.5 mg kg^{-1}, IV, the volume of distribution using area is 3.94 ± 0.27 L kg^{-1}, the clearance is 28.5 ± 3.1 mL min^{-1} kg^{-1}, the elimination half-life is 98 ± 5 minutes (Hall et al. 1988b).

In dogs, clinical doses of midazolam are between 0.1 to 0.5 mg kg^{-1}, administered by IV or IM routes (Plumb 2011). The cardiovascular effects of midazolam at doses between 0.25, 1 and 10 mg kg^{-1} are minimal in dogs (Jones et al. 1979). For all doses in the aforementioned study, HR increased by 10 to 20 % and CO increased by 10 to 12 % following midazolam administration (Jones et al. 1979). However, MAP decreased by 10 to 20 % and cardiac contractility decreased by 13 to 16 % at the 1 and 10 mg kg^{-1} doses (Jones et al. 1979). Moreover, SVR decreased when 1 and 10 mg kg^{-1} doses were given (Jones et al. 1979). Neither doses decreased stroke volume (SV) (Jones et al. 1979). Despite benzodiazepines deemed as rarely causing respiratory depression, some studies have shown respiratory depression, as evidenced by a decrease in tidal volume and oxygen saturation, and an increase in end-tidal CO_2 with clinical doses in anesthetized dogs (Heniff et al. 1997). Midazolam exhibits dose-dependent isoflurane and enflurane MAC reduction in dogs with maximum about 30% and 60-70 % respectively (Hall et al. 1988a; Seddighi et al. 2011).

Lidocaine

Lidocaine is one of the most extensively used local anesthetics. When used in regional anesthesia, it provides intermediate duration and fast onset. Intravenous infusions of lidocaine also provide anesthetic and analgesic effects (Tranquilli et al. 2007).

Co-induction with lidocaine, IV, in humans has been shown to decrease propofol injection pain (Borazan et al. 2012) in addition to suppression of coughing (Yukioka et al. 1985)

and sympathetic responses (Mark et al. 1987) associated with endotracheal intubation. Despite these benefits, dose sparing effect has not been shown in either people (Tan & Hwang 2003) or dogs with lidocaine co-induction administration with propofol (Braun et al. 2007; Jolliffe et al. 2007).

Furthermore, co-induction with lidocaine was not beneficial in decreasing the incidence of coughing or attenuating sympathetic responses in dogs induced with propofol (Jolliffe et al. 2007). No investigations have been performed of lidocaine co-induction with alfaxalone. More research is warranted to clearly outline the advantages and disadvantages of lidocaine co-administration with both propofol and alfaxalone in dogs.

Ketamine

Ketamine is a dissociative anesthetic that is used routinely in veterinary medicine with diazepam or midazolam for anesthetic induction without propofol or alfaxalone. However, it has also been used at lowered doses (1-2 mg kg^{-1}) in combination with propofol at induction. In this context, it is being used as a co-induction agent (Lerche et al. 2000; Mair et al. 2009; Martinez-Taboada & Leece 2014).

Ketamine has unique pharmacology. The main action of ketamine on the central nervous system is to interrupt the connection of cerebral cortex and thalamus and hence causes characteristic anesthesia status-catalepsy (Miller 2010). In addition to the dose reduction and analgesic effects, the rationale of using ketamine as a co-induction agent is the sympathomimetic effect (Miller 2010) that might counteract the cardiovascular depressive effects of propofol or potentially alfaxalone that occur, especially at higher doses.

However, ketamine also produces negative inotropic effects (Diaz et al. 1976) which are

often masked by the direct sympathetic stimulation in healthy animals. Hence, ketamine should still be used with caution in cardiovascular compromised patients. The use of ketamine, 0.25-0.5 mg kg^{-1}, IV, given one minute before propofol to effect, did not demonstrate a dose reduction or improved cardiovascular function in dogs (Mair et al. 2009). However, when ketamine was mixed with propofol to form 9 mg mL^{-1} of each drug, the total propofol dose (0.2 ± 0.1 mg kg^{-1}) was significantly lower than for propofol alone (0.4 ± 0.1 mg kg^{-1}). This was accompanied by a significant increase in MAP and HR (Martinez-Taboada & Leece 2014). In addition, ketamine, at 2 mg kg^{-1}, IV, given after propofol, at 2 mg kg^{-1}, IV, resulted in a higher HR than propofol alone, at 4 mg kg^{-1}, IV, despite similar MAP (Lerche et al. 2000). Hence, ketamine may counteract the negative cardiovascular effects of propofol induction with or without dose reduction in healthy dogs.

In summary, co-induction agents have the potential benefit of lowering the dose of the primary induction agent, thereby reducing any of the negative cardio-pulmonary effects. Yet, such cardio-pulmonary and dose reducing benefits are not always observed and the optimal protocol is not clearly defined in the research to date in dogs. No investigations are available in which co-induction agents are used in concert with alfaxalone in dogs other than a case series study investigating the induction effects of the alfaxalone and midazolam (Seo et al. 2015).

TOTAL INTRAVENOUS ANESTHESIA (TIVA)

History of TIVA

After induction from consciousness to unconsciousness with an injectable anesthetic intravenously, veterinary patients are typically maintained with inhalant anesthetics during the surgical or diagnostic procedure. However, in some instances the inhalant anesthetic may pose a

challenge or have physiologic disadvantages warranting maintenance of anesthesia with an injectable anesthetic, termed total intravenous anesthesia (TIVA). Of the injectable anesthetics available for veterinary use, propofol and alfaxalone possess ideal pharmacological profiles for TIVA. In fact, propofol has been used in human anesthesia as a maintenance agent since the late 80's (Shafer et al. 1988).

TIVA compared to inhalant anesthesia

The advantages of maintenance with inhalants are the predictability, rapid adjustment with only minimal metabolism and excretion (Waelbers 2009). However, specialized vaporizers and equipment are required for precise and safe delivery of inhalants. Moreover, pollution into the surrounding workspace space presents serious health (Ornoy 2012) and environmental (Goyal & Kapoor 2011) hazards with risks of chronic human exposure and accumulation of the exhausted inhalant in the atmosphere and ozone layer being identified.

With propofol and alfaxalone TIVA, occupational health and environmental concerns are alleviated and patient drug metabolism and excretion are less of a concern than for other injectable agents (Hatschbach et al. 2008). Other positive factors have been demonstrated in humans including lower levels of postoperative nausea and less emergence excitement (Lerman & Johr 2009). There is also evidence in dogs that inhalant maintenance is associated with more hypotension (Iizuka et al. 2013a) and requires more frequent use of vasopressors (Caines 2013), whereas propofol has been shown to better preserve MAP and aortic compliance (Deryck et al. 1996). The main disadvantage and concern with TIVA is the cost, especially when the duration of anesthesia required exceeds one hour (Short & Bufalari 1999). However, with proper co-administration of analgesics and sedatives, successful dose and cost reduction is achievable

(Waelbers 2009).

Use of alfaxalone as a total intravenous agent

Pharmacokinetics of alfaxalone

The pharmacokinetics of alfaxalone have been investigated in research dogs . The volume of distribution, elimination half-life, and plasma clearance of 2 mg kg^{-1}, IV bolus injection, are 2.4 ± 0.9 L kg^{-1}, 24.0 ± 1.9 minutes, and 59.4 ± 12.9 mL minute kg^{-1}, respectively; and for 10 mg kg^{-1} are 2.9 ± 0.4 L kg^{-1}, 37.4 ± 1.6 minutes and 52.9 ± 12.8 mL minute kg^{-1}, respectively (Ferre et al. 2006).

Similar short times to endotracheal intubation (less than a minute) have been shown in research dogs after a single bolus (Ferre et al. 2006; Muir et al. 2008). The rapid onset and recovery of alfaxalone make it suitable for TIVA in dogs.

Cardiovascular and respiratory effects of alfaxalone TIVA

Alfaxalone causes minimal cardiovascular changes when used as a maintenance agent. A dose of 0.07 mg kg^{-1} min^{-1} for 120 minutes in dogs maintained anesthetized without surgical stimulation did not significantly affect MAP, pulmonary artery pressures, right atrium pressure, pulmonary artery wedge pressure, HR, CI, SVI, and SVR compared to before induction (Ambros et al. 2008). Minimal to mild cardiovascular depression has been shown in two clinical studies using alfaxalone doses of 0.08-0.11 mg kg^{-1} min^{-1}, as a maintenance agent for normal healthy dogs during ovariohysterectomies (Suarez et al. 2012; Herbert et al. 2013).

Alfaxalone TIVA without surgical stimulation causes moderate respiratory depression (increased $PaCO_2$), despite acceptable PaO_2 values (FiO_2=1) (Ambros et al. 2008). With surgical stimulation (ovariohysterectomy), higher dose infusion of alfaxalone causes mild respiratory

depression (Suarez et al. 2012).

Use of propofol as a total intravenous agent

Pharmacokinetics of propofol TIVA

The pharmacokinetics of propofol have been determined in several studies and results varied with different premedications, concurrent anesthetics, age and breed: the volume of distiribution, elimination half-life and clearance ranged from 2.4 - 9.7 L kg^{-1}, 14 - 486 minutes and 34 -115 ml $minute^{-1}$ kg^{-1} (Cockshott et al. 1992; Nolan & Reid 1993; Nolan et al. 1993; Reid & Nolan 1993; Zoran et al. 1993; Hall et al. 1994; Mandsager et al. 1995; Reid & Nolan 1996). A single bolus of IV propofol, results in rapid uptake by the central nervous system and hence fast onset. This is followed by a rapid decrease in the plasma concentration due to rapid redistribution and metabolism (Short & Bufalari 1999). The volume of distribution for propofol is large. Hence, even though clearance and clinical recovery times are comparable to alfaxalone, propofol could reside in the body longer. Propofol also exhibits unique metabolism in that the metabolic clearance exceeds hepatic blood flow (Shafer 1993), suggesting extra-hepatic pathways are partly responsible for metabolism. This is supported by the detection of propofol metabolites during an-hepatic phases of orthotopic liver transplantation in humans (Veroli et al. 1992).

Cardiovascular and respiratory effects of propofol TIVA

Propofol causes no significant changes in HR, BP, CI, SVR, and mean pulmonary artery pressure during 120 minute infusions at 0.4 mg kg^{-1} min^{-1} (Keegan & Greene 1993b). In addition, both MAP and SVR are higher than during isoflurane maintenance (Keegan & Greene 1993b). In a canine study with a 120 minute infusion of propofol, the cardiovascular effects were not

significantly different to alfaxalone TIVA (Ambros et al. 2008).

Respiratory depression is the most common side effect of propofol single doses and is also observed when used as maintenance agent at the recommended doses of 0.25 mg kg^{-1} min^{-1} (Ambros et al. 2008). Hence, endotracheal intubation and oxygen supplementation are recommended during propofol TIVA (Duke 1995).

Recovery characteristics from alfaxalone and propofol

Recovery quality of alfaxalone

The recovery quality of alfaxalone is controversial. Most studies state that the overall recovery quality with alfaxalone is good to excellent (Ambros et al. 2008; Muir et al. 2008; Psatha et al. 2011; Suarez et al. 2012; Herbert et al. 2013). Furthermore, recovery from alfaxalone has been characterized as better than etomidate induction followed by isoflurane (Rodriguez et al. 2012) and comparable with propofol induction and TIVA (Ambros et al. 2008; Suarez et al. 2012) and diazepam/fentanyl induction followed by isoflurane (Psatha et al. 2011). However, dogs under alfaxalone induction during MRI under sevoflurane had poorer recovery scores compared to propofol induction (Jimenez et al. 2012). Also, some dogs were sensitive to external stimulation (Ferre et al. 2006) or demonstrated other adverse effects such as tremors, rigidity, and myoclonus at recovery (Maney et al. 2013). Hence, pre-medication as well as a quiet and undisturbed environment are recommended by the company (Jurox Pty Ltd, Australia).

Recovery time with alfaxalone

Due to the high clearance rate of alfaxalone, recovery time is rapid. Without premedication, the mean time to extubation after a single dose bolus of alfaxalone of 2 to 3, 6

and 10 mg kg^{-1}, IV, ranges from 6.4 to 25 minutes (Ferre et al. 2006; Muir et al. 2008; Rodriguez et al. 2012; Maney et al. 2013), 31.4 ± 6.9 minutes (Muir et al. 2008) and 75.1 ± 18.9 minutes (Muir et al. 2008), respectively. With sedation, the mean time to extubation after CRIs of alfaxalone of 80-130 minutes, with or without surgical procedures performed is 10-20 minutes post-CRI (Ambros et al. 2008; Suarez et al. 2012; Herbert et al. 2013). Time to sternal and time to stand after 120 minutes TIVA without surgery and 80 minutes TIVA with surgery are 14 ± 7, 35 ± 5, 43 ± 9 and 52 ± 10 minutes (Ambros et al. 2008) and 20 (11-22), 32 (29-40), 60 (46-61) and 90 (85-107) minutes (Suarez et al. 2012).

Recovery quality of propofol

In general, recovery from propofol TIVA has been described as smooth and excellent (Keegan & Greene 1993b; Ambros et al. 2008). However, some adverse events such as vomiting (Morgan & Legge 1989), tremors, vocalization, and myoclonus (Maney et al. 2013) may occur during the recovery process .

Recovery time with propofol

The recovery time following propofol TIVA in dogs is associated with premedication agents, and breed (Robertson et al. 1992) and with total TIVA time in cats (Pascoe et al. 2006). In pre-medicated and non-pre-medicated dogs, full recovery time ranged from 15 to 79.3 minutes and 22 to 33 minutes, respectively (Watkins et al. 1987; Morgan & Legge 1989; Vainio 1991; Robertson et al. 1992; Keegan & Greene 1993b; Thurmon et al. 1994).

Comparison between alfaxalone and propofol and for induction and maintenance

To date, there are only few studies comparing TIVA using alfaxalone and propofol in dogs. Among those studies, time to endotracheal intubation, induction quality, and maintenance quality, including the response to surgery, cardiovascular and respiratory depression, and adverse events, such as muscle twitching, paddling, or myoclonus were found to be comparable (Ambros et al. 2008; Suarez et al. 2012; Amengual et al. 2013; Maney et al. 2013). One study in dogs demonstrated that propofol was more likely to cause apnea than alfaxalone (Keates & Whittem 2012). When propofol was compared to alfaxalone induction for cesarean sections in dogs, puppies from the alfaxalone group demonstrated better neonatal vitality at birth however, neonatal survival rates at three months were similar between the agents (Doebeli et al. 2013).

The comparison of cardiovascular effects of TIVA using propofol or alfaxalone during mechanical ventilation in pre-medicated dogs requires further investigation as existing reports allowed spontaneous breathing.

Cardiac output (CO) measurements in research

In any research investigating the advantages and disadvantages of anesthetic agents, appropriate and accurate cardiovascular and respiratory measurements are required. Most veterinary researchers use measures such as direct arterial blood pressure, HR, RR, SPO_2, $ETCO_2$, arterial blood gases, temperature, and CO along with calculations of CI, SV, SVI, and SVR. The measurement of CO allows for an improved assessment of overall cardiovascular assessment. When using CO measurements in veterinary research, the methodology, correct instrumentation and appropriate interpretation are necessary for accurate final conclusions. The

following literature supports the use of lithium dilution CO measurements and continuous pulse contour CO measurements in our research.

Definition and importance of cardiac output

Cardiac output is "the quantity of blood pumped into the aorta each minute by the heart" (Hall & Guyton 2011). Both oxygen delivery and blood pressure are important in maintaining cell homeostasis and both affected by cardiac output. It has been shown in humans via numerous clinical trials, reviews and meta-analyses that optimizing oxygen delivery and global blood flow while under general anesthesia reduces mortality and morbidity, especially for those patients who are critically ill or high-risk (Boyd et al. 1993; Gan et al. 2002; Grocott et al. 2012; Cecconi et al. 2013; Salzwedel et al. 2013; Pearse et al. 2014). Moreover, it has also been shown that implementation of early optimization improves outcomes (Kern & Shoemaker 2002). Hence peri-operative monitoring and management of cardiac output could lead to better patient outcomes. Nevertheless in veterinary medicine, it's uncommon to measure CO due to the equipment requirements and specialized personnel training needed. Instead, blood pressure is the most commonly measured parameter used clinically to access cardiovascular function. However if the vascular system is simplified, according to Ohm's law, the flow through any vascular bed equals the pressure difference divided by resistance. Therefore, adequate perfusion pressure does not necessarily equate to adequate tissue blood flow.

Techniques of cardiac output measurement

The first reported CO measurement was done by A. Fick in 1870 (Fick 1870). Following that, G. N. Stewart published the indicator-dilution method that used saline as indicator in 1897

(Stewart 1897). Over decades, different techniques for measuring CO have been developed: indicator dilution methods, Fick methods, pulse contour analysis, electric impedance and imaging modalities. Indicator dilution methods include thermodilution, dye dilution, and lithium dilution. Fick methods include direct oxygen and indirect carbon dioxide based methodologies. Imaging modalities include ultrasound, MRI and nuclear scintigraphy.

Direct Fick method

Adolf Fick first postulated that CO can be obtained by assuming that the conservation of mass is valid in the body. Hence, CO is the oxygen consumption ($\dot{V}O_2$) divided by the oxygen content difference between artery (CaO_2) and vein (CvO_2):

$$\text{Cardiac output} = \frac{\dot{V}O_2}{CaO_2 - CvO_2} = \frac{(FiO_2 \times V_i) - (FeO_2 \times V_e)}{CaO_2 - CvO_2},$$

where FiO_2, FeO_2, V_i, V_e denote inspiration and expiration oxygen fraction and inspiration and expiration volume. The technique has been more widely used after the development of a pulmonary catheter and advances in oxygen concentration measurement, and deemed the reference standard for CO measurements.

In order to minimize the risks of instrumentation for the direct Fick method, indirect methods have been developed, which can use carbon dioxide instead of oxygen, providing a non-invasive, quick, and easier CO measurement. Similar to the direct Fick method, CO is also measured by assuming the conservation of mass:

$$\text{Cardiac output} = \frac{\dot{V}CO_2}{CaCO_2 - CvCO_2}$$

Moreover, cardiac output measurement can be simplified by allowing the subject to rebreathe:

$$\text{Cardiac output} = \frac{\dot{V}CO_{2nonrebreathe}}{CaCO_{2nonbreathe} - CvCO_{2nonbreathe}} = \frac{\dot{V}CO_{2rebreathe}}{CaCO_{2rebreathe} - CvCO_{2rebreathe}}$$

Because the venous side possesses larger carbon dioxide stores in the body and a relatively slower response time, the difference between two $CvCO_2$ is negligible. Hence one can acquire CO after rearranging the equation:

$$\text{Cardiac output} = \frac{\Delta \dot{V}CO_2}{\Delta CaCO_2}$$

To further simplify the measurement, $CaCO_2$ can be estimated by:

$$CaCO_2 = \left(6.957[Hb] + 94.864\right) \times \log\left(1 + 0.1933 P_A CO_2\right),$$

where P_ACO_2 denotes alveolar carbon dioxide partial pressure which can be extrapolated from end-tidal carbon dioxide partial pressure.

Indicator method

The original method by Stewart involves adding a known concentration (C_1) and volume (V_1) of sodium chloride to a central vein and collecting the blood in the femoral artery to measure the concentration in the blood (C_2). Also, an electrical resistance sensor is placed in the contralateral femoral artery to detect the arrival of the injectate. Once C_2 is measured, one can acquire the blood volume over the duration (V_2):

$$\text{Solute} = C_1V_1 = C_2V_2 .$$

Then CO can be calculated by dividing the blood volume by the duration(Stewart 1897):

$$\text{Cardiac output} = \frac{V_2}{t} = \frac{C_1 \cdot V_1}{C_2 \cdot t}$$

The main weakness of this method is omitting the concentration change over time as an explicit curve instead of a stepwise method because the blood flow is laminar and the dilution commenced from injection through sampling (Hamilton et al. 1932). Hence, Hamilton revised the theory in 1928 by using the area under curve to better describe the concentration changes over time (Hamilton et al. 1928).

$$\text{Cardiac output}=\frac{V_2}{t}=\frac{C_1V_1}{\int_t c(t)\,dt}$$

Following this, CO has been measured with indocyanine green as indicator for decades (Miller et al. 1962).

In 1954, Fegler and colleagues developed an intermittent bolus pulmonary artery thermodilution method based on thermodynamics (Fegler 1954). In brief, Fegler substitutes indocyanine green with cold solutions assuming the thermal energy is preserved in the circulation. Hence, the "negative" heat of the injectate corresponds to blood before injection would be the same as the blood volume over the duration compare to blood after equilibrium:

$$V_1\sigma_1\rho_1(T_B\text{-}T_1)=V_2\sigma_B\rho_B(T_B\text{-}T_2),$$

where σ, ρ denote specific heat and specific gravity and V_1 and T_1 for volume and temperature of the injectate, T_B for temperature of the blood, T_2 for blood temperature after equilibrium, V_2 for blood volume over time. Then again CO can be acquired by dividing the blood volume by duration:

$$\text{Cardiac output}=\frac{V_1}{t}\cdot\frac{\sigma_1\cdot\rho_1\cdot(T_B\text{-}T_1)}{\sigma_B\cdot\rho_B\cdot(T_B\text{-}T_2)}=\frac{V_2}{t}$$

To take the same consideration when using dye, area under the curve is used:

$$\text{Cardiac output} = \frac{V_1 \cdot (T_B - T_1) \cdot K_1}{\int_t \Delta T_B \, dt} = \frac{V_2}{t},$$

where K_1 denote $\frac{\sigma_1 \rho_1}{\sigma_B \rho_B}$.

There are several inherent errors for the thermodilution technique such as gain of temperature before, during and after injection by error in injectate volume, catheter dead space or unintentional warming by room temperature or tissue, all of which would overestimate the CO (Reuter et al. 2010). Other than mentioned above, patient status could also affect the accuracy and precision of this technique. For example, left-to-right shunt and differential decrease of detector site blood flow during one lung ventilation would underestimate the CO (Reuter et al. 2010). On the other hand, tricuspid regurgitation would both over- and underestimate the CO (Reuter et al. 2010). Finally, CO and baseline blood temperature fluctuation could also affect the measurement (Reuter et al. 2010).

In order to reduce the risks related to pulmonary artery catheterization, a trans-cardiopulmonary method has been investigated. In fact, in the very beginning of CO measurement development, the trans-cardiopulmonary approach was used by Stewart (Stewart 1897). Basically, trans-cardiopulmonary methods use the same concept as the pulmonary artery method but inject the indicator into the central vein and collect the data in the central artery instead. Hence, the same inherent errors apply. Numerous studies have shown good correlation and agreement between the two methods despite the physiological differences present in the methods (Reuter et al. 2010). For example, the trans-cardiopulmonary method uses the left ventricle instead of right for measurement, has more injectate loss, as well as recirculation of injectate, but less effects from respiratory oscillations.

Besides thermal dilution methods, lithium has been investigated as an indicator partly to reduce the influence of heat loss. In fact, numerous studies have proven the accuracy between the methods and that peripheral veins and arteries can be used (Reuter et al. 2010). It should be noted that lithium only distributes in the plasma, thus hemoglobin concentrations must be entered to estimate packed cell volume as well as sodium concentration for baseline voltage of the lithium dilution sensor interface.

Pulse contour method

To derive CO from the pulse contour method, mathematical modeling of how blood travel in the vessel after leaving the ventricles has been studied. Among different models, the Windkessel model has been used extensively. There are two basic assumptions in the model; first, conservation of mass: the net gain of the blood volume equals to the net loss of the blood volume in the vessel during the cardiac cycle; and second, the effect of compliance is predictable (Thiele et al. 2015).

The initial work estimates stroke volume from the arterial waveform by using two elements of the Windkessel model (Warner et al. 1953). This model includes compliance on top of resistance to describe the nature of the pulsatile blood flow in the aorta and arteries compared to the steady laminar flow in the model using the Hagen-Poiseuille Law of Friction. As the vessel expands and keeps part of the blood during systole, it also contracts and expels the stored blood during diastole (Sagawa et al. 1990). Stroke volume is divided into Q_S (systolic outflow) and Q_D (diastolic outflow). Q_D is proportionate to end-systolic pressure (P_{md}) (Warner et al. 1953):

$$Q_D = k \times P_{md}$$

Where k denotes a constant, which includes resistance and compliance. Next, assuming the resistance is constant through the cardiac cycle, the ratio between Q_s and Q_D equals to the ratio between the area under the pressure-time curve of each (A_s and A_D). After integrating the two equations, SV can be derived from the pulse contour as:

$$\mathrm{SV} = k \times P_{md}(1 + A_S / A_D)$$

Once the k is known by calibrating with another measurement method, a continuous measurement is provided.

Later on, the model evolved to include the wave reflection, the impedance which is the oscillating resistance to a pulsatile flow, and inertance which is the pressure required for flow rate changes (Westerhof et al. 2009).

The Modelflow technique uses three elements of the Windkessel model which includes impedance to derive stroke volume (Wesseling et al. 1993).

The pulse index continuous cardiac output (PiCCO) system allows both transthoracic thermodilution measurement ($PiCCO_{TD}$) and continuous pulse contour analysis ($PiCCO_c$). For later versions of PiCCO, aortic impedance and instantaneous pressure changes are taken into the calculation of SV and only the systolic portion of the pulse contour are used. Because of the differences among individual impedance values, calibration to the transthoracic measurement is recommended (Godje et al. 2002).

The PulseCO system also uses three elements of the Windkessel model. First, the machine uses a diagram to estimate central arterial pressure from the peripheral arterial pressure. Then, by corresponding pressure changes to the arterial compliance curve, a volume-time waveform is generated. Stroke volume is derived from the volume-time waveform and therefore CO after being adjusted for heart beat duration. Calibration with LiDCO measurement is

recommended by the company because the arterial compliance curves differ in the scale despite a similar shape (Linton & Linton 2001).

Instead of bringing data into a model based on theory, FloTrac/Vigileo system uses an empirical mathematic model to derive SV regardless of whether or not the model fits a physiological theory (Pratt et al. 2007). In this system, only two variables are used: standard deviation of mean arterial pressure over 20 seconds (σAP) and a conversion factor (k) which includes HR, body surface area, compliance, skewness and kurtosis, MAP, and standard deviation over 60 seconds. Because the model is based on empirical data, no calibration is required.

Ultrasound-based method

Echocardiography uses ultrasound to measure the doppler shift of blood to extrapolate blood flow velocity in the ascending aorta or left ventricle outflow tract though the equation:

$$V_b = \frac{f \times c}{2 \times f_0 \times \cos\theta}$$

with blood velocity (V_b), frequency shift (f), sound wave velocity in the blood (c), ultrasound beam frequency (f_0) and the angle between the ultrasound beam and red blood flow ($\cos\theta$). Then SV can be calculated by multiplying blood flow time velocity integral by the cross-sectional area of the vessel being interrogated. When using descending aorta, the distribution of cardiac output proximally needs to be corrected by a calibration factor.

There are two ways of acquiring cross-sectional area of the descending aorta: large population databases and M-mode echocardiography measurements. When using databases, individual variation could contribute to error. On the other hand, M-mode echocardiography is operator dependent since the angle of insonation and movement of the probe could lead to different measurements. Moreover, the cross-section area of the aorta changes over the cardiac

cycle so the timing of measurements could also affect the measurement. Nevertheless, ultrasound based techniques have shown minimal bias and good agreement with thermodilution techniques (Dark & Singer 2004; Thiele et al. 2015).

Thoracic electrical impedance method

This technique uses the electrode to detect the electrical impedance changes in the thorax and assumes that the only factor contributing to these changes is the changing blood volume from the beating heart. Hence SV can be derived from such signals. However, many confounding factors can attribute to the signal such as motion, abnormal anatomy or pathology and arrhythmias. Therefore this technique is more suitable for trending changes and is not necessarily of use for diagnosis (Raaijmakers et al. 1999).

Validation in dogs

Direct fick method

The Fick method has been deemed as the gold standard of CO measurement in the literature to evaluate other methods. Hence only a few studies investigate the accuracy of the direct Fick method when compare to a direct flow measurement. Nevertheless two studies done in 1950 compared directly measured blood flow by rotameter to the results acquired from direct Fick method and showed minimal bias with good correlation of r= 0.96 (Huggins et al. 1950; Seely et al. 1950).

Thermodilution method

Due to the complexity of acquiring CO through the direct Fick method, thermodilution has been used to replace the direct Fick method as clinical standard. Actually dogs were used in the study when Fegler first published the method in 1954 (Fegler 1954). In the study, thermodilution was compared to the direct Fick method and showed minimal bias. Moreover, in another study comparing thermodilution to Fick where heated saline was injected into blood instead of cold saline minimal bias was demonstrated (Khalil et al. 1966).

Lithium dilution method

The first published application of the lithium dilution measurement of CO (LiDCO) in dogs is in 2001 (Mason et al. 2001). In this study, they compared lithium dilution measurements to thermodilution measurements (TD) in halothane anesthetized dogs under four different hemodynamic conditions: light plane of anesthesia; dobutamine infusion; moderate - deep plane of anesthesia; deep plane of anesthesia or occlusion of the caudal vena cava. They also tested two different doses of lithium. They concluded that with either high or low dose lithium, clinically relevant ranges of CO (<5 L minute^{-1}) or pooled data all showed excellent correlations to TD, being more than 0.97 (Mason et al. 2001). The bias of pooled data and CO, less than 5 L minute^{-1}, between LiDCO and TD is 0.084 ± 0.465 and 0.002 ± 0.245 L minute^{-1}. Later on, the same research group validated that use of a peripheral vein for injection of lithium correlates well with central vein injection. In addition, background serum lithium concentration has limited clinical significance on the measurement (Mason et al. 2002a; Mason et al. 2002b).

Another study compared LiDCO to TD in sevoflurane anesthetized dogs under three hemodynamic conditions: normodynamic (one minimum alveolar concentration [MAC]);

hypodynamic (two MAC); hyperdynamic (noradrenaline infusion). The study showed a bias of -0.57 ± 0.96 L minute^{-1} m^{-2} during hypodynamic conditions; -0.05 ± 0.89 L minute^{-1} m^{-2} during normodynamic conditions; -0.03 ± 2.42 L minute^{-1} m^{-2} during hyperdynamic conditions; and -0.11 ± 1.55 L minute^{-1} m^{-2} when all data was pooled together (Morgaz et al. 2014). In contrast to the previous study by Mason, this study showed a higher bias, especially in hypodynamic conditions, although they had a higher standard deviation overall.

Pulse contour methods

PulseCO

The first research investigating the PulseCO^{TM} (PulseCO) in dogs was performed in 2005. In this study, PulseCO was compared to LiDCO in isoflurane anesthetized dogs after calibration with LiDCO during six different hemodynamic conditions: light plane (1-1.5 MAC); deep plane (2-2.5 MAC); dopamine or dobutamine infusions of 7μg kg^{-1} min^{-1}; dopamine or dobutamine infusions to achieve MAP between 65-80 mmHg. The overall correlation coefficient was moderate (r=0.6289). The limits of agreement and bias, in the same order as mentioned above, were 0.55 to 1.82; 1.24 to 4.12; 0.24 to 0.81; 0.46 to 1.51; 0.3 to 0.98; 0.36 to 1.18 L minute^{-1} (Chen et al. 2005). In the study methods, PulseCO generally tracked the changes in CO along with LiDCO despite the overestimation with PulseCO during deep planes of anesthesia. Nevertheless, the authors of this study recommended recalibration whenever significant hemodynamic or vascular changes occurred.

Similar overestimation during hypodynamic conditions was also shown in mild to moderate (Dyson & Sinclair 2006) and severe hemorrhage(Cooper & Muir 2007) canine experimental models. Despite the findings that the PulseCO did not require recalibration in four

hours of use in a human critical care unit, (Cecconi et al. 2008) a small-scale veterinary clinical case series showed a large percentage of error despite an acceptable bias in natural occurring systemic inflammatory response syndrome in dogs (Duffy et al. 2009). Hence, recalibration is recommended with the PulseCO methods for enhanced accuracy.

PiCCO

The first research investigating the application of both $PiCCO_{TD}$ and $PiCCO_c$ in dogs was performed in isoflurane anesthetized research dogs (Shih et al. 2011). The research compared both PiCCO systems to LiDCO with three different hemodynamic conditions: intermediate (0.9-1.4% ETIso); high (0.9-1.4% ETIso with artificial pacing heart rate of 120 bpm); and low (2.1-2.7% ETIso). This study compared the manufacturer recommended femoral artery use with measurement in the metatarsal artery. Nevertheless, $PiCCO_c$ at both sampling sites resulted in low precision despite an acceptable accuracy with femoral artery site (Shih et al. 2011).

In another study, $PiCCO_{TD}$ not only correlated well with traditional thermodilution measurements (r=0.915) but also showed minimal bias (-0.04 ± 1.19 L $minute^{-1}$) despite moderate precision. Moreover $PiCCO_c$ tracked along well with PulseCO (Morgaz et al. 2014).

FloTrac/Vigileo

Only two published research studies the application of FloTrac/Vigileo in anesthetized dog (Valverde et al. 2011; Bektas et al. 2012). These studies inputted 15 or 20 years old as age and converted height from body surface area, while measuring CO under different hemodynamic conditions. Nevertheless both of the studies showed poor accuracy and precision and deemed the modality unreliable in monitoring CO in dogs.

Indirect Fick Method

NICO (Non-invasive cardiac output)

The only commercial machine uses indirect Fick method to measure CO is the NICO® by Novametrix Medical Systems Inc. NICO® has been compared to the thermodilution method and LiDCO™ in dogs. NICO® showed precision of 13.8%, bias of -1.4% and r= 0.93 in the study comparing it to the thermodilution method (Haryadi et al. 2000). When compared to LiDCO™, NICO® showed r=0.888, relative error of 2.4± 24.7% and mean difference of measurement from LiDCO™ to NICO® is 1.11 time NICO® (Gunkel et al. 2004). However, NICO® produced significant lower values when compared to thermodilution in another study and showed percentage error of 56 % (Yamashita et al. 2007). The authors attributed the difference to the size of the dogs.

Thoracic electrical impedance method

Thoracic electrical impedance changes on SV prediction has been used in dogs (Ito et al. 1976). Perfusion of the aorta with sinusoidal and pulsatile wave blood flow in two dogs induced changes in the recorded impedance. With this method, the relative instead of actual SV is acquired and the frequency of the sinusoidal wave greatly affects the results. Several in vivo studies also show good correlation between electrical impedance to indicator dilution measurement under different hemodynamic conditions despite a certain degree of bias (Hill et al. 1976; Kiesler et al. 1990; Sherwood et al. 1991; Adamicza et al. 1994). Nevertheless, in a more recent study comparing electrical impedance to thermodilution measurements under different cardiac outputs by manipulating sevoflurane concentration and dobutamine infusion, high limits of agreement of -0.58 ± 1.56 L min^{-1} and percentage error of 75.4% were demonstrated

(Yamashita et al. 2007). It is important to point out that the different module, electrodes placements, and recording might account for part of the difference.

Ultrasound-based method

Transthoracic Doppler CO measurement of pulmonary blood flow (DP) has been compared to TD in dogs and correlates better than aortic blood flow (DA). The bias of TD to DP and DA is -0.04 ± 0.22 (95% CI=-0.11 to 0.03) L minute^{-1} and -0.87 ± 0.54 (95% CI= -0.69 to -1.04) L minute^{-1}. The limit of agreement of TD to DP and DA is -0.49 (95% CI= -0.36 to -0.61) to 0.4 (95% CI= 0.52 to 0.28) and -1.96 (95% CI= -1.65 to -2.26) to 0.22 (95 CI= 0.52 to -0.08) L minute^{-1} (Lopes et al. 2010).

Besides traditional echocardiography, USCOM^{TM} is a commercial modality being developed and validated in dogs. Critchley and colleagues compared USCOM^{TM} to a surgically instrumented ultrasound flow probe around the aorta in halothane anesthetized dogs with various levels of CO created by variations in inhalant concentrations and dopamine infusions. Instead of using the human database they measured the aortic diameter during the surgery. In the study, they showed bias of -0.01 (95% CI= -0.34 to 0.31) L minute^{-1} and percentage of error of 13% (Critchley et al. 2005).

Another study comparing the USCOM^{TM} to TD in isoflurane anesthetized dogs measured the aortic diameter before anesthesia through traditional echocardiography. Furthermore, they measured CO under four different hemodynamic conditions: baseline (0.5-1.5% isoflurane); deep anesthesia (2-3.5% isoflurane); a colloid solution infusion (right atrial pressure more than 15 mmHg); dobutamine infusion (5μg kg^{-1} min^{-1}). The overall bias when measured from the subxiphoid and thoracic inlet windows is -0.03 ± 0.73 and -0.2 ± 0.8 L minute^{-1} respectively. The

limit of agreement when measured from subxiphoid and thoracic inlet is -1.47 to 1.41 and -1.76 to 1.36 L minute^{-1} with a percentage of error of ± 46% and ± 53% (Scansen et al. 2009). The variations in measurement seem smaller during low CO conditions, which is more commonly encountered in those patients that may benefit from CO monitoring.

Transesophageal echocardiography (TEE), in which the ultrasound probe is passed orally into the thoracic esophagus to image the heart base more accurately, has gained growing interest in human medicine. In dogs, however, accuracy seems dependant on the hemodynamic conditions. In a study comparing TEE to thermodilution measurements under different sevoflurane concentrations in dogs, a limit of agreement of 0.03 ± 0.26 L minute^{-1} and percentage of error of ± 12.3% was noted (Yamashita et al. 2007). Another study compared TEE to a surgically placed ultrasound probe around the aorta and TD under moderate to severe hemorrhage and resuscitation. The study shows TEE overestimates CO in general and has a moderate correlation despite a good correlation during severe hemorrhage (de Figueiredo et al. 2004).

Summary of cardiac output methods

The direct Fick method is still deemed as the gold standard. However, for clinical or even practical research use, LiDCO is well validated and confirmed as being reliable in dogs. For pulse contour analysis methods, the low precision would generally limit the application and some techniques (FloTrac/Vigileo) have no applicability in dogs due to algorithms based on humans used by this technology. With proper calibration, especially after significant hymodynamic changes, PulseCO matched well with LiDCO except for during hypodynamic conditions. For the indirect Fick method, NiCO is an acceptable alternative except in smaller

size dogs. Because of different modules and models being used, electrical impedance has not shown great potential for CO measurement in dogs. Hence, further studies are warranted. Ultrasound based methods have shown great potential but measurements largely rely on personnel skill and experience.

LITERATURE REVIEW SUMMARY

This study will provide insight regarding the usefulness of co-administration of midazolam with propofol or alfaxalone versus other studies that administer midazolam after the initial propofol bolus with various pre-medication. The results will contribute to the debate of the cardiovascular benefits of co-administration of midazolam with either induction agent, by measuring cardiac output and direct arterial blood pressure. This study will also provide a direct comparison between propofol and alfaxalone for TIVA in pre-medicated mechanically ventilated dogs during a diagnostic procedure, without significant surgical insult. Suggestions on recovery quality and differences can be made without the impact of pain or discomfort on the recovery results. It is anticipated that these results will be applicable to everyday clinical canine anesthesia.

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Table 1. Summary of cardiovascular effects of induction with alfaxalone in dogs.

	Doses [mean(SD)] (mg kg^{-1})	Baseline [mean(SD)]	1 minutes [mean(SD)]	5 minutes [mean(SD)]	References
HR (bpm)	4.15(0.7)	127(16)	178(13)*	160(14)*	(Rodriguez et al. 2012)
	2.6(0.4)	121(25)	144(46)	145(33)	(Maney et al. 2013)
	1.5	104(22)	NA	114(28)	(Amengual et al. 2013)
	2	120(21)	155(18)	143(17)	(Muir et al. 2008)
	6	112(28)	158(33)*	150(20)*	
	20	128(33)	162(16)*	131(19)	
	2	87(21)	NA	100(21)	(Ambros et al. 2008)
MAP (mmHg)	4.15(0.7)	126(8)	113(13)	103(6)*	(Rodriguez et al. 2012)
	2.6(0.4)	102(11)	106(10)	81(11)	(Maney et al. 2013)
	1.5	98(15)	NA	72(13)*	(Amengual et al. 2013)
	2	120(12)	115(18)	114(9)	(Muir et al. 2008)
	6	113(12)	122(28)	101(18)*	
	20	123(13)	94(29)*	65(13)*	
	2	76(7)	NA	67(6)	(Ambros et al. 2008)
CI (L $minute^{-1}$	4.15(0.7)	3.33(0.7) a	4.1(0.7)*a	3.84(0.6)*a	(Rodriguez et al. 2012)

m^{-2}) = a or (mL kg^{-1} $minute^{-1}$) = b	2	229(60) b	245(53) b	231(77) b	(Muir et al. 2008)
	6	218(62) b	238(80)* b	222(71) b	
	20	246(71) b	221(60)* b	190(64)* b	
	2	155(45) b	NA	164(47) b	(Ambros et al. 2008)
SVR/ SVRI (dynes second cm^{-5} m^{-2}) = a or (dynes second cm^{-5}) = b	4.15(0.7)	7526(1700 a	5181(923) a	4984(632) a	(Rodriguez et al. 2012)
	2	2865(1207) b	2537(980) b	2906(1739) b	(Muir et al. 2008)
	6	2830(905) b	2803(1057) b	2441(1004) b	
	20	2657(654) b	2180(664) b	1781(350) b	
	2	1826(410) b	NA	1580(591) b	(Ambros et al. 2008)

* Indicates paramters that are significantly different from baseline.

Table 2. Induction Doses and Quality with Alfaxalone.

Dose (SD) (mg kg^{-1})	Subjects	Premedication	Induction quality	Reference
2*	Research beagles	None	N/A	(Ferre et al. 2006)
1.9(0.07)	Client-owned healthy dogs	Acepromazine/Morphine	Smooth	(Suarez et al. 2012)
1.5(0.57)	Client-owned healthy dogs	Buprenorphine/Acepromazine or Dexmedetomidine	Good to smooth	(Herbert et al. 2013)
2*	Crossbred research dogs	Acepromazine/Hydromorphone	Smooth	(Ambros et al. 2008)
1.2(0.4)	Client-owned healthy dogs	Medetomidine	5.8% poor, 17.6% fair, 70.5% excellent, 5.8% unknown	(Maddern et al. 2010)
1.2(0.4)		Butorphanol		
0.8(0.3)		Medetomidine/butorphanol		
1.91 (0.29)	Client-owned clinical compromised dogs	Methadone	N/A	(Psatha et al. 2011)
4.15(0.7)	Research beagles	None	Smooth	(Rodriguez et al. 2012)
1.5*	Client-owned healthy dogs	Acepromazine/meperidine	Smooth (one needs additional dose)	(Amengual et al. 2013)

2.6(0.4)	Crossbred research dogs	None	Good to smooth	(Maney et al. 2013)
2*	Crossbred research dogs	None	Good to smooth	(Muir et al. 2008)
1.7(0.3)	Client-owned healthy less than 12 weeks of age dogs	Acepromazine/ atropine/ morphine	Smooth	(O'Hagan et al. 2012)

* Indicates fixed bolus doses instead of titration to effect.

CHAPTER II

INDUCTION DOSE AND RECOVERY QUALITY OF PROPOFOL AND ALFAXALONE WITH OR WITHOUT MIDAZOLAM CO-INDUCTION FOLLOWED BY TOTAL INTRAVENOUS ANESTHESIA IN DOGS

SUMMARY

Objective To compare the induction dose and recovery quality of propofol and alfaxalone with or without midazolam followed by total intravenous anesthesia (TIVA) in dogs.

Study design Prospective, randomized, incomplete Latin-square crossover, blinded trial.

Animals Ten research dogs weighing a mean (SD) of 24.5 (3.1) kg.

Methods Dogs were randomly assigned to four treatments, Propofol (P) with saline (S), P-S; Alfaxalone (A) with S, A-S; P with Midazolam (M) P-M; A-M. Fentanyl (7 μg kg-1, IV) was administered 10 minutes prior to an IV bolus of P (1 mg kg^{-1}) or A (0.5 mg kg^{-1}) followed by M (0.3 mg kg^{-1}, IV) or S and additional boluses (Add-Dose) of P or A every 6 seconds for intubation, followed by maintenance with P/A TIVA. Quality of sedation (SedQ), induction (IndQ), maintenance (AnesQ), extubation (ExtQ) and recovery (RecQ) were scored. Total dose (TotalD) and Add-Dose of P or A, TIVA rates, time from sedation to TIVA discontinuation (T1), times from TIVA discontinuation to extubation (T4) and standing (T5) were recorded. Analysis included a general linear mixed model with *post hoc* analysis ($p < 0.05$).

Results The IndQ was better in A-M versus A-S; P-M versus P-S, and A-M versus P-S. The TotalD was lower in P-M versus P-S and A-M versus A-S. The Add-Dose were

fewer in A-M versus A-S; P-M versus P-S; and A-M versus P-S. The TIVA rate of P-M was lower than P-S but similar between A-M and A-S. Scores for SedQ, ExtQ, and RecQ, and times for T1 and T4 were similar between treatments. The T5 was longer for A than P, but similar within A or P treatments.

Conclusions and clinical relevance In fentanyl sedated dogs, M improved IndQ and reduced TotalD and Add-Dose for both P and A, but only reduced TIVA rate of P.

Keywords alfaxalone, co-induction, dog, midazolam, propofol

INTRODUCTION

The optimal anesthetic induction agent in small animal practice would be cost effective, easy to administer intravenously (IV) without pain or irritation to allow for a smooth induction with endotracheal intubation, without any negative cardiopulmonary side effects, and with a fast and calm recovery. Propofol (P) and alfaxalone (A) are two commonly used induction agents in small animals, which have good qualities; however, anesthetic induction may not always be smooth, necessitating higher induction doses and increasing the negative cardiopulmonary side effects. Co-induction agents can be used with propofol or alfaxalone with the goal of promoting a smooth induction, reducing the induction dose, and thereby the negative cardiopulmonary effects.

The main co-induction agents used in veterinary medicine are diazepam, midazolam, lidocaine, and ketamine. The veterinary literature indicates both positive and negative findings of induction dose reduction with co-induction agents (Lerche et al. 2000; Ko et al. 2006; Braun et al. 2007; Jolliffe et al. 2007; Covey-Crump & Murison 2008; Mair et al. 2009; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Martinez-Taboada & Leece 2014). The variability in results with benzodiazepines in dogs is associated with differences in premedication agents, which benzodiazepine and dose is used, as well as order and speed of administration. With midazolam co-induction with propofol, the dose reduction is most consistent at doses of 0.2-0.5 mg/kg and when the midazolam is given after an initial bolus of propofol (Robinson & Borer-Weir 2013; Sanchez et al. 2013). An observational study investigated the dose reduction effects of using of midazolam as a co-induction agent with alfaxalone in dogs (Seo et al. 2015). Both alfaxalone and propofol have the advantage of pharmacologic

profiles that allow administration for total intravenous anesthesia (TIVA). In general, recovery from propofol TIVA has been described as smooth and excellent (Keegan & Greene 1993; Ambros et al. 2008; Suarez et al. 2012). However, the recovery quality of alfaxalone is controversial. Most studies state that the overall recovery quality with alfaxalone is good to excellent (Ambros et al. 2008; Muir et al. 2008; Psatha et al. 2011; Suarez et al. 2012; Herbert et al. 2013). Recovery from alfaxalone TIVA has been reported as comparable to propofol TIVA (Ambros et al. 2008; Suarez et al. 2012). Recovery from alfaxalone induction was better than etomidate (Rodriguez et al. 2012) or diazepam/fentanyl induction (Psatha et al. 2011) when followed by isoflurane maintenance. However, dogs receiving alfaxalone induction followed by sevoflurane for MRI had poorer recovery scores compared to those induced with propofol (Jimenez et al. 2012). With alfaxalone, dogs may be sensitive to external stimulation (Ferre et al. 2006) or demonstrate tremors, rigidity, and myoclonus at recovery (Maney et al. 2013). Hence pre-medication as well as a quiet and undisturbed recovery are recommended by the manufacturer (Jurox Pty Ltd, Australia). To the authors knowledge, a direct comparison of the TIVA maintenance quality and recovery characteristics of propofol and alfaxalone TIVA when co-induction with midazolam in fentanyl pre-medicated dogs for diagnostic computerized tomography (CT) or magnetic resonance imaging (MRI) is not available.

The hypothesis of this study is that there are no differences regarding the induction dose, quality, TIVA dose, ease of maintenance, and overall recovery characteristics between propofol and alfaxalone with or without midazolam co-induction in fentanyl sedated dogs.

MATERIALS AND METHODS

Animals

All procedures were approved by the Animal Care Committee, University of Guelph, and followed the Canadian Council on Animal Care Guidelines. Ten healthy research crossbred hound dogs, mean (range) age 3.4 (1.9 – 5.5) years, mean (SD) weight 24.5 (3.1) kg were used. Health status was based on general physical examination, complete blood count, and biochemistry panel.

Study Design

The sample size was calculated to detect 30% difference of propofol or alfaxalone induction dose with type 1 error of 0.05 and power of 80%. A minimum of four dogs in each treatment was needed. This study was a prospective, blinded, randomized, incomplete Latin-square crossover research trial with at least a seven days washout between five separate anesthetic events that included three MRI and two CT scans. A random sequence was generated using a computer algorithm (GraphPad Prism, CA, USA) to ensure blinded allocation of dogs between the treatments. Papers containing the anesthetic treatment allocation of dog for the research day were organized and opened by anesthesia research technicians. The research technicians also prepared the syringes for the randomized drugs for induction, additional doses, constant rate infusions, as well as adjustment of TIVA doses. Drapes were used to cover the syringes and infusion lines to prevent either anesthetist (MS, PL) from identifying the drug used.

Dogs underwent MRI (first, third and fourth anesthetic event), a CT-guided intervertebral disc injection of gelified ethanol (CT1; second event) in a parallel but

unrelated study (Mackenzie et al. 2016) and a CT scan without injection (CT2; fifth event) while maintained on propofol or alfaxalone TIVA. The results of the cardiopulmonary variables are presented elsewhere.

Anesthesia and instrumentation (see Figure 1)

The dogs were fasted for at least 12 hours but given free access to water prior to general anesthesia. Topical local anesthetic cream (Maxilene, RGR Pharma Ltd., Canada) was applied pre-emptively to the clipped area over the planned catheterization sites of the cephalic vein and dorsal pedal artery at least ten minutes before. A 20-gauge catheter (Insyte-W; Becton Dickinson Infusion Therapy Systems, UT, USA) was inserted into a cephalic vein and 0.1 mg kg^{-1} of meloxicam (Metacam® 5 mg mL^{-1}, Boehringer Ingelheim Canada LTD, Canada), was administered intravenously prior to sedation.

With the dogs in lateral recumbency and monitored for cardiopulmonary parameters as part of a second study, fentanyl was administered at 7 µg kg^{-1}, IV (Fentanyl 50 µg mL^{-1}, Sandoz Canada Inc., Canada). Sedation was scored on each dog 10 minutes later, prior to administration of the induction agent *(*SedQ, Sedation Quality Score Appendix 1*)*. Dogs were randomly assigned to one of four treatments for anesthetic induction with propofol (Propofol 10 mg mL^{-1}, Pharmascience Inc, Canada) or alfaxalone (Alfaxan® 10 mg mL^{-1}, Jurox Pty Limited, Australia) with or without midazolam (Midazolam 5 mg mL^{-1}, Pharmaceutical Partners of Canada Inc, Canada) or normal saline (0.9% Sodium Chloride, Hospira, Canada), and maintained by TIVA with the respective injectable agent as follows: Treatment P-M: propofol (1 mg kg^{-1}, IV) and midazolam (0.3 mg kg^{-1}, IV); Treatment A-M: alfaxalone (0.5 mg kg^{-1}, IV) and midazolam (0.3 mg kg^{-1},

IV); Treatment P-S: propofol (1 mg kg^{-1}, IV) and equal volume of saline (0.06 mL kg^{-1}, IV); Treatment A-S: alfaxalone (0.5 mg kg^{-1}, IV) and equal volume of saline (0.06 mL kg^{-1}, IV). Initial doses of propofol or alfaxalone were administered as a bolus, flushed with 2 mL of saline, IV, and then the midazolam or equal volume of saline was immediately administered. An additional 25% of the bolus dose of propofol or alfaxalone was administered as a bolus every 6 seconds upon request until successful endotracheal intubation could be performed (MS). No attempts to intubate were made until confirmed loss of lateral palpebral reflex and then relaxation of jaw tone. Induction and intubation scores based on quantity of additional boluses required for intubation (Add-Dose), speed of relaxation, response to laryngoscope placement, and endotracheal intubation, or presence of excitement was assessed and scored by the same researcher unaware of treatments allocation (MS) (IndQ, Induction and Intubation Quality Score Appendix 2).

Once intubated, TIVA with the respective injectable was administered by syringe pump (Medfusion 3500, Smiths Medical Canada, Canada; Graseby 3500 Anesthesia Pump; Smiths Medical International Ltd, UK) for maintenance at the following initial rates: 250 µg kg^{-1} $minute^{-1}$ of propofol or 70 µg kg^{-1} $minute^{-1}$ of alfaxalone. Dogs were connected to a small animal anesthesia machine with rebreathing circuit (Universal F-Circuit; Dispomed, Canada) using an oxygen flow of 1.5-2.5 L $minute^{-1}$ with commencement of entidal carbon dioxide partial pressure ($PE´CO_2$) and respiratory rate (f_R) measurements. Respiratory rate was acquired from capnography and rectal temperatures (Temp; ˚C), which were measured and recorded at each blood gas determination. Dogs were allowed to breathe spontaneously for 15 minutes in lateral

recumbency. A manual breath was administered if the dog did not breathe spontaneously for more than 30 seconds. After 15 minutes of spontaneous ventilation, mechanical ventilation was initiated with a tidal volume of 10 mL kg^{-1} and f_R adjusted to $PE'CO_2$ of 35 to 45 mmHg and the dog transferred to initiate the CT or MRI. Depth of anesthesia was evaluated and kept at the lightest possible plane by a researcher unaware of treatment allocation (PL). For minor changes in depth, TIVA rate adjustments by 25 μg kg^{-1} $minute^{-1}$ for propofol and 7 μg kg^{-1} $minute^{-1}$ for alfaxalone were made. When a rapid increase in depth was warranted, boluses of propofol (0.25 mg kg^{-1}) or alfaxalone (0.125 mg kg^{-1}) were administered. Anesthetic depth was assessed with physical signs every 5 minutes; indications of inadequate depth included movement, brisk palpebral reflex, increased jaw tone, spontaneous blinking, or continual increases in heart rate (HR), f_R, or direct arterial blood pressure. Anesthetic administration was decreased in the same fashion to increase when a progressive decrease in arterial pressure was noted in the absence of respiratory fluctuations or attempts were made to ventilate spontaneously during mechanical ventilation, in addition to lack of palpebral reflexes and jaw tone. The ease of TIVA anesthesia maintenance quality was scored every 5 minutes throughout (AnesQ, see Anesthetic Maintenance Quality Score Appendix 3). Hypotension was defined as a mean arterial pressure (MAP) < 60 mmHg for more than 5 minutes with an appropriate anesthetic depth, and treated with an infusion of dopamine (2–10 μg kg^{-1} $minute^{-1}$) at the researcher's discretion if depth adjustment was not sufficient.

After the MRI or CT procedure, the dogs were transferred back to the induction area for recovery. Total anesthesia time recorded from the start of induction (T3) to TIVA discontinuation, and from administration of sedation to TIVA discontinuation (T1)

were recorded. Extubation was initiated once a strong medial palpebral reflex just prior to the swallow reflex was present and recorded as time to extubation (T4) from TIVA discontinuation. Dogs were left undisturbed on the recovery table for 10 minutes and extubation quality scored immediately after extubation, and subsequently at 5 and 10 minutes before being moved to a cage (ExtQ, see Extubation Quality Score Appendix 4), where they were observed for recovery quality at 15, 30, 45 and 60 minutes after extubation (RecQ, see Recovery Quality score Appendix 5) During this period the time to standing (T5) from the end of TIVA was also recorded. The ExtQ and RecQ was scored on site by a researcher unaware of treatment allocation (PL) as well as video recorded for 10-15 seconds at each assessment. Three board certified anesthesiologists unaware of the treatments allocation, imaging modalities and time point also scored the ExtQ and RecQ through video clips (MS, AV, CM).

Statistical analysis

Statistical analyses were performed with standard computer software (SAS OnlineDoc 9.2; SAS Institute Inc., North Carolina, USA). Normality of data was tested using Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises and Anderson-Darling test (Proc UNIVARIATE, SAS). Continuous data that were not normally distributed were log transformed for analysis, unless log transformation provided no improvement to distribution. The inter-rater agreement of the ExtQ and RecQ was examined by weighted kappa statistic. A general linear mixed model was used to model the results using Proc MIXED. Fixed effect for SedQ, TotalD, Add-Dose, IndQ, and T2 was treatment, whereas for T1, T3, T4, and T5 was treatment and imaging procedure,

including up to two-way interactions, and for ExtQ and RecQ were treatment, imaging procedure and time, including up to three-way interactions. For AnesQ and TIVA rate, different phases (see Figure 1) including sedation, induction, procedure, and end were also considered fixed effects in addition to treatment, imaging procedure and time within phases with up to three-way interactions. No interaction was tested between phases and times within phases. Dog was considered a random effect and treated as a blocking variable. To model for the effects of repeated measures over time for TIVA rate, AnesQ, ExtQ, and RecQ on each dog, due to treatment and within a specific phase, the following correlations structures, offered by SAS, were attempted: ar(1), arh(1), sp(pow)(time), toep, banded toep, toeph, banded toeph, and un and banded un. The error structure, among those that converged, was chosen based upon the lowest Akikie Information Criteria. Terms in the model were removed if non-significant, but preserving model hierarchy. Appropriate adjustments (Tukey or Dunnet test) for multiple comparisons were employed. Significance was set at $p < 0.05$. Residuals were examined to assess the ANOVA assumptions and plotted against the predicted values and the explanatory variables used in the model. Such analyses help reveal outliers, unequal variance, the need for data transformation, and other issues that need addressing.

The results are presented with adjusted mean if data are normally distributed or ordinal and adjusted median if not normally distributed based on a log transformation with 95% confidence interval (CI). The adjustment was done by applying standard ANOVA least-squares methods to estimate and test the results as if the data were in a complete Latin-square, crossover design. When comparing between treatments, for

those normally distributed continuous data and ordinal data, the effect size is provided as the difference between treatments with 95% CI. The *p*-value is provided for those not normally distributed and log transformed.

RESULTS

All dogs recovered uneventfully from anesthesia without complications. There was a significant reduction in the TotalD with both A-M and P-M treatments with effect size (95% CI) of 0.36 mg kg^{-1} (0.07 – 0.65) for A-S compared to A-M and 0.52 mg kg^{-1} (0.22- 0.81) for P-S compared to P-M. The IndQ score was significantly better for A-M versus either A-S or P-S with effect sizes (95% CI) of 0.97 (0.25 – 1.69) and 1.69 (0.96 – 2.41) respectively. The IndQ score was also significantly better for P-M versus P-S with effect size (95% CI) of 1.41 (0.68 – 2.15). The number of Add-Dose was lower for A-M versus A-S; P-M versus P-S; and A-M versus P-S with effect size (95% CI) of 1.9 (0.6 – 3.2); 1.8 (0.5 – 3.2); 3.0 (1.7 – 4.3). However, there were no significant differences between treatments for SedQ or T2. (see Table 3).

The overall median TIVA rates (95% CI) for P-S, P-M, A-S, and A-M were 310 μg kg^{-1} min (274 - 351), 268 μg kg^{-1} min (233 - 309), 87 μg kg^{-1} min (77 - 98) and 83 μg kg^{-1} min (74 - 94), respectively (see Table 4). The overall TIVA rate of P-M was significantly lower than P-S ($p = 0.013$) but there was no difference between A-M and A-S. The TIVA rate of CT1 after induction was significantly higher than CT2 ($p < 0.001$). The TIVA rate of CT1 during the procedure was significantly higher than MRI ($p = 0.041$) and CT2 ($p < 0.001$). The TIVA rate of CT1 during the procedure and the end was higher than after induction ($p < 0.001$). The TIVA rate of MRI after the procedure was higher than after induction ($p = 0.003$). There was no significant difference between anesthetic events in CT2.

The AnesQ was not different between treatments (see Table 4). However, the overall AnesQ had significant changes related to the first and second CT event or MRI

and the different phases. After induction, the AnesQ of CT1 was significantly higher than MRI and CT2 with an effect size (95% CI) of 0.35 (0.14 – 0.56) and 1.05 (0.74 – 1.35); the AnesQ of the MRI was also significantly higher than CT2 with an effect size (95% CI) of 0.70 (0.43 – 0.97). In addition, the AnesQ during the procedure was significantly higher in CT1 than CT2 with an effect size (95% CI) of 0.27 (0.02 – 0.52).

Related to the anesthetic phases of the CT1 and the MRI, the AnesQ after induction was significantly higher than during the procedure or the end with an effect size (95% CI) of 1.05 (0.82 – 1.23) and 1.39 (1.08 – 1.70) for the CT1 and 0.82 (0.68 – 0.97) and 0.83 (0.63 – 1.02) for the MRI; during the procedure of the CT1 it was also significantly higher than the end with an effect size (95% CI) of 0.34 (0.05 – 0.64). There was no significant difference for AnesQ between different anesthetic phases for CT2.

The T1, T2, and T3 were not significantly different between treatment treatments or imaging modalities. The T4 was not significantly different between treatments but was significantly longer during CT1 with an effect size (95% CI) of 4.9 (2.9 – 7.0) to MRI and 5.5 (2.5 -8.5) minutes to CT2. The T5 was significantly longer for A-S compared to P-S or P-M with effect sizes (95% CI) of 22.0 (10.6 – 33.4) and 18.0 (6.2 – 29.8) minutes, respectively. It was also significantly longer for A-M compared to P-S or P-M with effect sizes (95% CI) of 21.6 (9.9 – 33.3) and 17.6 (5.7 – 29.5) minutes.

The recovery score data are presented in Table 5. The inter-rater agreement of (MS) to (PL) and (AV) to (CM) was substantial (Landis & Koch 1977) with weighted kappa (95% CI) coefficient of 0.7988 (0.6870 – 0.9106); 0.8014 (0.6920 – 0.9107); 0.7010 (0.5645 – 0.8376), respectively. Hence only the ExtQ and RecQ directly scored

by a researcher (PL) were used. There was no difference between treatments regarding to ExtQ or RecQ. The ExtQ immediately after extubation was significantly lower than the score at five and 10 minutes post-extubation with effect sizes (95% CI) of 0.41 (0.14 – 0.68) and 0.53 (0.21 – 0.85). The RecQ significantly decreased over 15, 30, 45 and 60 minutes post-extubation ($p < 0.0001$).

DISCUSSION

This study demonstrates that in fentanyl sedated dogs, co-induction with midazolam reduces the induction dose requirement and improves the induction quality for endotracheal intubation for both alfaxalone and propofol. The quality of induction was shown to be better with the inclusion of midazolam in the induction protocol, compared to the saline treatment, and the A-M treatment also scored better in comparison to P-S. This induction quality score has the number of additional induction boluses required as part of the scoring, hence, Add-Dose not surprisingly varies in a manner similar to the IndQ.

All dogs had a mild to moderate sedation with fentanyl, before administration of the induction drug. The investigators were not aware of the treatments allocation and the induction was always scored and performed by the same researcher to prevent bias and to make comparisons from this study more objective. In general, a smooth induction process with drugs that are safe and effective to allow endotracheal intubation is desired, especially in critically ill patients. Both P-M and A-M demonstrated the smoothest induction quality with a significant reduction in the total anesthetic dose of the induction drug. In addition, A-M also appeared superior to P-S. The real benefit of this dose reduction in healthy animals may merely be cost and ease, but in sick, compromised patients, the reduction in dose may potentially also equate to better cardiovascular stability although further studies are required to evaluate this. The actual mechanism by which benzodiazepines, as co-induction drugs, help promote a dose reduction of the induction anesthetic drug and allow for a smoother induction is still unclear. Synergism and/or additive effects with the primary induction anesthetic drug

are most likely. *In vitro* research shows that benzodiazepines potentiate both GABA and a variety of $GABA_A$ receptor allosteric agonists by inhibiting transitions from the open state to the longest-duration closed states (Li et al. 2013).

Benzodiazepine co-induction with propofol induction in dogs has shown mixed results regarding a dose reduction of propofol. The different results could be attributed to multiple factors, including sedation level of the dogs, which benzodiazepine is used, dose of the benzodiazepine, speed of injection of the benzodiazepine, sequence of administration with propofol, and initial dose and rate of propofol administration. One investigation in dogs reports a dose reduction of 36% of propofol when diazepam (0.4 mg kg^{-1}, IV) was given before propofol but not with a lower diazepam dose (0.2 mg kg^{-1}, IV) (Ko et al. 2006); similarly others have not shown a dose reduction irrespective of the dose, sequence, or speed of administration (Ko et al. 2006; Braun et al. 2007; Robinson & Borer-Weir 2013).

Midazolam has the potential to be more reliable in causing a reduction in the induction dose of propofol, related to the lower potency and lipid solubility characteristics of diazepam when compared to midazolam (Mohler & Okada 1977; Reves et al. 1978; Buhrer et al. 1990; Horikawa et al. 1990). We administered midazolam after an initial bolus of the primary induction anesthetic since the benefits on dose reduction are more reliable when administered in this order. Several studies have shown signs of excitement when midazolam is administered before propofol, which may interfere with the required total dose of propofol to achieve induction and intubation. In one study, midazolam, 0.25 mg kg^{-1}, IV, administered over 30 seconds 2 minutes prior to propofol titrated to effect at a rate of 4 mg kg^{-1} min^{-1}, IV, did not result in a dose reduction but

resulted in excitement in 95% of the dogs, despite intramuscular (IM) sedation with acepromazine (0.025 mg kg^{-1}) and morphine (0.25 mg kg^{-1}) 30 minutes before induction (Covey-Crump & Murison 2008). In contrast, midazolam, 0.25 mg kg^{-1}, IV, administered over 1 minute, and 30 seconds prior to propofol, titrated to effect at a rate of 2 mg kg^{-1} min^{-1}, IV, resulted in a 47% dose reduction versus propofol alone (1.7 mg kg^{-1} versus 3.2 mg kg^{-1}) but excitement was still noted in 45% of the dogs, despite prior IM sedation with acepromazine (0.02 mg kg^{-1}) and morphine (0.4 mg kg^{-1}) 30 minutes before induction (Sanchez et al. 2013). Similarly, this same dose of midazolam (0.25 mg kg^{-1}, IV) given over 15 seconds, immediately prior to propofol titrated to effect (3 mg kg^{-1} min^{-1}), showed an 18% dose reduction versus propofol alone (2.8 versus 3.4 mg kg^{-1}), despite signs of excitement in 55% of the dogs, despite prior IM sedation with acepromazine (0.025 mg kg^{-1}) and morphine (0.25 mg kg^{-1}) 30 minutes before induction (Hopkins et al. 2013). Conversely, when midazolam (0.2 – 0.5 mg kg^{-1}, IV) was administered after an initial bolus of propofol, 1 mg kg^{-1}, IV, and propofol titrated to effect at rate of 2 - 4 mg kg^{-1} min^{-1}, the incidence of excitement was less (12-18%) and there was a more consistent dose reduction (38-66%) (Robinson & Borer-Weir 2013; Sanchez et al. 2013).

In this study, we chose to administer an initial IV bolus of alfaxalone of 0.5 mg kg^{-1} or propofol of 1 mg kg^{-1}, which is lower than the average induction dose with or without midazolam co-induction used in dogs in other studies. This was done to ensure the results were able to demonstrate any potential dose reduction. Considering this lowered initial dose, two dogs each in A-S and A-M and one dog in P-M did not require any additional doses to allow endotracheal intubation, suggesting that we could have

potentially administered an even lower initial bolus dose. Nevertheless, the initial dose was chosen in our study to avoid potential excitement of furthered lower initial induction dosages and subsequent inability to demonstrate a potential dose reduction with midazolam co-induction. The fact that the mean number of additional doses was similar between A-S and P-S, and A-M and P-M indicates that the initial boluses were equivalent between the propofol and alfaxalone treatments.

The speed of injection of the induction agent is also an important factor that can influence the quality of induction. In sedated humans, the slower the administration of propofol during induction, the greater the effect on lowering the total dose required for loss of verbal contact (Stokes & Hutton 1991). Similarly, in sedated cats, the slower the administration of alfaxalone, the greater the effect on lowering the total dose required for endotracheal intubation (Bauquier et al. 2015). In the technical note provided by the pharmaceutical company, the induction dose of alfaxalone (2 -3 mg kg^{-1}, IV) is recommended to be given as a slow infusion over 60 seconds or a quarter given every 15 seconds. In our study, the titration rate of propofol and alfaxalone were approximately 2.5 mg kg^{-1} min^{-1} and 1.25 mg kg^{-1} min^{-1}, respectively. Our injection rate of propofol during induction was at the low end of the range used in other studies (2-4 mg kg^{-1} min^{-1}) (Covey-Crump & Murison 2008; (Hopkins et al. 2013; Robinson & Borer-Weir 2013; Sanchez et al. 2013). Comparative results for alfaxalone and midazolam co-induction are not available.

A limitation of our study is that we did not standardize the speed of injection of the propofol or alfaxalone during the induction process with a syringe pump. However, we chose our methods to allow our results to predict the effects in a private practice

setting and not necessarily a specialty clinic or academic setting. We believe that our injection rate was slow enough to allow evaluation of depth and assessment of induction quality.

In our study, the midazolam co-induction provided a dose reduction of 25% for propofol and 37% for alfaxalone without any excitement in fentanyl sedated healthy research dogs. The percentage of dose reduction of propofol in our study is less than previous studies when midazolam was administered after a bolus of propofol (Robinson & Borer-Weir 2013; Sanchez et al. 2013). This may due to the administration of fentanyl, which reduced the induction dose, overriding the impact of midazolam. In our study, mild to moderate sedation was noted from 7 ug kg $^{-1}$, IV, of fentanyl without any clinical excitement. In dogs, peak concentrations of fentanyl are achieved in the brain tissue at 10-15 min after an IV injection of 12.5 ug kg $^{-1}$ (Ainslie et al. 1979). There was a 17% reduction in the propofol induction dose when 2 μg kg^{-1}, IV, fentanyl was given 2 minutes before propofol was titrated to effect at a rate of 4 mg kg^{-1} min^{1} (Covey-Crump & Murison 2008). Moreover, the induction doses of the two control treatments, A-S and P-S, were relatively lower than the doses of propofol or alfaxalone reported in the literature in pre-medicated dogs supporting a dose reduction effect of fentanyl in our study with the median time of fentanyl administration to the start of induction ranging from 9 to 14 minutes.

The TIVA rate of propofol alone used in this study (310 [274-351] μg kg^{-1} min^{-1}) in healthy dogs was higher than the rate required in clinically non-sedated sick dogs undergoing an MRI (292 ± 119 μg kg^{-1} min^{-1}) (Caines et al. 2014) and lower than in clinically healthy dogs sedated with subcutaneous acepromazine (0.01 mg kg^{-1}) and

morphine (0.4 mg kg^{-1}) undergoing surgery (370 ± 90 μg kg^{-1} min^{-1}) (Suarez et al. 2012). The TIVA rate of alfaxalone alone in our study (87 [77-98] μg kg^{-1} min^{-1}) was higher than the dose required in healthy research dogs sedated with IV acepromazine (0.02 mg kg^{-1}) and hydromorphone (0.05 mg kg^{-1}) (70 μg kg^{-1} min^{-1}) (Ambros et al. 2008) and lower than in clinically healthy dogs undergoing surgery (110 ± 10 μg kg^{-1} min^{-1}) (Suarez et al. 2012).

Interestingly, in our study midazolam lowered the required TIVA dose of propofol (268 [233-309] versus 310 [274-351]; μg kg^{-1} min^{-1}) but not alfaxalone (83[74-94] versus 87 [77-98]; μg kg^{-1} min^{-1}). Plasma concentrations of midazolam were not measured in this study, but would allow quantifying if differences exist on midazolam's pharmacokinetics when administered with alfaxalone or propofol or if different drug interactions exist. Aside of the impact of midazolam, the TIVA rate was also significantly influenced by the diagnostic procedure of CT or MRI either after induction, during the procedure or at the end of the procedure. For the first CT, the dogs underwent an intervertebral disc injection of gelified ethanol for an unrelated study {Mackenzie, 2016}. The dose rate for the first CT was higher irrespective of treatments during, and at the end of the procedure when compared to the second CT or the MRI TIVA rates. This was to be expected and is likely related to the greater expected or real stimulation associated with the injection itself that, despite treatment blinding, resulted in dose adjustments from those monitoring the dogs for the injection. The TIVA dose was also increased over time in the first CT and MRI but was not significantly different during the second CT. This too is expected, and is related to the injection during the first CT or the scanning noise during the MRI. These periods of TIVA dosing

adjustments would not be expected to be impacted by the treatments themselves, as our results indicate, but by the phases of the anesthetic period.

The adjustments in rate and maintenance with either propofol or alfaxalone TIVA were readily achieved in all of our dogs. There was no difference in the ability to maintain TIVA for the CT or MRI, as indicated by similar AnesQ. However, as with the TIVA rate alteration, the AnesQ changes were related to the first or second CT or MRI as well as the anesthetic event during the diagnostic procedure. A higher AnesQ, indicative of a lighter anesthetic plane, was present after induction versus when the dogs were undergoing the procedure or the end.

The time to extubation was approximately 6.4 – 7.1 minutes, which is shorter than the reported range of 10 – 15 minutes in previous studies (Ambros et al. 2008; Suarez et al. 2012). Our criteria for extubation may be the main reason contributing to this difference. In our study, extubation was initiated once a strong medial palpebral reflex was present in combination with the dog's eye rolling up, but just prior to the swallow. Other studies use the swallow reflex as an end-point. In our study, it was common, during the extubation process, for dogs to swallow in response to movement of the cuff of the endotracheal tube past the rima glottis, indicating that they were also ready for extubation, but rather than the swallow being spontaneous, it was induced. The purpose of this type of extubation was to minimize any chance of extubation-related excitement that may obscure the effects of the anesthetic on recovery parameters.

The recovery quality after propofol and alfaxalone TIVA in dogs has been compared and reported in dogs. Without pre-medication, dogs were reportedly sensitive to external stimulation or demonstrated adverse effects such as tremors, rigidity, or

myoclonus at recovery after propofol or alfaxalone induction (Morgan & Legge 1989; Ferre et al. 2006; Maney et al. 2013). Other research (Ambros et al. 2008) and clinical investigations of TIVA for ovariohysterectomy (Suarez et al. 2012) in dogs did not find a significant difference between propofol and alfaxalone with regard to recovery times or quality, which was reported as good to excellent. However, both of these studies pre-medicated the dogs with drugs that are longer acting - acepromazine and morphine (Suarez et al. 2012) or acepromazine and hydromorphone (Ambros et al. 2008) - compared to fentanyl, which was used in our study. In our study, RecQ was not different between propofol and alfaxalone with or without midazolam and was in general smooth with only mild excitement in some dogs. The mild excitement seen in some dogs in our study could have been minimized if longer-duration sedatives were used or additional sedatives were administered prior to recovery. However, our study design was to simulate the anesthetic protocol commonly used in critical canine patients for diagnostic procedures. It is possible that excitement may not be noted in clinical cases with other confounding factors such as a compromised health status.

Dogs in the alfaxalone treatments required a longer time to stand than dogs in the propofol treatments (65 minutes versus 45 minutes), despite no difference in the time to extubation between the treatments. The time to standing after alfaxalone TIVA in our study is similar to those from other studies, where it ranged from 52 -74 minutes (Ambros et al. 2008; Suarez et al. 2012); whereas the time to standing after propofol TIVA was shorter than the range of 70 – 90 minutes reported in other studies (Ambros et al. 2008; Suarez et al. 2012). Comparisons with other studies should take into account the type of pre-medication, TIVA dose and time, and type of procedure performed. We handled

both treatments the same way and, therefore, it is not clear why the time to standing was different in the propofol treatments but not the alfaxalone treatments, compared to other studies.

In conclusion, midazolam is a suitable co-induction agent with either propofol or alfaxalone due to the reduced induction dose, improved induction quality and satisfactory recovery characteristics. Improvement of induction quality and primary injectable dose reduction could also benefit clinical case management. However, further research is warranted to investigate the effects of midazolam co-induction in critical cases.

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Figure 1. Study timeline with administration of fentanyl (F); propofol (P) or alfaxalone (A) with either saline (S) or midazolam (M); initiation (//) and discontinuation (//) of total intravenous anesthesia (TIVA) is indicated. The arrows between phases indicate transfer of dogs. Times are as follows; time from sedation to TIVA discontinuation: T1; time from sedation to induction: T2; time from induction to TIVA discontinuation: T3; time from TIVA discontinuation to extubation: T4; time from TIVA discontinuation to dogs standing: T5. Dogs were scored at time of endotracheal extubation, 0, as well as 5 and 10 min after. Additional recovery scoring continued for 45 minutes at time points 15, 30, 45 and 60 min post-extubation.

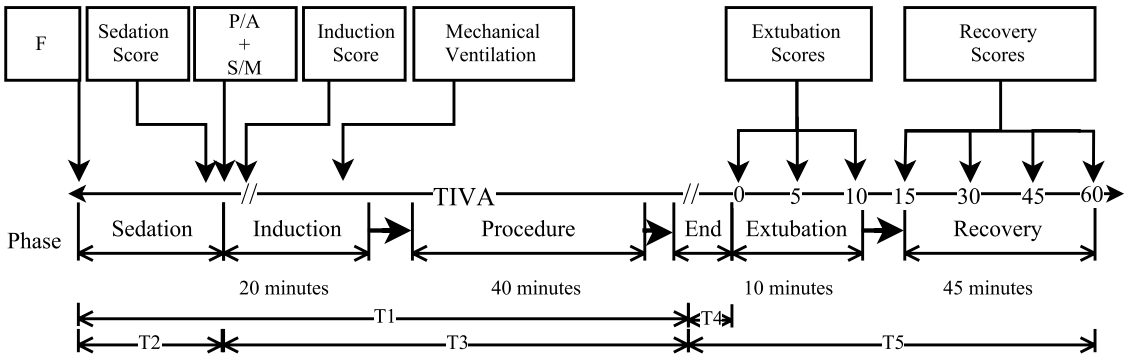

Table 3. Descriptive quality scores for Sedation (SedQ) (0-none to 3-profound), time from premedication to induction (T2), induction quality (IndQ) (0-smooth to 4-not possible), number of additional doses during anesthetic induction (Add-Dose), and total anesthetic dose (TotalD). All dogs were randomly assigned to one of the 4 treatments; Propofol (P) + Midazolam (M) (P-M); Alfaxalone (A) + M: (A-M); P + saline (S) (P-S); and A + S (A-S). Treatments were as follows: Fentanyl (F) (7 μg kg^{-1}, IV) was administered, followed by an initial IV bolus of P (1 mg kg^{-1}) or A (0.5 mg kg^{-1}) 10 min after F. Either M (0.3 mg kg^{-1}, IV) or S was administered immediately after the initial P or A bolus followed by additional boluses of the respective induction drug every 6 seconds (Add-Dose) to allow endo-tracheal intubation.

	PS	PM	AS	AM
SedQ (0 - 3)	1.9 (1.2 - 2.5)	2.4 (1.7 - 3.1)	1.7 (1.0 - 2.3)	2.0 (1.3 - 2.6)
T2 (min)	9.0 (6.4 - 12.7)	14.2 (9.9 - 20.2)	13.0 (9.3 - 18.1)	12.8 (9.1 - 18.1)
IndQ (0 - 4)	2.3 (1.8 - 2.9)^{a}	0.9 (0.4 - 1.5)^{bc}	1.6 (1.1 - 2.1)^{ac}	0.7 (0.1 - 1.2)^{b}
Add-Dose (number)	3.9 (2.8 – 5.1)^{ac}	2.1 (0.9 – 3.3)^{ad}	2.8 (1.7 – 4.0)^{a}	0.9 (-0.3 – 2.1)^{bd}
TotalD (mg kg^{-1})	2.1 (1.8 - 2.3)^{*a}	1.5 (1.3 - 1.8)^{*b}	0.98 (0.7 - 1.2)$^{\#c}$	0.62 (0.4 - 0.9)$^{\#d}$

Data are presented as mean with 95% confidence interval, except for (T2) presented as median with 95% confidence interval. Difference superscript letters indicates statistical difference between the treatments. TotalD was not compared between P and A. Symbols are as follows for treatment comparisons PS vs. PM (*) and AS vs AM ($^{\#}$).

Table 4. Total intravenous anesthesia doses (TIVA), time from administration of sedation to TIVA discontinuation (T1), total anesthesia time from the start of induction to TIVA discontinuation (T3), time from TIVA discontinuation to extubation (T4), time from TIVA discontinuation to standing (T5), and simple descriptive anesthesia maintenance quality scores (AnesQ) (0-no adjustments to 4-intervention required) following induction with either propofol (P) + Midazolam (M) (PM); Alfaxalone (A) + M: (AM); P + saline (S) (PS); and A + S (AS). (see Table 3 for key).

	PS	PM	AS	AM
TIVA rate $\mu g\ kg^{-1}\ min$	310[a] (274 - 351)	268[b] (233 - 309)	87 (77-98)	83 (74 - 94)
T1 (min)	105.0 (114.0 - 96.0)	110.4 (119.6 - 101.2)	105.9 (114.6 - 97.3)	107.5 (116.5 - 98.4)
T3 (min)	94.4 (85.7 - 104.1)	89.5 (80.8 - 99.1)	88.9 (81.6 - 96.9)	93.1 (84.7 - 102.2)
T4 (min)	6.4 (4.1 – 8.7)	6.6 (4.3 – 8.9)	7.7 (5.7 – 9.6)	7.1 (4.9 – 9.3)
T5 (min)	43.8 (53.8 - 33.8)[a]	47.8 (58.3 - 37.3)[a]	65.9 (75.7 – 56.0)[b]	65.4 (75.6 – 55.2)[b]
AnesQ (0-4)	0.48 (0.32 – 0.64)	0.35 (0.18 – 0.52)	0.43 (0.29 – 0.57)	0.40 (0.25 – 0.56)

Data are presented as mean with 95% confidence interval except for TIVA rate presented as median with 95% confidence interval. Difference superscript letters indicates statistical difference between the treatments. TIVA was not compared between P and A.

Table 5. Descriptive quality scores of extubation (ExtQ) (0-very calm to 4- extreme excitement) and recovery (RecQ) (0-excitable to 3-profound sedation) after extubation following propofol (P) or alfaxalone (A) total intravenous anesthesia for diagnostic imaging. Each dog was randomly assigned to induction agents as follows: P + Midazolam (M) (PM); A + M: (AM); P + saline (S) (PS); and A + S (AS). The ExtQ was assessed immediately, 0, and 5 and 10 minutes after extubation. The RecQ was assessed 15, 30, 45 and 60 minutes after extubation.

	Time after extubation (min)	PS	PM	AS	AM
ExtQ	0	0.0 (-0.7 – 0.6)	0.3 (-0.4 – 1.0)	0.5 (-0.2 – 1.1)	0.1 (-0.5 – 0.8)
	5	0.4 (-0.2 – 1.0)	0.8 (0.1 – 1.4)	0.6 (0.0 – 1.3)	0.7 (0.1 – 1.4)
	10	0.6 (0.0 – 1.2)	0.3 (-0.4 – 1.0)	0.9 (0.3 – 1.5)	1.2 (0.5 – 1.8)
RecQ	15	2.1 (1.4 – 7.8)	2.5 (1.8 – 3.2)	2.6 (1.9 – 3.2)	2.7 (2.0 – 3.3)
	30	1.2 (0.6 – 1.9)	1.7 (1.0 – 2.4)	2.3 (1.7 – 3.0)	2.3 (1.7 – 3.0)
	45	0.3 (-0.3 – 1.0)	0.8 (0.1 – 1.5)	1.2 (0.6 – 1.8)	1.3 (0.7 – 2.0)
	60	0.1 (-0.6 – 0.8)	0.2 (-0.4 – 1.0)	0.4 (-0.2 – 1.1)	0.6 (-0.1 – 1.3)

Data are presented as mean with 95% confidence interval. Difference superscript letters indicate statistical difference between the treatments.

Appendix 1. Simple descriptive quality scores for sedation prior to anesthetic induction (SedQ) in dogs, 10 minutes after administration of fentanyl, 7 μg kg^{-1}, IV. (modified from Caines et al. 2014)

Sedation Quality Score	
0	Bright and alert - no sedation and/or excitable- dysphoric (excited, anxious, difficult to restraint in lateral recumbency, very interactive and responsive, vocalizing, very reactive to noise or touch
1	Calm - minimal sedation, quiet but still alert and aware of surroundings, mild resistance to restraint in lateral recumbency, moderate response to noise or touch
2	Mild to moderate sedation - quiet, relaxed, minimal restraint required in lateral recumbency, mild response to noise or touch
3	Profound sedation - quiet, very relaxed, no restraint necessary in lateral recumbency, no response to noise or touch

Appendix 2. Simple descriptive quality scale for induction and intubation (IndQ) with propofol or alfaxalone with or without midazolam co-induction after sedation with fentanyl in dogs.

Induction and Intubation Quality Score	
0	Smooth with no Resistance - Dog relaxes within 30 seconds, no jaw tone, no lateral palpebral, no tongue tone, no response to laryngoscope placement. Dog easily intubated with the initial bolus dose within 45 seconds.
1	Slight Resistance but Smooth - Dog relaxes within 30 seconds, no jaw tone, no lateral palpebral, no tongue tone, no response to laryngoscope placement. However, dog does cough on intubation and/or swallows once intubated. Requires 1-2 additional subsequent boluses of the induction drug. Dog is intubated within 45 seconds.
2	Mild-Moderate Resistance - Dog relaxes within 30 seconds, no jaw tone, no lateral palpebral. However, dog responds to laryngoscope placement with tongue curl. Requires 1-2 additional subsequent boluses of the induction drug to proceed. Cough and or swallow may also be noted. Dog is intubated within 60 seconds.
3	Moderate Resistance – Unacceptable Quality - Dog does not relax initially within 30 seconds and requires 2-3 subsequent injectable boluses of the induction drug to proceed to intubation. Resistance to intubation attempt within 45 seconds (cough, tongue curl, and or other movement) requiring subsequent additional doses during the intubation process. Dog relaxes after intubation without further movement but is at a light plane. Dog is intubated within 60 seconds.
4	Excitement - Paddling, hyperkinesis, vocalizing, defecation, urination. Unable to intubate without significant number of subsequent doses of the induction drug. Intubation takes more than 60 seconds.

Appendix 3. Simple descriptive quality scores for anesthetic maintenance (AnesQ) with propofol or alfaxalone TIVA with or without midazolam co-induction after sedation with fentanyl, during diagnostic CT or MRI in dogs. (modified from Caines et al. 2014)

Anesthetic Maintenance Quality Score	
0	No adjustments required in the TIVA rate of propofol or alfaxalone during transfer or maintenance in MRI/CT. Relaxed jaw tone, slight to no medial palpebral response, muscle relaxation during positioning or procedures.
1	One additional bolus of propofol or alfaxalone and an increase in the TIVA rate during transfer or maintenance in MRI/CT. Dog appears light with strong jaw tone and medial palpebral during depth assessment, but no doses are required. No movement is noted. Change in anesthetic depth happens only once.
2	One to two additional boluses of propofol or alfaxalone and an increase in the TIVA rate during transfer or maintenance in MRI/CT. Signs noted include slight increases in HR, BP, bucking ventilator, increased jaw tone, strong medial palpebral reflexes during the MRI or disc injection, muscle tone, and rigidity. Change in anesthetic depth occurs 2-3 times but is easily controlled.
3	Two to three additional boluses of propofol or alfaxalone with increases in the TIVA rate during transfer or maintenance in MRI/CT. Signs noted include slight increases in HR, BP, bucking ventilator, increased jaw tone, strong medial palpebral reflexes during the MRI or disc injection, periodic movement. Change in anesthetic depth occurs 2-3 times or more and is not easily controlled.
4	Four plus additional boluses of propofol or alfaxalone with increases in the TIVA rate during transfer or maintenance in MRI/CT. Signs noted include dramatic changes in HR, BP, bucking ventilator, strong jaw tone, movement, brisk palpebral, and overall increased responsiveness during the MRI or disc injection.

Appendix 4. Simple descriptive quality scores for extubation (ExtQ) immediately after extubation and 5 and 10 minutes after extubation in dogs recovering from propofol or alfaxalone TIVA with or without midazolam co-induction after sedation with fentanyl, during diagnostic CT or MRI in dogs. (modified from Caines et al. 2014)

Extubation Quality Score	
0	Very calm, smooth, no excitement. No paddling, vocalization or trembling
1	Smooth, with slight short excitement of < 30 seconds. No paddling, vocalization or trembling
2	Moderately smooth with mild excitement. Some paddling, vocalization and trembling.
3	Not smooth and with excitement. Paddling, vocalization and trembling. Vomiting may be observed.
4	Extreme excitement. Paddling, vocalization and/or aggression. Vomiting may be observed. Convulsions may be observed. Sedation/therapy required.

Appendix 5. Simple descriptive quality scores for recovery (RecQ) 15, 30, 45 and 60 minutes after extubation in dogs recovering from propofol or alfaxalone TIVA with or without midazolam co-induction after sedation with fentanyl, during diagnostic CT or MRI in dogs. (modified from Caines et al. 2014)

Recovery Quality Score	
0	Excitable with no apparent sedation or depression (excited, ambulatory, difficult to restraint in lateral at recovery for transport or in cage, very interactive, responds to voice and caregivers, attempting to go sternal within 15 minutes of extubation and/or ambulatory after 30 min. Animal is bright and looks similar to their status prior to anesthesia).
1	Calm with no apparent sedation or depression (alert, mild to moderate resistance to restraint in lateral for transport or in cage, moderately interactive, responds to voice and caregivers, no attempts to sternal recumbency after 15-30 minutes and/or not ambulatory after 30-60 minutes).
2	Apparent sedation/depression (quiet, minimal restraint required to keep animal in lateral recumbency for transport or in cage, mild response to voice or touch – no attempts to sternal recumbency and/or non ambulatory after 1 hour).
3	Profound sedation/depression (dull, minimal to no restraint required to keep animal in lateral recumbency for transport or in cage, does not respond to voice or touch, - no attempts to sternal recumbency and/or non-ambulatory for >1 hour post recovery).

CHAPTER III

CARDIO-PULMONARY EFFECTS OF PROPOFOL OR ALFAXALONE WITH OR WITHOUT MIDAZOLAM CO-INDUCTION FOLLOWED BY TOTAL INTRAVENOUS ANESTHESIA IN FENTANYL SEDATED DOGS

SUMMARY

Objective To compare cardio-pulmonary function between propofol (P) and alfaxalone (A) with or without midazolam (M) during induction followed by total intravenous anesthesia (TIVA) for diagnostic imaging in fentanyl sedated dogs.

Experimental design Prospective, randomized, incomplete Latin-square crossover, blinded trial.

Animals Ten research dogs weighing a mean (SD) of 24.5 (3.1) kg.

Methods Dogs were randomly assigned to P with saline (S), A-S, P-M, and A-M. Fentanyl (7 μg kg^{-1}, IV) was administered 10 minutes prior to an IV bolus of P (1 mg kg^{-1}) or A (0.5 mg kg^{-1}) followed by M (0.3 mg kg^{-1}, IV) or S and additional boluses of P or A for intubation, followed by maintenance with P or A TIVA. Heart rate (HR), systolic (SAP), mean (MAP) and diastolic (DAP) blood pressure, cardiac index (CI), respiratory rate (f_R), end-tidal carbon dioxide partial pressure ($P_E'CO_2$) and arterial blood gas analysis were compared. Analysis included a general linear mixed model with post-hoc analysis ($p < 0.05$).

Results After induction, HR was higher in A-M than A-S ($p = 0.049$) and P-S ($p < 0.001$). During imaging, HR of A-S ($p = 0.012$) and A-M ($p = 0.021$) were higher than P-S. Before recovery, HR of A-M was higher than P-S ($p = 0.009$). The overall SAP of A-S was significantly higher than A-M ($p < 0.001$) and P-M ($p = 0.001$). There was no significant treatment difference for MAP, DAP, CI, f_R, prevalence of apnea, $P_E'CO_2$, and blood gas

values. However, CI and HR significantly decreased at the end of imaging compared to other phases ($p < 0.001$).

Conclusions and clinical relevance

There is no significant cardio-pulmonary difference between treatment despite different P or A dosing. The decrease in CI and HR at the end warrants close monitoring.

Keywords propofol, alfaxalone, midazolam, dog, TIVA

INTRODUCTION

In veterinary anesthesia, co-induction agents may be used during the induction period principally to reduce the dose of the primary induction agent and ensure a smooth overall endotracheal intubation process. Co-induction with benzodiazepines has been most extensively studied with propofol induction in dogs. Midazolam shows the most consistent dose-reduction results especially when given after the initial bolus of propofol however the cardio-pulmonary benefit has not been clearly defined (Robinson & Borer-Weir 2013; Sanchez et al. 2013).

The cardio-pulmonary depression produced with propofol and alfaxalone induction is generally dose-dependent (Ismail et al. 1992; Puttick et al. 1992; Muir & Gadawski 1998; Muir et al. 2008; Keates & Whittem 2012). A potential goal associated with the dose reduction of propofol or alfaxalone provided by co-induction agents is to minimize the negative cardio-pulmonary effects. However, the benefit of combining the primary injectable anesthetic with a co-induction agent on the overall cardiovascular performance, and incidence of hypoventilation or apnea have not been clearly defined, and their combined use remains controversial in both human and veterinary anesthesia (Anderson & Robb 1998; Jones et al. 2002; Goel et al. 2008; Hopkins et al. 2013). In addition, most studies looking at the effects of co-induction agents on primary induction anesthetics have been completed using healthy patients and little is known of the combined effect in critical patients. The scientific literature has primarily focused on co-induction investigations with propofol to date, with minimal information on alfaxalone.

Total intravenous anesthesia (TIVA) has some advantages over inhalant anesthesia for maintenance, especially during advanced imaging, including reduced equipment need and potential workplace hazards from inhalant exposure to personnel. Propofol has the ideal

pharmacokinetic profile for TIVA use (Waelbers et al. 2009) and was demonstrated to have better cardiovascular function when compared to isoflurane in research dogs (Keegan & Greene 1993; Deryck et al. 1996; Iizuka et al. 2013) and in clinical dogs with intracranial disease undergoing magnetic resonance imaging (MRI) (Caines et al. 2014). Alfaxalone has been remarketed for almost a decade and has shown similar anesthetic effects to propofol in dogs (Ambros et al. 2008; Suarez et al. 2012; Maney et al. 2013). However, detailed comparisons between propofol and alfaxalone TIVA for diagnostic imaging are lacking.

To the authors' knowledge, scientific studies investigating cardio-pulmonary measurements, such as direct systolic (SAP), mean (MAP) and diastolic (DAP) arterial blood pressure and cardiac output (CO), during co-induction with midazolam and either propofol or alfaxalone followed by TIVA are not available, but could offer clarification of the cardio-pulmonary benefit of their combination. The objective of this research is to compare cardio-pulmonary function between propofol and alfaxalone with or without the co-administration of midazolam during anesthetic induction followed by TIVA for computer tomography (CT) or magnetic resonance imaging (MRI) in fentanyl sedated research dogs. We hypothesize that in healthy ASA I dogs there will be no difference in cardio-pulmonary effects during the anesthetic induction with propofol or alfaxalone with or without midazolam nor differences during TIVA maintenance.

MATERIALS AND METHODS

Animals

All procedures were approved by the Animal Care Committee, University of Guelph, and followed Canadian Council on Animal Care Guidelines. Ten healthy research crossbred hound dogs, mean (range) age 3.4 (1.9 – 5.5) years, mean (SD) weight 24.5 (3.1) kg, ASA classification I were used. Health status was based on a general physical examination, complete blood count and biochemistry panel. Dogs were included in a simultaneous aligned study evaluating the dose reduction and anesthesia quality of alfaxalone or propofol during induction and TIVA as well as recovery characteristics with or without midazolam detailed in the anesthetic methods below.

Study Design

This study was a prospective, blinded, randomized, incomplete Latin-square crossover research trial with at least a seven days washout between 5 separate anesthetic events. Randomization was performed using a computer software program (GraphPad, California, USA) to ensure blinded allocation of dogs between the treatments. Papers containing the anesthetic treatment allocation of dog for the research day were organized and opened by anesthesia research technicians. The research technicians also prepared the syringes for the randomized drugs for induction, additional doses, constant rate infusions, as well as adjustment of TIVA doses. Drapes were used to cover the syringes and infusions lines to prevent either investigator (MS; PL) from identifying the drug by color during induction dose assessments and collection of cardio-pulmonary data.

Dogs underwent MRI (first, third and fourth anesthetic event), a CT guided intervertebral disc injection of gelified ethanol (CT1; second event) in a parallel but unrelated

study (Mackenzie et al. 2016) and computed tomography without injection (CT2; fifth event) while maintained on propofol or alfaxalone TIVA. The results of the induction dose and quality, TIVA dose and maintenance and recovery characteristics are available elsewhere (Liao et al. 2015a; Liao et al. 2015b).

Anesthesia (see Figure 2)

Preparation and instrumentation

The dogs were fasted for at least 12 hours but given free access to water prior to general anesthesia. Topical local anesthetic cream (Maxilene, RGR Pharma Ltd, Canada) was applied pre-emptively to the clipped area over the cephalic vein and dorsal pedal artery and the sites bandaged. Ten minutes later, the bandage over the cephalic vein site was removed and a 20-gauge catheter (Insyte-W; Becton Dickinson Infusion Therapy Systems, Utah, USA) was inserted and 0.1 mg kg^{-1} of meloxicam (Metacam®, Boehringer Ingelheim Canada Ltd, Canada) administered intravenously (IV) prior to anesthesia. Thirty minutes after IV catheter placement, dogs were manually restrained in lateral recumbency, the bandage over the dorsal pedal artery removed and lidocaine (Lidocaine, Alveda Pharmaceuticals, Canada) (2%, 0.5 mL) infiltrated subcutaneously to facilitate the catheterization of the artery with a 20- or 22-gauge catheter.

Monitoring

Continuous ECG display (lead II), pulse-oximetry (SpO_2), SAP, MAP and DAP, and capnography, which provided respiratory rate (f_R) and end-tidal carbon dioxide partial pressure ($P_E'CO_2$), were monitored in the preparation area with a multi-channel monitor (PM-9000 Express, Mindray Medical International Ltd, China). The f_R was manually counted over 30 seconds in the awake dog. Another multichannel monitor (CC5; Cardiocap/5, GE

Datex Ohmeda, Canada) was used to monitor the same variables except ECG and SpO_2, while the animals were in the magnetic resonance room. The SpO_2 was monitored by a separate magnetic compatible pulse-oximeter (Nonin 8600v, Nonin Medical Inc, Minnesota, USA). Similarly, in the CT room, variables were monitored with a CC5 or PM-9000 monitor, depending on the availability of the equipment.

The arterial catheter was connected by non-compliant extension tubing (Arterial Pressure Tubing, ICU Medical Inc, Califonia, USA) to a pressure transducer (Transducer set; Becton Dickinson Critical Care System Pte, Ltd, Singapore) and the multi-channel monitor for determination of SAP, MAP and DAP, and pulse contour cardiac output measurement (PulseCO hemodynamic monitor, LiDCO Ltd, UK). With the dog in lateral recumbency, the level of the right atrium was assumed to be at the level of the manubrium and used as the zero reference for all blood pressure determinations. The equipment used for blood pressure measurement was assessed for accuracy at 100 mmHg against a mercury manometer (Mercurial Sphygmomanometer, Japan) at the start of each study day. The infrared airway gas monitor was calibrated daily with gases (Anesthesia calibration gases, Scott Medical Products, Pennsylvania, USA) specific for the monitor and attached to a line sampling at the mouth end of the endotracheal tube.

Arterial blood was sampled from the dorsal pedal arterial catheter less than 5 minutes before every lithium cardiac output measurement (LiDCO plus Hemodynamic Monitor, LiDCO Ltd, UK) and analyzed immediately for arterial partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), pH, hemoglobin (Hb), lactate (Lac) and electrolyte concentrations including sodium (Na^+), potassium (K^+) and chloride (Cl^-) (ABL 750; Radiometer, Denmark). The remaining arterial blood was placed on ice and used to determine hematocrit and total proteins on the same day. Rectal temperature (Temp; ^0C) was measured at each blood gas determination.

Cardiac output measurement

The CC5 monitor was connected to the LiDCO to allow for PulseCO determinations using a 1-volt analog signal for 100 mm Hg pressure. With each LiDCO determination the PulseCO monitor was calibrated with the LiDCO. Steps for preparing the lithium sensors (Flow through Cell Electrode Assembly, CM10, LiDCO Ltd, UK), checking for suitable sensor voltage and stable baseline signal were as described in the operation manual (LiDCO Plus Hemodynamic Monitor User's Manual 1.0, LiDCO Ltd, UK). For LiDCO determinations, lithium chloride (6 μmol kg^{-1}) (Lithium Chloride Injection, LiDCO Ltd, UK) was injected rapidly into the cephalic vein catheter 6 seconds after starting the injection phase on the LiDCO computer and simultaneously arterial blood was withdrawn by a peristaltic pump (LiDCO Flow Regulator; LiDCO Ltd, UK) into a disposable blood collection bag (Disposable blood collection bag and tube; LiDCO) at a flow of 4 mL $minute^{-1}$ across the lithium sensor. Cardiac index, stroke volume index and systemic vascular resistance index were calculated from the CO measured by LiDCO (CIL, SVIL, SVRIL) and cardiac index from the PulseCO (CIP) using the formulas below and assuming a central venous pressure (CVP) of 5 mmHg.

Cardiac index (mL kg^{-1} min^{-1}) = CO (mL min^{-1}) ÷ body weight (kg)

Stroke volume index (mL kg^{-1} $beat^{-1}$) = CI ÷ HR

Systemic vascular resistance index (mmHg mL^{-1} min^{-1} kg^{-1}) = (MAP – CVP) ÷ CI

Anesthesia

With the dogs in lateral recumbency and attached to the multichannel monitor for continuous measurement of HR, SAP, MAP and DAP, PulseCO, and ECG, fentanyl (7 μg kg^{-1}, IV) was administered (Fentanyl 50 μg mL^{-1}, Sandoz Canada Inc, Canada). Dogs were randomly assigned to one of 4 treatments for anesthetic induction with propofol (Propofol 10

mg mL^{-1}, Pharmascience Inc, Canada) or alfaxalone (Alfaxan® 10 mg mL^{-1}, Jurox Pty Limited, Australia) with or without midazolam (Midazolam 5 mg mL^{-1}, Pharmaceutical Partners of Canada Inc, Canada) or saline (0.9% Sodium Chloride, Hospira, Canada) and maintained by TIVA with respective injectable agent as follows; Treatment P-M: propofol (1 mg kg^{-1}, IV) and midazolam (0.3 mg kg^{-1}, IV); Treatment A-M: alfaxalone (0.5 mg kg^{-1}, IV) and midazolam (0.3 mg kg^{-1}, IV); Treatment PS: propofol (1mg kg^{-1} IV) and an equal volume of saline (0.06 mL kg^{-1}, IV); Treatment A-S: alfaxalone (0.5 mg kg^{-1} IV) and an equal volume of saline (0.06 mL kg^{-1} IV). Initial doses of propofol or alfaxalone were administered as a bolus, flushed with 2 mL of saline IV and then the midazolam or an equal volume of saline was immediately administered. An additional 25% of bolus dose of propofol or alfaxalone was administered every 6 seconds upon request until successful endotracheal intubation could be performed (MS). No attempts to intubate were made until confirmed loss of lateral palpebral reflex and then relaxation of jaw tone occured.

Once intubated, dogs were maintained on TIVA with the same induction anesthetic, administered via syringe pump (Medfusion 3500, Smiths Medical Canada, Canada; Graseby 3500 Anesthesia Pump; Smiths Medical International Ltd, UK) at the following initial rates: 250 µg kg^{-1} $minute^{-1}$ of propofol or 70 µg kg^{-1} $minute^{-1}$of alfaxalone. Dogs were connected to an anesthetic machine with a rebreathing circuit (Universal F-Circuit; Dispomed, Canada) using an oxygen flow of 1.5-2.5 L $minute^{-1}$. A manual breath was administered if the dog did not spontaneously ventilate for longer than 30 seconds in the first 15 minutes after induction. Thereafter, mechanical ventilation was initiated with a tidal volume of 10 mL kg^{-1} and f_R adjusted to $P_E'CO_2$ between 35 and 45 mmHg.

For the MRI, earplugs were placed in the ears and the dogs were disconnected from the anesthesia machine and monitor, transferred into the magnetic bore and positioned in dorsal recumbency. In the MRI acquisition room, the dogs were connected to another

anesthesia machine and monitor, both non-MRI compatible and therefore situated next to the control room workstation; the anesthetic machine was previously set up with breathing hoses that reached from the patient to the machine, and the monitor set up with extension tubing that reach the arterial catheter (944 cm). Intermittent depth assessments between the scan sequences were done by an anesthetist unaware of treatment allocation (PL).

For the CT scan, the dogs were transferred to the CT acquisition room with the induction anesthetic machine and PM-9000 monitor or switched to a separate anesthetic workstation and the CC5 monitor depending on the availability of anesthetic equipment. The dogs were positioned in the gantry in sternal recumbency. Depth of anesthesia was evaluated by an anesthetist unaware of treatment allocation (PL).

Adjustments to the TIVA rate, based on physical signs and physiological variables, were made every 5 minutes to maintain a light plane of anesthesia. Signs of inadequate depth included movement, brisk palpebral reflex, increased jaw tone, spontaneous blinking, or continual increases in HR, f_R or SAP, MAP and DAP. When inadequate depth was present, TIVA rates were adjusted by 25 μg kg^{-1} $minute^{-1}$ for propofol and 7 μg kg^{-1} $minute^{-1}$ for alfaxalone for minor depth change requirements. When a rapid increase in depth was warranted, top-up doses of propofol (0.25 mg kg^{-1}) or alfaxalone (0.125 mg kg^{-1}) were administered. Anesthetic administration rate was decreased when a progressive decrease in arterial pressure was noted, without respiratory fluctuations or attempts to ventilate spontaneously during mechanical ventilation, in addition to lack of palpebral reflexes and jaw tone. Hypotension was defined as MAP < 60 mmHg for more than 5 minutes. Hypotension was treated with an infusion of dopamine (2–10 μg kg^{-1} $minute^{-1}$) at the anesthetist's discretion if depth adjustment was not sufficient to reestablish normotension.

Cardio-pulmonary measurements

Cardio-pulmonary measurements were recorded in 4 different phases: 1) before and after fentanyl sedation (SED), 2) immediately after induction and for 15 minutes during spontaneous ventilation followed by commencement of intermittent positive pressure ventilation before the imaging procedure (IND), 3) during the CT or MRI imaging (PROC), and 4) after imaging prior to recovery from anesthesia (END). Following instrumentation the following phase measurements were recorded: SED: HR, f_R and SAP, MAP, and DAP were recorded before (S-30), and 4 minutes after fentanyl (S-34); IND: HR, f_R, SAP, MAP, DAP, SpO_2, and $P_E'CO_2$ were recorded immediately after endotracheal intubation (I-0) and every 5 min for 15 min (I-5, I-10, I-15) with spontaneous ventilation in lateral recumbency and then at 20 minutes after IPPV started (I-20) and prior to PROC; PROC: HR, f_R, SAP, MAP, DAP, SpO_2, and $P_E'CO_2$ were performed every 5 minutes (P-0 to P-55); END: HR, f_R, SAP, MAP, DAP, SpO_2, and $P_E'CO_2$ were performed once the dog was back to the induction area (E-0) and 5 minutes later (E-5). LiDCO was measured at S-34, I-15 and E-5, and PulseCO was measured during IND, and END, but not during PROC.

Statistical analysis

Statistical analyses were performed with standard computer software (SAS OnlineDoc 9.2; SAS Institute Inc., North Carolina, USA). Normality of data was tested using Shapiro-Wilk, Kolmogorov-Smirnov, Cramer-von Mises, and Anderson-Darling tests (Proc UNIVARIATE, SAS). Continuous data that were not normally distributed were log transformed for analysis, unless log transformation provided no improvement to distribution. A general linear mixed model was used to model the results using Proc MIXED. Fixed effects for HR, SAP, MAP, DAP, f_R, and $P_E'CO_2$ were treatment, imaging procedure, phase and time points; for CI, SVI, SVRI, temperature, and arterial blood gas analysis they were

treatment, imaging procedure and phases, including up to three-way interactions. Phases and time points were as outlined in the methods for analysis. Dog was considered a random effect and treated as a blocking variable. To model for the effects of repeated measures over time for HR, SAP, MAP, DAP, f_R, and $P_E'CO_2$ on each dog, due to treatment and within a specific event of anesthesia, the following correlation structures, offered by SAS, were attempted: ar(1), arh(1), sp(pow)(time), toep, banded toep, toeph, banded toeph, and un and banded un. The error structure, among those that converged, was chosen based upon the lowest Akaike Information Criteria. Terms in the model were removed if non-significant, but preserving model hierarchy. Appropriate adjustments (Tukey or Dunnet test) for multiple comparisons were used. The chi square test was used to test if significant associations in the proportion of dopamine infusions between imaging modalities and treatments. Significance was set at $p < 0.05$. Residuals were examined to assess the ANOVA assumptions and plotted against the predicted values and the explanatory variables used in the model. Such analyses help reveal outliers, unequal variance, the need for data transformation, and other issues that need addressing.

The results are presented with adjusted mean if data are normally distributed or ordinal and adjusted median if not normally distributed based on a log transformation with 95% confidence interval (CI). The adjustment was done by applying standard ANOVA least-squares methods to estimate and test the results as if the data were in a complete Latin-square, crossover design. When comparing between treatments, for those normally distributed continuous data and ordinal data, the effect size is provided as the difference between treatments with 95% CI. The *p*-value is provided for those not normally distributed and log transformed.

RESULTS

Data for all the cardio-pulmonary variables, TIVA rate, f_R, Hb, PaO_2, and HCO_3^- were not normally distributed. All dogs recovered without complications from anesthesia. The PROC duration ranged from 35-55 min and was not significantly different between treatments and data during this phase are reported for up to 40 minutes only.

The mean (95% CI) induction dose for the 4 treatments during cardio-pulmonary measurements was: P-S 2.1 mg kg^{-1} (1.8 - 2.3); P-M 1.5 mg kg^{-1} (1.3 - 1.8); A-S 0.98 mg kg^{-1} (0.7 - 1.2); and A-M 0.62 mg kg^{-1} (0.4 - 0.9). The overall median TIVA rate (95% CI) of the P-S, P-M, A-S and A-M were 310 μg kg^{-1} min^{-1} (274 - 351), 268 μg kg^{-1} min^{-1} (233 - 309), 87 μg kg^{-1} min^{-1} (77 - 98), and 83 μg kg^{-1} min^{-1} (74 - 94), respectively. Detailed induction and TIVA dosing results are presented elsewhere (Liao et al. 2015a; Liao et al. 2015b).

The HR, SAP, MAP and DAP are presented in Figure 3 and Table 6. Heart rate decreased after fentanyl administration in all treatments (phase SED), although this change was not significant. For the P-M treatment, HR during SED was higher than PROC (p = 0.003). During IND, HR for A-M was significantly higher than A-S (p = 0.049) and P-S (p < 0.001). During PROC, HR for A-S (p = 0.012) and A-M (p = 0.021) were higher than P-S. During END, HR for A-M was higher than P-S (p = 0.009). For specific times during IND, there were no differences between treatments; HR decreased significantly in all treatments at I-5 with respect to I-0 (p = 0.037), I-15 (p = 0.006), and I-20 (p < 0.001). The HR was also significantly higher at I-20 than at I-0 (p = 0.048). The HR at END was significantly lower than for all other phases (p < 0.001).

The HR was significantly higher during the CT1 for A-S (p = 0.028), A-M (p = 0.028), and P-M (p = 0.028) than for P-S; during the CT2, HR in the A-M treatment was significantly higher than A-S (p = 0.012) and P-S (p = 0.001); and during MRI there were no

differences between treatments. Comparisons between imaging modalities within treatments resulted in higher HR for A-S during CT1 than for CT2 ($p = 0.013$) and MRI ($p = 0.042$), while for A-M the HR during CT2 was higher than for MRI ($p = 0.006$).

Systolic arterial pressure in the A-S treatment was significantly higher than A-M ($p < 0.001$) and P-M ($p = 0.001$). The SAP of all treatments at S-34 was significantly higher than other time points ($p < 0.001$). During induction, the SAP of all treatments at I-0 was significantly higher than I-5 to I-20 ($p < 0.001$), and I-15 was also higher than I-20 ($p = 0.001$). During CT2, the SAP of all treatments at IND was significantly higher than PROC ($p = 0.002$). The SAP of all treatments at P-35 ($p = 0.001$) and P-40 ($p < 0.001$) was significantly higher than at P-0. During the MRI, the SAP of all treatments was significantly lower during PROC than for other phases ($p < 0.001$), as well as lower than CT1 ($p < 0.001$) and CT2 ($p = 0.036$). The DAP followed similar trends to SAP.

The MAP of all treatments was significantly higher at S-34 than for the rest of the time points ($p < 0.001$). The MAP in SED had imaging and treatment differences as follows: A-M resulted in higher MAP during MRI than CT1 ($p = 0.045$); P-M resulted in higher MAP during CT1 ($p = 0.009$) and CT2 ($p = 0.012$) than MRI; MAP was higher in A-M than P-M during CT1 ($p = 0.049$). There were no significant treatment differences for MAP during IND; however, the MAP at I-0 was significantly higher than I-5 to I-20 ($p < 0.001$) for CT2 and MRI, and higher than I-10 to I-20 in CT1 ($p < 0.001$).

Differences in MAP were associated with the phase of the research but not the treatment. The MAP was significantly lower at the time of PROC than for other phases ($p < 0.001$). Despite the lack of a treatment effect, the MAP of P-M, A-S, and A-M increased significantly at END after the MRI, but remained low in the P-S treatment.

Comparisons between imaging modalities showed a higher MAP during both the CT1 ($p = 0.013$) and CT2 ($p < 0.001$) than during the MRI in A-S; a higher MAP during the CT1

than during the CT2 ($p < 0.001$) and MRI ($p < 0.001$) in A-M; and a higher MAP during CT1 than during the MRI ($p < 0.001$) in P-S. In addition, the MAP of A-M during the CT1 was higher than for P-M ($p = 0.043$); the MAP of A-S during the CT2 was higher than for A-M ($p = 0.012$).

The CIL and CIP were similar between treatments (Table 7 and Table 8) and both were significantly higher during SED and IND than during END ($p < 0.001$).

The SVIL during SED was significantly higher than during IND ($p < 0.001$) and END ($p < 0.001$). The SVRIL during SED and END was significantly higher than during IND ($p < 0.001$).

The need for dopamine was not significantly different between treatments and imaging modalities, despite the use of dopamine to treat hypotension in 30.4% of cases in the MRI during PROC as follows: 10% in A-S; 0% in A-M, 22.2% in P-S, and 44.4% in P-M. Dopamine was not necessary during the CT1 and CT2.

Respiratory variables are presented in Table 9. The *f*R was significantly higher in all treatments at S-34 than at the other time points ($p < 0.001$), and the *f*R at I-0 was significantly lower than at other time points ($p < 0.001$). There were no significant differences in the occurrence of apnea between treatments: A-S (9 out of 10 dogs), A-M (6 out of 9), P-S (5 out of 9), and P-M (7 out of 9). The $P_E'CO_2$ was not significantly different between treatments, but was higher during IND than PROC ($p < 0.001$) and END ($p < 0.001$), and PROC was significantly higher than END ($p = 0.037$).

There were no significant treatment differences in blood gas analysis, but there were significant differences between phases (Table 10). The pH was significantly higher during SED than IND ($p < 0.001$) and END ($p < 0.001$), and significantly higher during END than IND ($p < 0.001$). The $PaCO_2$ was significantly higher during IND than SED ($p < 0.001$) and END ($p < 0.001$), and significantly higher during END than SED ($p < 0.001$). The PaO2 was

significantly higher during END than SED ($p < 0.001$) and IND ($p = 0.018$), and significantly higher during IND than SED ($p < 0.001$). The Na^+ was significantly higher during IND than SED ($p < 0.001$) and END ($p = 0.002$). The K^+ was significantly higher during END than SED ($p = 0.001$) and IND ($p < 0.001$), and significantly higher during SED than IND ($p < 0.001$). The Cl^- was significantly higher during SED ($p < 0.001$) and IND ($p < 0.001$) than END. The Hb was significantly higher during SED ($p < 0.001$) and IND ($p < 0.001$) than END. The Hb of A-S was significantly higher than P-M ($p = 0.024$). The lactate was significantly higher during IND than SED ($p < 0.001$) and END ($p < 0.001$). The temperature was significantly higher during SED than END ($p < 0.001$) and IND ($p < 0.001$), and was significantly higher during IND than END ($p < 0.001$).

DISCUSSION

This investigation demonstrated no differences in cardiovascular or respiratory variables during induction with propofol or alfaxalone with or without midazolam co-induction in healthy fentanyl sedated research dogs. In addition, no difference in cardiovascular variables was noted with either propofol or alfaxalone TIVA with mechanical ventilation during diagnostic imaging or in the recovery phase. Despite a dose reduction in requirements for propofol and alfaxalone demonstrated with midazolam co-induction (Hopkins et al. 2013; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Liao et al. 2015a) we did not demonstrate a benefit in cardio-pulmonary function. Currently only a few investigations have assessed cardio-pulmonary variables during induction. One study compared the effects of propofol with or without midazolam co-induction on indirect blood pressure in healthy dogs and demonstrated lower blood pressures when midazolam co-induction was included (Hopkins et al. 2013). We did not demonstrate a difference in blood pressure using a more accurate method of direct measurement. Moreover, additional measurements, not previously reported and included in our study, of cardiac output and derived hemodynamic variables were also similar between treatments receiving co-induction midazolam and those receiving the induction anesthetic alfaxalone or propofol alone.

One potential explanation for the lack of significant improvement in hemodynamic function may be related to the use of healthy research dogs, since the decrease in cardio-pulmonary function after induction with potent anesthetics mainly originates from sympatholysis, rather than direct injectable anesthetic depression. It has been demonstrated that within a clinical range of propofol plasma concentrations (less than 10 μg mL^{-1}) (Joubert 2009), direct myocardial depression and arterial vasodilation is minimal (Ismail et al. 1992; Nakamura et al. 1992; Belo et al. 1994) in dogs. An earlier study also demonstrated that the

decrease in systemic vascular resistance caused by propofol was more pronounced after autonomic abolishment than within clinical plasma concentrations in dogs (Goodchild & Serrao 1989). The decrease in HR, MAP, and CI observed immediately after induction (I-0) may also be related to physiological changes, since similar drops of 10% – 20% in HR, MAP, and CI have been determined in chronically instrumented healthy research dogs after falling asleep and undergoing sympatholysis (Schneider et al. 1997).

There are no similar reports detailing the cardiovascular effects of alfaxalone during induction. However, in a study comparing cardio-pulmonary function after induction with tiletamin/zolazepam, ketamine/diazepam, propofol, and alfaxalone in healthy research dogs, no differences were noted (De Caro Carella et al. 2015). It is important to note that healthy research dogs might not be a suitable model to represent the cardio-pulmonary effects of induction anesthetics in sick animals, and that the possible benefits of co-induction agents may only be apparent in sick and critically ill patients.

Arterial blood pressure is a useful and commonly used variable to assess the safety of anesthesia. In our study, MAP gradually decreased to the 60 – 70 mmHg range after induction, and remained in that range during the imaging procedures, similar to other studies comparing propofol and alfaxalone in healthy research dogs without surgery (Ambros et al. 2008). Higher MAP value of 70 – 110 mmHg have been reported in another study comparing propofol and alfaxalone TIVA in client-owned dogs undergoing ovariohysterectomy (Suarez et al. 2012). Sympathetic stimulation from surgery is responsible for this difference and also demands a higher TIVA rate (Ambros et al. 2008; Suarez et al. 2012; Reed et al. 2015). Considering these differing study results, the impact of stimulation needs to be taken into consideration when interpreting the cardiovascular data in anticipation of what would be noted in clinical patients.

Midazolam co-induction decreased the TIVA rate of propofol throughout the

maintenance period of anesthesia, but this reduction in dose was not associated with cardiovascular differences between P-S and P-M in our study. Similar findings have been shown in human patients in which MAP was even lower if a midazolam infusion was added to the maintenance rate in addition to its use as co-induction (Adams et al. 2002).

Interestingly, the MAP during MRI tended to be lower than during CT in all treatments except for the P-M treatment. In addition, MAP was lower during the MRI imaging than during any other study phase in all treatments. In a similar study using patients with clinical neurological disease, there were no differences in MAP between the MRI imaging and other phases of anesthesia, and MAP remained within 80 – 90 mmHg in that study, although some patients required dopamine support (Caines et al. 2014). Compared to the current study, in which MAP was approximately 60 during MRI, the propofol rate used was similar and the same criteria were used to institute a dopamine infusion to treat for hypotension. Therefore it seems likely that differences in MAP between the two studies are related to several factors, including the health status of the animal and sympathetic drive, which is likely increased in critical or compromised patients. Another possible explanation for the lower MAP during the MRI with respect to the CT scans is the noise generated by the MRI, which may affect the depth of anesthesia and the dose of TIVA for maintenance. In human patients under propofol sedation, noise has been shown to increase consciousness (Kim et al. 2001) and less propofol is required when the noise is blunted (Tharahirunchot et al. 2011). We placed earplugs in our dogs during the MRI scan and a lower rate was required during the imaging for the MRI than the CT1, but not the CT2. Additionally, although CT image acquisition is quieter then MRI, CT image acquisition involves movement of the patient table within the gantry, which can reasonably be expected to be stimulating. Another factor contributing to differences in MAP is the dorsal positioning of dogs in MRI versus sternal for CT. Cardio-pulmonary effects between right lateral and dorsal recumbency

showed that HR was 33% higher, SAP, MAP and DAP were 30% lower, and systemic vascular resistance was 17% lower in dogs in dorsal recumbency (Gartner et al. 1996).

A decrease in CI associated with a decrease in HR was observed after completion of the procedures in all treatments. Dogs were positioned in lateral recumbency for recovery and the decrease in HR could be the result of an arterial baroreflex that resulted from an increase in SVRI secondary to increased sympathetic activity from the stimulation of being moved.

There were no significant differences regarding the occurrence of apnea or hypoventilation between all treatments, similar to other studies (Ambros et al. 2008; Amengual et al. 2013; Maney et al. 2013). Apnea with alfaxalone does not occur in healthy unsedated dogs until 10 times the clinical dose is administered (20 mg kg^{-1}), while propofol caused apnea in 2 out of 6 dogs with 5 times clinical dose (32 mg kg^{-1}) (Keates & Whittem 2012). The occurrence of apnea and hypoventilation are dose-dependent in both propofol and alfaxalone (Muir & Gadawski 1998; Muir et al. 2008; Keates & Whittem 2012) and midazolam co-induction did reduce both propofol and alfaxalone induction dose and P TIVA rate. However, midazolam causes respiratory depression in the presence of other anesthetics (Heniff et al. 1997) even though it is clinically deemed to cause minimal respiratory depression when used alone.

In conclusion, this study demonstrates that, despite a reduction in the induction and TIVA dose of propofol or alfaxalone when midazolam is used as a co-induction drug, there was no significant difference between treatments in cardio-pulmonary variables in healthy research dogs during the induction phase, TIVA maintenance for advanced imaging, or the recovery phase. The MAP pressure during MRI with dorsal positioning was lower than during CT imaging, necessitating dopamine infusion in 30% of cases. Overall, the cardiovascular effects of TIVA with propofol and alfaxalone for imaging were comparable in the current study.

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Figure 2. Study timeline with administration of fentanyl (F); propofol (P) or alfaxalone (A) with either saline (S) or midazolam (M); initiation (//) and discontinuation (//) of total intravenous anesthesia (TIVA) indicated. The arrows between phases indicated transfer of dogs and hence interruption of monitoring.

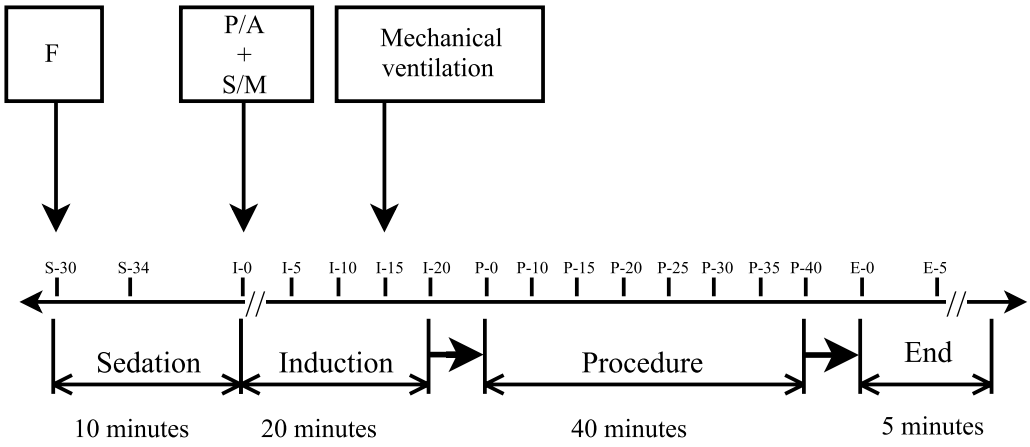
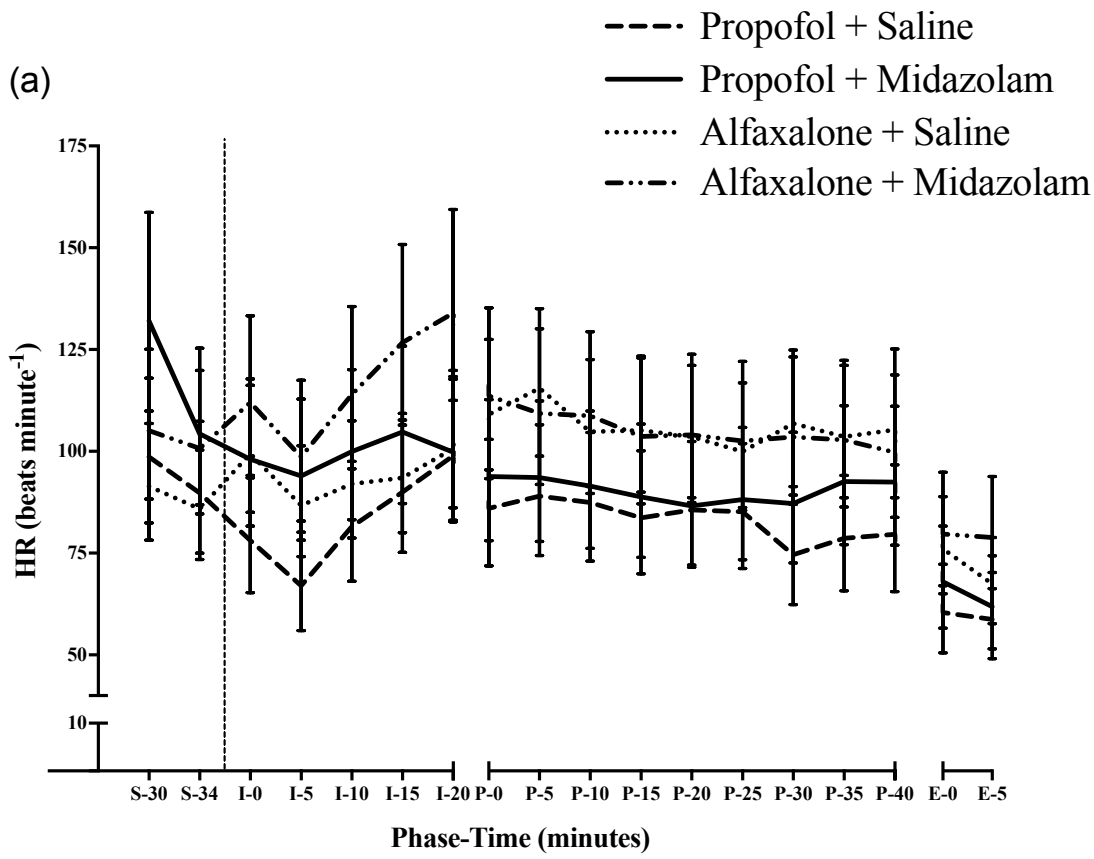


Figure 3. Median and 95% confidence interval for (a) heart rate (HR), (b) mean (MAP) arterial pressure in dogs randomly assigned to one of the four treatments: Propofol (P) + Midazolam (M) (PM); Alfaxalone (A) + M: (AM); P + saline (S) (PS); and A + S (AS). Treatments were as follows: Fentanyl (F) (7 μg kg^{-1}, IV) was administered 10 minutes prior to an initial IV bolus of P (1 mg kg^{-1}) or A (0.5 mg kg^{-1}). Either M (0.3 mg kg^{-1}, IV) or S was administered immediately after the initial P or A bolus followed by additional boluses of the respective induction drug every 6 seconds to allow endo-tracheal intubation and then followed by total intravenous anesthesia with the same induction anesthetic. Time points are presented with phase-time, in which phases include SED, 30 minutes before sedation with F (S-30) and 4 minutes after F (S-34); IND, at the time of intubation after administration of the induction anesthetic (I-0), and 5 (I-5), 10 (I-10), and 15 (I-15) minutes while breathing spontaneously, and at 20 (I-20) minutes once on mechanical ventilation; PROC, at the beginning of the imaging procedure (P-0) and every 5 minutes for up to 40 minutes (P-40) during imaging; and END, once the dog returned to the induction area (E-0) and 5 minutes later (E-5), prior to recovery . The dotted vertical line indicates induction.


(a)
Propofol + Saline
Propofol + Midazolam
Alfaxalone + Saline
Alfaxalone + Midazolam
HR (beats minute-1)
175
150
125
100
75
50
10
S-30 S-34 I-0 I-5 I-10 I-15 I-20 P-0 P-5 P-10 P-15 P-20 P-25 P-30 P-35 P-40 E-0 E-5
Phase-Time (minutes)

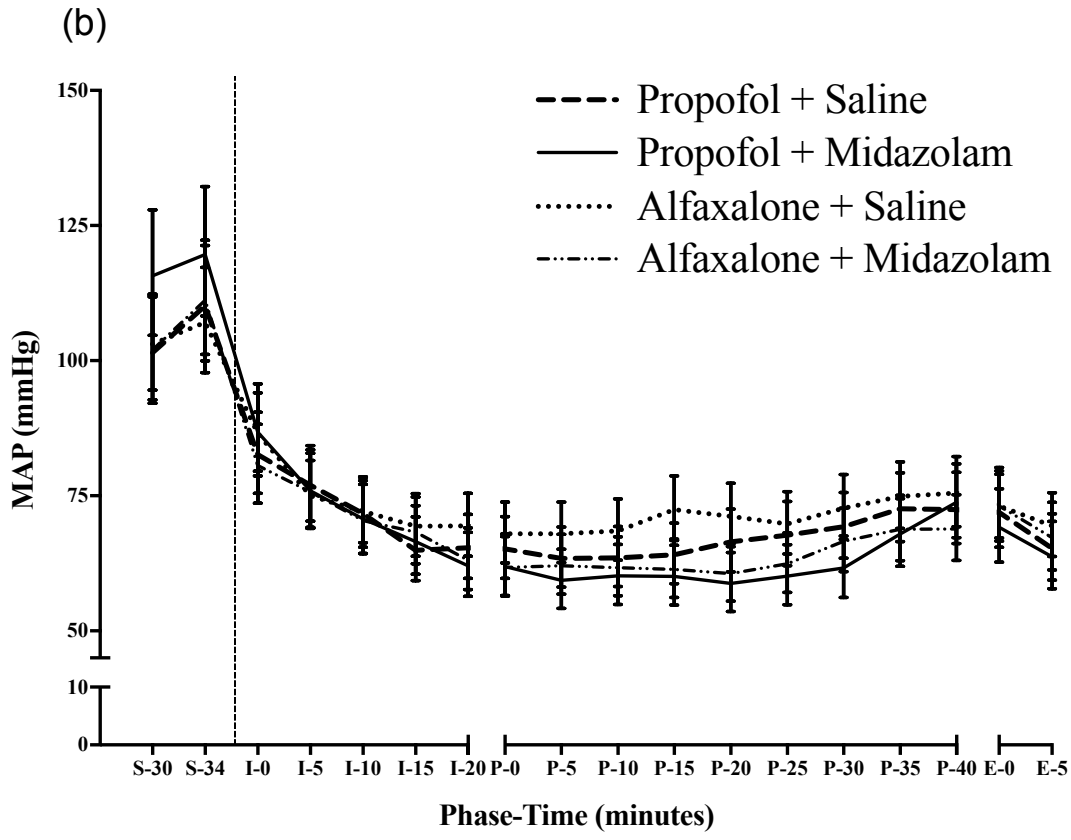

(b)
Propofol + Saline
Propofol + Midazolam
Alfaxalone + Saline
Alfaxalone + Midazolam
MAP (mmHg)
150
125
100
75
50
10
0
S-30 S-34 I-0 I-5 I-10 I-15 I-20 P-0 P-5 P-10 P-15 P-20 P-25 P-30 P-35 P-40 E-0 E-5
Phase-Time (minutes)

Table 6. Median and 95% confidence interval for systolic (SAP) and diastolic (DAP) blood pressure. (see Figure 3 for key).

		PS[*+]	PM[+]	AS[*]	AM[+]
SAP (mmHg)	S-30[a]	139.7 (126.4 - 154.4)	149.3 (134.3 - 165.9)	140.3 (127.6 - 154.3)	142.5 (128.8 - 157.7)
	S-34[A]	171.6 (155.3 - 189.6)	167.5 (150.7 - 186.2)	161.5 (146.2 - 178.3)	170.6 (154.2 - 188.8)
	I-0[aB]	128.5 (116.5 - 141.6)	126.4 (113.4 - 141)	134.4 (122.3 - 147.6)	120.1 (108.7 - 132.7)
	I-5[ab]	119.7 (108.6 - 132)	112.7 (101.7 - 125)	121.7 (110.9 - 133.7)	112.8 (102.1 - 124.5)
	I-10[ab]	109.9 (99.7 - 121.2)	103.1 (93 - 114.3)	114.7 (104.5 - 125.9)	105.4 (95.5 - 116.4)
	I-15[abC]	100.3 (91 - 110.6)	97.1 (87.6 - 107.6)	109.8 (100 - 120.6)	101.5 (91.9 - 112.1)
	I-20[abc]	93.6 (84.9 - 103.2)	86.6 (78.0 – 96.0)	108.7 (99 - 119.4)	87.0 (78.7 - 96.1)
	P-0[aD]	92 (83.6 - 101.3)	85.2 (76.8 - 94.4)	91.3 (83.2 - 100.3)	81.4 (73.7 – 90.0)
	P-5[a]	85.7 (77.8 - 94.4)	80.2 (72.4 - 88.9)	91.9 (83.7 - 100.8)	83.9 (75.9 - 92.7)
	P-10[a]	84.4 (76.7 – 93.0)	81.2 (73.4 – 90.0)	92.1 (83.9 - 101.1)	83.8 (75.9 - 92.6)
	P-15[a]	85.5 (77.6 - 94.2)	81.6 (73.7 - 90.4)	98.4 (89.7 - 108)	82.9 (75.1 - 91.5)
	P-20[a]	89.5 (81.2 - 98.5)	81.3 (73.4 – 90.0)	97.9 (89.2 - 107.4)	84.9 (77.0 - 93.7)
	P-25[a]	92.3 (83.8 - 101.6)	84.7 (76.5 - 93.8)	95.4 (87.0 - 104.7)	87.4 (79.2 - 96.4)
	P-30[a]	97.4 (88.5 - 107.3)	85.8 (77.5 – 95.0)	99.8 (91.0 - 109.5)	92.3 (83.6 - 101.8)
	P-35[ad]	104.9 (95.2 - 115.5)	94.2 (85.1 - 104.4)	104 (94.8 - 114.1)	95.3 (86.4 - 105.2)
	P-40[ad]	104.6 (94.5 - 115.6)	102.9 (92.9 - 114.1)	106.6 (96.7 - 117.5)	98.6 (89.3 - 108.9)
	E-0[a]	112.5 (101.9 - 124.2)	100.1 (90.1 - 111.2)	114.8 (104.5 - 126.2)	102.5 (92.7 - 113.4)
	E-5[a]	99.9 (90.5 - 110.2)	99.1 (89.2 - 110.1)	110.3 (100.4 - 121.2)	97.4 (88.1 - 107.8)
DAP (mmHg)	S-30[a]	87.7 (79.5 - 96.7)	91.9 (82.8 - 102.1)	85.6 (78.0 – 94.0)	87.6 (79.3 - 96.8)
	S-34[A]	91.2 (82.7 - 100.6)	92.1 (83.0 - 102.3)	85.2 (77.3 - 93.8)	87.8 (79.5 – 97.0)

I-0^{aB}	61.1 (55.5 - 67.2)	71.2 (64.0 - 79.2)	69.2 (63.1 - 75.9)	64.6 (58.5 - 71.3)
I-5^{ab}	60.2 (54.7 - 66.3)	62.3 (56.3 – 69.0)	59.8 (54.5 - 65.6)	60.5 (54.9 - 66.7)
I-10^{ab}	55.5 (50.4 - 61.1)	57.5 (51.9 - 63.6)	57.9 (52.9 - 63.5)	56.0 (50.8 - 61.7)
I-15^{ab}	52.9 (48.0 - 58.2)	52.7 (47.6 - 58.4)	56.1 (51.2 - 61.5)	54.7 (49.6 - 60.3)
I-20^{ab}	50.8 (46.1 - 55.9)	50.5 (45.6 – 56.0)	55.7 (50.8 - 61.1)	51.3 (46.5 - 56.6)
P-0^{aC}	53.6 (48.7 - 58.9)	50.1 (45.3 - 55.5)	54.6 (49.8 - 59.8)	54.7 (49.6 - 60.3)
P-5^{a}	53.2 (48.4 - 58.5)	52.2 (47.2 - 57.7)	55.5 (50.7 - 60.8)	55.4 (50.2 - 61.1)
P-10^{a}	53.6 (48.7 - 58.9)	53.7 (48.6 - 59.4)	57.3 (52.3 - 62.7)	54.3 (49.3 - 59.9)
P-15^{a}	54.8 (49.9 - 60.3)	53.9 (48.8 - 59.6)	59.4 (54.2 – 65.0)	54.7 (49.7 - 60.3)
P-20^{a}	57.3 (52.1 – 63.0)	52.8 (47.7 - 58.4)	59.4 (54.2 - 65.1)	54.2 (49.2 - 59.7)
P-25^{a}	57.7 (52.5 - 63.4)	54.5 (49.3 - 60.2)	58.2 (53.1 - 63.7)	55.9 (50.8 - 61.6)
P-30^{ac}	58.4 (53.1 - 64.2)	54.0 (48.8 - 59.7)	60.6 (55.3 - 66.4)	59.3 (53.8 - 65.3)
P-35^{ac}	60.3 (54.9 - 66.3)	60.7 (54.9 - 67.1)	62.1 (56.7 – 68.0)	60.3 (54.7 - 66.4)
P-40^{ac}	60.8 (55.1 - 67.1)	66.7 (60.2 - 73.8)	61.8 (56.2 – 68.0)	59.5 (54.0 - 65.6)
E-0^{aD}	57.5 (52.1 - 63.3)	60.5 (54.6 - 67.1)	61.9 (56.4 - 67.9)	60.3 (54.6 - 66.6)
E-5^{ad}	51.9 (47.1 - 57.2)	55.3 (49.8 - 61.3)	58.0 (52.9 - 63.7)	55.9 (50.7 - 61.8)

Same superscript letters but different case indicates there is a significant difference between time points. Different superscript symbols (* and +) indicates significant difference between treatments of SAP ($p < 0.05$).

Table 7. Median and 95% confidence interval for cardiac index (CIL), stroke volume index (SVIL) and systemic vascular resistance index (SVRIL) calculated from cardiac output (CO) measured by LiDCO. The CO was measured 4 minutes after sedation with fentanyl (7 μg kg^{-1}, IV) prior to induction (SED), 15 minutes after induction (IND) and 5 minutes after returning to the induction area prior to recovery (END). (see **Figure 3** for key).

		PS	PM	AS	AM
CIL (mL kg^{-1} min^{-1})	SED	158.50 (124.68 - 201.50)	123.44 (98.27 - 155.05)	136.29 (111.22 - 167.02)	172.92 (140.54 - 212.77)
	IND	133.45 (107.99 - 164.91)	117.25 (96.05 - 143.14)	122.16 (100.65 - 148.25)	136.44 (110.88 - 167.88)
	END*	80.07 (64.8 - 98.95)	77.64 (63.6 - 94.78)	86.94 (71.63 - 105.51)	81.71 (66.41 - 100.54)
SVIL (mL kg^{-1} $beat^{-1}$)	SED*	1.59 (1.32 - 1.93)	1.51 (1.27 - 1.79)	1.56 (1.34 - 1.82)	1.76 (1.50 - 2.06)
	IND	1.46 (1.24 - 1.73)	1.27 (1.09 - 1.48)	1.29 (1.12 - 1.50)	1.10 (0.94 - 1.29)
	END	1.30 (1.10 - 1.54)	1.29 (1.11 - 1.50)	1.34 (1.12 - 1.55)	1.17 (0.99 - 1.37)
SVRIL (mmHg mL^{-1} min^{-1} kg^{-1})	SED	0.67 (0.53 - 0.86)	0.84 (0.66 - 1.06)	0.75 (0.61 - 0.93)	0.63 (0.51 - 0.78)
	IND*	0.40 (0.35 - 0.54)	0.52 (0.42 - 0.64)	0.52 (0.43 - 0.64)	0.47 (0.38 - 0.58)
	END	0.75 (0.60 - 0.93)	0.79 (0.64 - 0.97)	0.75 (0.62 - 0.92)	0.75 (0.60 - 0.92)

There was a significant difference between phases but not between treatments.

* Significantly different from the other two phases ($p < 0.05$).

Table 8. Median and 95% confidence interval for cardiac index (CIP) calculated from cardiac output (CO) measured by PulseCO. Measurement was discontinued during imaging procedure. (see Figure 3 for key)

		PS	PM	AS	AM
CIP (mL kg^{-1} min^{-1})	S-34[ab]	167.6 (126.5 - 222)	140.8 (102.1 - 194.2)	138.4 (103.6 - 184.8)	132.1 (100.1 - 174.2)
	I-0[ab]	185 (143.5 - 238.7)	136.8 (103.1 - 181.4)	151.8 (113.5 - 203)	178.9 (137.6 - 232.6)
	I-5[ab]	155.4 (120.5 - 200.5)	129.2 (97.2 - 171.7)	158.6 (119 - 211.5)	162 (124.8 - 210.4)
	I-10[ab]	187.4 (145.3 - 241.7)	154.6 (117 - 204.2)	171.9 (129 - 229.2)	197 (151.7 - 255.8)
	I-15[ab]	170.3 (132.1 - 219.7)	149.4 (113.1 - 197.4)	132.6 (99.4 - 176.8)	145.5 (112.1 - 189)
	I-20[ab]	160.96 (124.8 - 207.62)	129.72 (97.84 - 172)	133.14 (99.55 - 178.07)	119.81 (92.14 - 155.78)
	E-0[a]	102.5 (79.5 - 132.2)	58.8 (44.3 - 78)	65.9 (50.2 - 86.5)	58.8 (45.2 - 76.4)
	E-5[b]	86.5 (67.1 - 111.6)	69.2 (52.3 - 91.4)	63.6 (48.6 - 83.3)	63 (48.5 - 81.9)

Different superscript letters indicates there is a significant difference between time points. ($p < 0.05$).

Table 9. Mean and 95% confidence intervals (CI) for respiratory rate (*f*R) and median and 95% CI end-tidal carbon dioxide ($P_E'CO_2$). The *f*R from I-0 – I-15 corresponds to spontaneous ventilation. The $P_E'CO_2$ during Proc and End are presented as the summation of the whole phase. (see Figure 3 and Table 6 and Table 7for key)

		PS	PM	AS	AM
*f*R (min^{-1})	S-0[a]	24.2 (19.1 – 29.2)	29.3 (24.9 – 33.7)	27.8 (23.5 – 32.0)	31.6 (27.6 – 35.7)
	S-30[a]	26.6 (22.6 – 30.5)	29.3 (24.9 – 33.7)	22.9 (18.8 – 27.0)	28.1 (24.1 – 32.1)
	S-34[a]	27.5 (20.7 – 34.3)	30.5 (23.8 – 37.2)	30.0 (25.3 – 34.7)	31.5 (25.9 – 37.1)
	I-0[b]	6.9 (3.2 – 10.6)	2.0 (-2.2 – 6.2)	0.5 (-0.3 – 4.2)	6.1 (2.3 – 9.9)
	I-5[c]	14.8 (11.1 – 18.5)	9.2 (5.0 – 13.4)	6.0 (2.2 – 9.7)	7.0 (3.1 – 10.8)
	I-10[c]	12.4 (8.6 – 16.2)	9.0 (4.8 – 13.2)	9.4 (5.6 – 13.1)	4.5 (0.7 – 8.3)
	I-15[c]	9.2 (5.5 – 12.9)	7.1 (2.9 – 11.3)	9.5 (5.7 – 13.2)	7.0 (3.2 – 10.9)
$P_E'CO_2$ (mmHg)	I-0[a]	33.9 (30.6 – 37.1)	40.3 (36.5 – 44.1)	39.0 (35.2 – 42.9)	38.6 (34.7 – 42.5)
	I-5[b]	38.8 (35.5 – 42.0)	40.1 (36.4 – 43.9)	42.3 (39.0 – 45.6)	46.3 (42.4 – 50.2)
	I-10[c]	43.7 (40.3 – 47.1)	45.2 (41.6 – 48.7)	47.0 (43.8 – 50.3)	48.9 (45.2 – 52.7)
	I-15[d]	47.5 (44.1 – 50.9)	50.3 (46.7 – 53.8)	48.8 (45.5 – 52.1)	52.9 (49.4 – 56.4)
	Proc	39.1 (37.4 – 40.9)	39.8 (37.8 – 41.7)	40.8 (39.2 – 42.4)	39.3 (37.6 – 41.0)
	End	37.9 (35.5 – 40.3)	38.6 (36.0 – 41.1)	39.2 (37.0 – 41.3)	38.6 (36.2 – 40.9)

Different superscript letters indicates there is significant difference between time points ($p < 0.05$).

Table 10. Median and 95% confidence interval for temperature and arterial blood gas analysis, including pH, arterial carbon dioxide (P_aCO_2), oxygen (P_aO_2) partial pressure, sodium (Na^+), potassium (K^+), chloride (Cl^-), hemoglobin (Hb), and lactate (Lac) concentration. (see Figure 3 and Table 6 for key).

		PS	PM	AS	AM
pH	SED[a]	7.37 (7.35 - 7.40)	7.36 (7.34 - 7.39)	7.36 (7.34 - 7.39)	7.35 (7.33 - 7.38)
	IND[b]	7.22 (7.20 - 7.25)	7.21 (7.18 - 7.24)	7.24 (7.22 - 7.27	7.21 (7.18 - 7.23)
	END[c]	7.31 (7.28 - 7.34)	7.30 (7.28 - 7.33)	7.31 (7.2 9 - 7.34)	7.31 (7.28 - 7.34)
P_aCO_2 (mmHg)	SED[a]	35.0 (31.3 - 38.7)	37.2 (33.6 - 40.7)	37.0 (33.5 - 40.5)	37.7 (34.2 - 41.3)
	IND[b]	53.9 (50.2 - 57.6)	55.9 (52.2 - 59.7)	50.0 (46.6 - 53.4)	56.2 (52.7 - 59.8)
	END[c]	43.0 (39.4 - 46.7)	43.6 (39.8 - 47.3)	43.3 (39.8 - 46.8)	43.0 (39.3 - 46.7)
P_aO_2 (mmHg)	SED[a]	86.1 (76.8 - 96.5)	83.8 (75.3 - 93.2)	84.3 (75.8 - 94.0)	86.6 (77.8 - 96.3)
	IND[b]	517.2 (461.5 - 579.6)	503.2 (449.6 - 563.3)	486.8 (439.5 - 539.1)	457.5 (411.0 - 509.2)
	END[c]	544.3 (485.7 - 610.0)	520.8 (465.3 - 582.9)	542.1 (486.8 - 603.6)	546.8 (488.2 - 612.4)
Na^+ (mmol L^{-1})	SED[a]	146.8 (145.5 - 148.0)	146.4 (145.0 - 147.7)	145.7 (144.5 - 146.9)	145.4 (144.1 - 146.7)
	IND[b]	147.9 (146.7 - 149.1)	147.3 (146.0 - 148.6)	147.0 (145.8 - 148.2)	147.6 (146.3 - 148.8)
	END[a]	146.0 (144.8 - 147.2)	147.1 (145.7 - 148.4)	146.7 (145.4 - 147.9)	146.9 (145.6 - 148.1)
K^+ (mmol L^{-1})	SED[a]	3.7 (3.5 - 3.9)	3.7 (3.5 - 3.8)	3.6 (3.5 - 3.8)	3.8 (3.6 - 3.9)
	IND[b]	3.4 (3.2 - 3.6)	3.3 (3.1 - 3.5)	3.3 (3.1 - 3.4)	3.4 (3.2 - 3.6)
	END[c]	4.0 (3.8 - 4.1)	3.9 (3.7 - 4.1)	3.7 (3.5 - 3.8)	3.8 (3.7 - 4.0)
Cl^- (mmol L^{-1})	SED[a]	118.3 (117.3 - 119.3)	117.0 (115.9 - 118.0)	117.4 (116.4 - 118.4)	117.5 (116.5 - 118.5)
	IND[a]	118.1 (117.1 - 119.1)	117.1 (116.1 - 118.2)	117.4 (116.4 - 118.4)	117.3 (116.3 - 118.3)
	END[b]	116.2 (115.2 - 117.2)	115.5 (114.4 - 116.6)	116.2 (115.2 - 117.2)	116.2 (115.2 - 117.3)
Hb (g dL^{-1})	SED[a]	16.2 (15.3 - 17.3)	16.6 (15.6 - 17.6)	16.2 (15.2 - 17.1)	16.5 (15.6 - 17.5)

	IND[a]	15.8 (14.8 - 16.7)	16.8 (15.8 - 17.9)	15.5 (14.6 - 16.4)	16.0 (15.1 - 17.0)
	END[b]	13.5 (12.7 - 14.3)	13.7 (12.8 - 14.5)	13.3 (12.6 - 14.2)	13.3 (12.5 - 14.1)
Lac (mmol L^{-1})	SED[a]	1.1 (0.7 - 1.5)	1.4 (1.0 - 1.8)	1.0 (0.6 - 1.3)	1.0 (0.6 - 1.4)
	IND[b]	1.4 (1.0 - 1.8)	2.1 (1.7 - 2.5)	1.3 (1.0 - 1.7)	1.5 (1.1 - 1.9)
	END[a]	0.8 (0.4 - 1.2)	0.9 (0.5 - 1.3)	0.8 (0.4 - 1.2)	1.0 (0.6 - 1.4)
Temp (°C)	SED[a]	38.6 (38.2 – 38.9)	38.8 (38.4 – 39.1)	38.5 (38.2 – 38.9)	38.7 (38.4 – 39.0)
	IND[b]	37.5 (37.2 – 37.8)	37.8 (37.4 – 38.1)	37.4 (37.1 – 37.8)	37.7 (37.4 – 38.0)
	END[c]	36.0 (35.7 – 36.3)	36.3 (36.0 – 36.7)	36.0 (35.7 – 36.3)	36.2 (35.9 – 36.5)

Different superscript letters indicate there is a significant difference between phases ($p < 0.05$).

CHAPTER IV

GENERAL DISCUSSION AND CONCLUSIONS

Research to assess the combined effects of primary induction agents with co-induction agents is warranted to fully define the interactions between the drugs in terms of dose requirements of the induction anesthetic and its cardio-pulmonary effects. The premise is that reducing the dose of the induction anesthetic can potentially reduce the depressive cardio-pulmonary effects and their duration. However, the inherent cardio-pulmonary effects of co-induction agents need to be considered and may result in additive or synergistic effects with those of the induction anesthetic.

This research was initiated to answer if midazolam, used as a co-induction agent, could reduce the dose of two current primary induction anesthetics, propofol and alfaxalone. If a reduction in dose was achieved, an additional aim was to determine if it would also ameliorate any the potential negative cardio-pulmonary effects of these induction anesthetics. In our study, the use of midazolam co-induction in fentanyl sedated healthy research dogs improved the induction quality and reduced the induction dose requirement of propofol and alfaxalone. In addition, for propofol but not alfaxalone, midazolam co-induction also reduced the maintenance dose required for total intravenous anesthesia (TIVA) to perform advanced imaging for up to one hour. Despite dose reductions in propofol or alfaxalone during induction and/or maintenance, there were no cardio-pulmonary differences for propofol or alfaxalone treatments between those that did receive midazolam and those that did not, and no significant recovery quality differences. This research has therefore answered the question that, in healthy dogs, the dose reduction in propofol and alfaxalone caused by midazolam co-induction does not result in any benefit in cardio-pulmonary function.

The effect of a higher dose of midazolam on the dose of propofol or alfaxalone was not assessed in this study. We tested midazolam at 0.3 mg/kg, IV, administered after the

initial bolus of the induction anesthetic. It has been shown that midazolam co-induction with propofol is more effective when midazolam is given at doses of 0.2-0.5 mg/kg, after an initial bolus of propofol (Robinson & Borer-Weir 2013; Sanchez et al. 2013). Similar information for alfaxalone was not available before our study, except for one observational study (Seo et al. 2015). This study is the first to demonstrate that midazolam co-induction with alfaxalone reduces the induction dose in healthy dogs.

In our study we measured blood pressure and cardiac output as part of the cardiovascular assessment for the effects of injectable anesthetics and the influence of co-induction with midazolam. Blood pressure and cardiac output are not always correlated due the interplay between pressure, resistance, and flow. In this study, there was no significant difference for mean arterial pressure (MAP) between treatments. A trend, although not significant, was observed for saline treatments to have a higher MAP than treatments that received midazolam, as well as for both alfaxalone treatments to have higher MAP than the propofol treatments during the imaging phase. Our prospective power analysis estimated that with regard to MAP, 8 dogs were required in each treatment to denote a 10 mmHg difference in the mean value for MAP and a standard deviation of 7, with a power of 80%, and an α level of 0.05. We used 9 to 10 dogs in each treatment; the difference in the MAP of all treatments was generally less than 10 mmHg and the MAP was always higher than 60 mmHg, which is considered an acceptable lower limit for MAP (Ruffato et al. 2015). Therefore, our conclusion is that regardless of the trends observed, all protocols resulted in clinically acceptable MAP.

Cardiac output (CO) values were similar between all treatments. Cardiac output is measured with less frequency than direct blood pressure in clinical cases; however in the research setting, CO provides important information that can reflect on tissue perfusion and requirements. In our study, CO decreased significantly at the end of the imaging procedure

before the recovery phase, associated with a decrease in heart rate and no change in stroke volume. This change was short lasting and did not impact tissue perfusion considering that lactate measurements did not change when compared to periods in which the CO was higher. Normal values reported for CO and standardized as cardiac index (CI) in conscious dogs vary by as much as 25% (Gerard et al. 1990; Haskins et al. 2005), probably as a result of body function, including sympathetic tone, activity of the dog, and tissue demands, but also may depend on the method used to determine the CO. Cardiac output can drop by as much as 20% during sleep (Schneider et al. 1997), and with this in mind it should be considered that CO is always adequate if it meets the demands of the tissues. Likewise, in an anesthetized patient, CO values decrease due to changes in sympathetic tone and vascular resistance, in addition to the effects of anesthetics on myocardial contractility. The lowest values measured prior to the recovery period ranged between 78-87 mL kg min^{-1}, compared to higher values measured during the sedation phase (123-173 mL kg min^{-1}) and maintenance phase (117-136 mL kg min^{-1}). Despite these differences, values for CI in our study were considered clinically acceptable at all times.

In conclusion, based on measured MAP and LiDCO, all treatments had acceptable clinical values and therefore these is no evidence to favor any of the induction and TIVA protocols for this type of research population using ASA 1 patients.

LIMITATIONS OF THE STUDY

There are some potential limitations of this study. First, the use of an incomplete Latin square crossover design that included three types of imaging procedure, namely MRI and CT with or without intervertebral disc injection, may decrease the power of this study because of patient allocation. The reason for this design was to incorporate the research with another parallel but unrelated study and meet the 3R principle: reduce, replace and

refine, according to the recommendations of animal use in research. Despite the use of appropriate statistical models used to analyze the data from this study design, which included a general linear mixed model, there were only 5 dogs in the CT2 and only one dog in AM, PS and PM treatment each, which lowers the power of those treatments for definitive conclusions.

Another limitation was the injection of the induction anesthetic drug by intermittent hand injection for the initial bolus and additional doses, instead of administration by constant rate infusion using a syringe pump. In theory, a constant rate infusion by pump provides better control of the rate and reduces human error and bias. However, this study intended to provide a clinical scenario and it was deemed important to mimic those conditions by performing the injections by hand.

During the maintenance phase, anesthesia depth assessment could only be done intermittently for the safety of personnel during the imaging. This could impact the dose requirements during that phase because the assessments had to be interrupted and close monitoring was not possible. In addition, the requirements determined in this study refer to diagnostic procedures, which are different from those that result from surgical stimulation.

Another consideration was how the monitoring equipment was adapted among the different imaging procedures. First, the length of extension tubing for direct arterial blood pressures differs significantly between MRI and CT procedures, and also during the MRI acquisition and other the other phases. Different lengths of extension tubing could result in different natural frequencies and damping coefficients within the pressure monitoring system, affecting the blood pressure waveform and readings (Miller 2015). All precautions and recommended materials were used during the measurement of cardiovascular parameters to reduce the impact of these technical differences. Second, we used different monitors for the different phases and imaging procedures due to availability of the monitors. It is expected

that minimum discrepancy occurs between the different monitors and calibrations were always performed prior to use.

Finally, there was a one-year gap between first and second (third MRI and second CT) round of data collection (see for CONSORT flow diagram). During this time, dog numbers changed due to the adoption of some of them. Also one of the dogs participated only in the second round of data collection. Due to the concern of further lowering the number of subjects in each treatment, the third MRI data were pooled with first and second MRI for analysis, while the second CT was analyzed separately since significant differences were expected from the injection performed in the unrelated study. This could have created some bias considering the TIVA rate and quality of anesthesia of CT2 was significantly lower than CT1, even after induction before the imaging procedure commenced.

STRENGTHS OF THE STUDY

In this study, descriptive scoring systems were employed for a more objective evaluation of sedation, induction and intubation, maintenance, extubation, and recovery. Compared to subjectively assigning a qualitative evaluation, a descriptive scoring system describes different aspects of the event and allows for better post hoc comparisons. Moreover, we included videotaping of each event with the descriptive scoring system with multiple blinded researchers doing the scoring, allowing post hoc comparisons and improving the validity of the evaluation by minimizing subjective bias.

To date, many studies have mask induced the animals with inhalant, instrumented them while anesthetized and later recovered the patients before initiating the data collection. The research dogs in this study were acclimatized to the anesthesia preparation area and topical local anesthetic cream and lidocaine infiltration were used to desensitize the catheterization sites. This facilitated the instrumentation for direct arterial blood pressures

and cardiac output (LiDCO and PulseCO) measurements in conscious dogs. This process was not stressful to the dogs, was repeatable with multiple arterial catheters placed over the crossover design, and in the author's opinion was less stressful to the animals compared to inhalant mask induction. Prior to data collection the dogs were sedated with fentanyl and the stress of a laboratory environment was further minimized prior to initiation of induction. The size of the dog was also considered important for the repeatability of our methods, that is dogs > 15-20 kg are ideal. One beagle research dog, 7 kg, was originally enrolled in the study, however, due to her size, arterial catheterization was difficult while conscious and had to be completed after induction. Due to her size and loss of data, this dog was excluded from the study (see Figure 4for CONSORT flow diagram).

AREAS FOR FUTURE RESEARCH

This research was conducted in healthy research dogs and has provided substantial information as to how co-induction with midazolam impacts dose requirements for induction anesthetics and the resultant cardio-pulmonary effects in ASA I patients. However, the true goal is to assess the impact of co-induction agents in sick clinical cases, ASA 3 or higher. Therefore, further investigations should include the following: different premedications; longer acting sedatives and/or more potent sedatives; different physiologic patient conditions (such as hemorrhage, anemia, sepsis, and hypoxemia); different age populations (neonatal, pediatric, and geriatric); and different species (cats, rabbits, avian, ruminants, and equine). Such studies would be more applicable to client-owned cases. In addition to the induction process and dosing, further investigations into the hemodynamic changes (decrease in HR and CO) during the final stages of advanced imaging in clinical cases warrants further research. Additional pharmacokinetic studies to support the pharmacodynamic observations of co-induction agents would also strengthen their use.

Future research projects with these questions in mind could include:

1. Investigation of midazolam co-induction in various subject species, populations, conditions or premedications in the laboratory.
2. Investigation of midazolam co-induction in various subject species, populations, conditions or with opioid/acepromazine premedication in clinical patients
3. Retrospective investigation of heart rate before, during and after diagnostic imaging
4. Investigation of the application of midazolam co-induction techniques with alfaxalone and propofol by veterinary students, technicians, or general practitioners in cats or dogs.
5. Pharmacokinetic interactions of midazolam co-induction to propofol or alfaxalone induction and TIVA doses.

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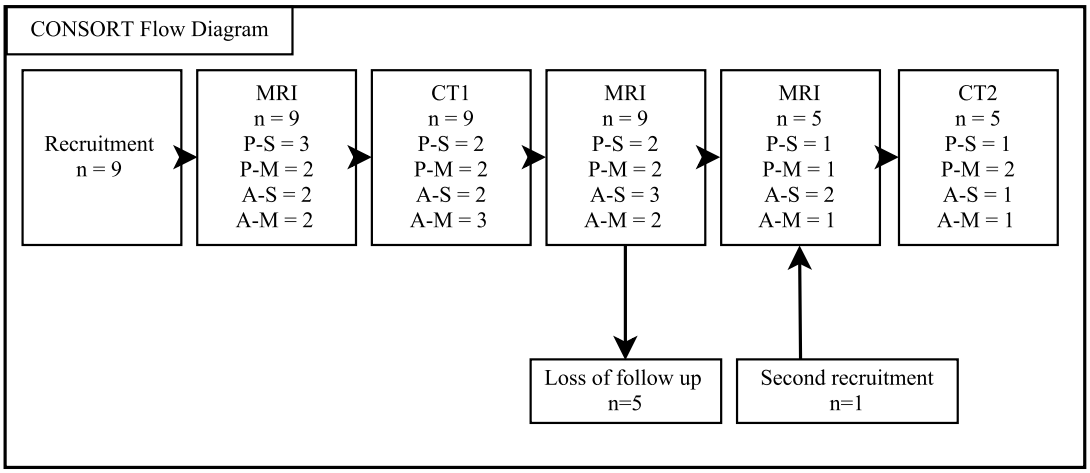
Figure 4. Study CONSORT diagram demonstrates sample numbers in each imaging modalities including magnetic resonance imaging (MRI); computer tomography with intervertebral disc injection (CT1); computer tomography without intervertebral disc injection (CT2) and the treatments distribution: propofol (P) - saline (S); P – midazolam (M); alfaxalone (A) – S; AM.



Appendix 1: program codes for the general linear mixed model

```
title &trans is the response and transform, if any;
libname sasuser    'c:\sasdata';
data cardio;    set sasuser.pentingtest;    format device $4.;
   if group=11 then trt='AS';
   if group=12 then trt='am';
   if group=21 then trt='PS';
   if group=22 then trt='pm'
   if tx in (1,3,5) then device = 'MRI';
   if tx = 2 then device ='CT1';
   if tx = 4 then device ='ct2';
   if zone in ('pre','novent') then device='none';
if zone='endpro' and time=3 then delete;
if zone='reco' and time=0 then delete;
if zone='Vent' and time=45 or time=50 or time=55 then delete;
if zone='pre' and time=33 then delete;
if device='none' then delete
proc sort;    by sex dog trt zone time device;
data pre33; set cardio; if zone='pre' and time=33; keep sex dog trt sec_scr saliva nausea
defec device;
data pre35;    set cardio;    if zone='pre' and time=35;    keep sex dog trt ind_scr no_top
ind_dose tpm_ind device;
data cardio;    set cardio; drop ind_scr no_top ind_dose tpm_ind sec_scr saliva nausea defec;
data cardio;    merge cardio pre33 pre35;    by sex dog trt;    format junk1 $6. junk2 $2.;
drop junk1 junk2; junk1=zone;    junk2=time; ZT=junk1||junk2;
proc print;var dog zone time trt zt sex device lidco bwt    cil lcil;
proc mixed noitprint noclprint covtest cl method=reml;
  class dog zone time trt sex zt device;
model cil = trt sex device        /outp=new;        *** starter model--start with this for each new
response;
*random zone(dog trt sex device); *** this statement or next but NOT both;
* repeated / subject=zone(dog trt sex ) type=ar(1);
    *** types:    ar(1) arh(1) sp(pow)(time) toep toep(2)-toep(11) toeph toeph(2)-toeph(11)
un un(2)-un(11);
  lsmeans    trt sex device          / cl adjust=tukey tdiff; make lsmeans out=mean;
data mean;    set mean;    drop stderr df alpha probt tvalue lower upper;
  LL=exp(lower); Median=exp(estimate); UL=exp(upper);
proc print noobs;
data diff;    set diff;    drop stderr df alpha tvalue lower upper;
  LL=exp(lower); Ratio=exp(estimate);UL=exp(upper);
proc print noobs;
proc univariate plot normal data=new;    var resid;
proc plot data=new;    plot resid*(pred trt zone sex dog zt time device);
run; quit;
```

Appendix 2.1: Raw data of dog 1

	HR	RR	TEMP	Attitude	**Date:_____Oct 6__2014_____**
Pre-Instrumentation	100	pant	38.5	nervous	Randomization Dog number: _____
	Time	Response		Attempts	Dog ID#: _____
EMLA application					Dog Name: _____Alonzo_____
Cephalic vein					
Meloxicam	1125				**Dog Weight:_____27_____KG**
Dorsal pedal artery					

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas:_____	126	42	173	106	84		4.7/4.8/4.9		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1252_____	3.9	Yes	No	No	

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 1259	89	108	185	104	80		3.1/3		
BloodGas:_____	103	pant	191	106	77	3.71/CI 4.11	3.6/3.7/3.8	148	

Time Starting Induction: _____1305_____

P/A Vol: _____	Time: 1305	Time: 1306	Time: 1306	Time: 1306	Time: 1307	Time:	Time Intubation:	_____1307_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume								_____
Attempt to Intubate				x	x			Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing				X	X			
Swallowing				X	x			
Paddling								
Vocalization								

Alonzo Oct/06/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post
TIME	1307	1312	1317	1322		1327	1336	1341	1346	1351	1356	1401	1406	1411	1416	1421	1426	1431	1436	1443		1446	1457
Fluid Rate							135																
P or A rate	250/70->325/91	350/98	375/105					425/119				400/112				425/119			400/112				
P/A Top Up#	1309,1310,1311	1312	1319				1336												1436				
HR bpm	75	75	105	90	112	100	97	174	176	177	163	187	104	108	99	101	96	103	80	85	92	83	110
SAP mmHg	129	122	107	98	93	97	81	73	60	71	75	91	101	107	111	125	129	130	129	101	94	94	118
DAP mmHg	51	63	55	51	49	50	58	56	50	58	59	67	73	74	79	86	89	94	58	50	50	49	64
MAP mmHg	71	74	68	64	61	65	66	64	54	65	66	77	82	86	89	100	104	106	77	63	62	62	78
Temp °C		38.2																					
SPO_2	97	97	97	97		96	98	98	97	98	98	98	98	98	98	98	98	98	98	97		96	93
ET CO_2	35	49	53	50		45	45	45	42	42	43	45	44	43	45	47	40	40	42	42		42	
RR	0	0->15	19	11		10	12	12	12	12	12	12	12	12	12	12	12	12	10	10		10	
LiDCO																				2.19/CI 2.42			
PulseCO	2.4/2.6/2.9	2.3/2.4	3.2/3.3/3.4	3.5/3.6/3.7	3.1/3.2	3.1/3.2													2.6/2.7/2.9	2.6/2.7	2.1/2.2/2.4	1.8/1.9/2/2.1	2.5/2.8/2.7
PulsCO IND	2.1/2.4 1min		2.1/2.4/2.5 2min			2.4/2.5 3min		2.2/2.4/2.7 4min															
Anesth	2	1	1	0		0	1	1	0	0	0	0	0	0	0	0	0	0	1	0			

Alonzo Oct/06/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1446	1452	1457	1502	1507	1522	1537	1552		
Score		R0	R0	R0	P3	P3	P1	P0		
Other							Sternal: 1536	Stand:1537		
PlasmaSample										

Alonzo Oct/06/14	3min after fentanyl	Pre-Vent	End MRI
Na+	148	149	148
Cl -	122	121	118
K+	3.5	3.6	4.3
Hb	19.1	16.5	14.8
pH	7.385	7.211	7.259
PCO2	31.2	55.8	49.5
PaO2	85.5	532	512
HCO3-	17.7	21.2	21.5
ABE	-4.6	-6.9	-5.7
Lactate	2.1	1.4	0.9
PCV (%)	55	48	48
TP (mg/dL)	64	60	60
Plasma Sample:			

	HR	RR	TEMP	Attitude
Pre-Instrumentation	100	20	38.4	BAR/nervous

Date:_____Oct 14 2014_____

Randomization Dog number: _____

Dog ID#: _____

Dog Name: _____Alonzo_____

Dog Weight:_____27.5_____KG

	Time	Response	Attempts
EMLA application	0930		
Cephalic vein	Good		
Meloxicam	1035		
Dorsal pedal artery	Left easy		

After 30 min rest Time:_____ Blood Gas:_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
	107	12	164	118	96		3		

Fentanyl Admin Time: _____1102_____	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
	3.9	Yes	No	No	2

3 min after premed Time: BloodGas:_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
	104	pant	217	123	93		3.1		
	85		195	126	96		3		
	79		187	116	88	3.73/CI 3.95	3.6/3.7/4/4.1/3.9/3.8		

Time Starting Induction: _____1110_____

P/A Vol: _____	Time: 1110	Time: 1111	Time: 1111	Time:	Time:	Time:	Time Intubation:	_____1111_____
Mid/Sal Vol: _____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume								_____1_____
Attempt to Intubate		x						Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Alonzo Oct/14/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	1111	1116	1121	1126		1132	1144	1149	1154	1159	1204	1209	1214	1219	1224	1232	1237		1240	1248
Fluid Rate							135													
P or A rate	250/70	275/77					300/ 84-325 / 91													
P/A Top Up#		1116					1138													
HR bpm	83	70	83	80	79	74	145	162	97	94	88	77	113	105	102	75	73	64	69	86
SAP mmHg	154	137	129	126	123	124	95	95	119	138	153	150	150	152	151	124	120	119	108	108
DAP mmHg	66	54	54	53	57	55	55	53	65	70	76	74	77	76	77	60	61	58	58	63
MAP mmHg	89	73	71	70	73	71	67	65	79	88	93	92	95	96	96	78	77	72	73	76
Temp °C																				
SPO_2	96	98	97	97		97	97	96	96	96	99	97	97	97	97	98	98		97	94
ET CO_2	34	38	48	46		44	41	45	44	44	44	45	45	45	45	39	38		39	
RR	0	5	10	10		9	9	9	9	9	9	9	9	9	9	9	9		9	
LiDCO				2.37/CI 2.51													2.24/CI 2.3			
PulseCO	4.3/4.4/ 4.1	3.5/3.6	3.5/3 .7	3.6/3 .7	2.3/2 .2/2. 4	2.1/2. 2										1.7/ 1.73 /1.7 5	1.69/1 .66	2.2/ 2.6/ 2.7/ 2.1		2.5/2.6/2.5/2 .6
PulsCO IND	3.2/3.6/ 3.4 1min		3.2/3 .4/3. 5 2min			3.2/3. 4/3.5 3min		3.4/3.3/ 3.5 4 min												
Anesth score	0	1	0	0		0	1	0	0	0	0	0	0	0	0	0	0			

Alonzo Oct/14/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1240	1243	1248	1253	1258	1313	1328	1343		
Score		R0	R0	R0	P3	P3	P3	P1		
Other								Sternal 1342		
								Stand 1403		
PlasmaSample										

Alonzo Oct/14/14	3min after fentanyl	Pre-Vent	End MRI
Na+	147	148	148
Cl -	119	118	117
K+	3.5	3.3	3.9
Hb	17.6	15	13.2
pH	7.347	7.215	7.279
PCO2	35.4	53.7	46.8
PaO2	92.4	525	528
HCO3-	18.4	20.6	21.5
ABE	-5.2	-7.1	-5.1
Lactate	1.2	0.8	0.5
PCV (%)	50	44	38
TP (mg/dL)	60	58	52
Plasma Sample:			

Appendix 2.2: Raw data of dog 2

	HR	RR	TEMP	Attitude	**Date:_____Oct 17 2013_____**
Before Instrumentation	86	panting	38.5	BAR-relaxed	Randomization Dog number: _____7_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application					Dog Name: _____Baby_____
Cephalic vein					
Meloxicam	1305(0.42ml)				**Dog Weight:_____19.5_____KG**
Dorsal pedal artery	1311	no	1		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____1317___	176		137	110	88		8.7		
Blood Gas:_1312_	182	panting	146	122	99	4.2/CI5.21	8.5		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1323____	2.6	Yes	No	No	

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 1326									
Blood Gas:_____	144	panting	165	120	95	NA	7.0		

Time Starting Induction: _____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:		Time Intubation:	_____1331_____
Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume	y	y	y	y	y	y	y	5ml	_____3_____
Attempt to Intubate						y			Comments:
Relaxed jaw tone									
Lateral palpebral									
Medial palpebral									
Coughing									
Swallowing									
Paddling									
Vocalization									

Baby Oct/17/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery	
TIME	1331	1336	1341	1346	1350	1400	1405	1410	1415	1420	1425	1430	1435	1440	1445	1451	1456	
Fluid Rate						100	100	100	100	100	100	100	100	100	100			
P or A rate	250->275	275	300	325->350	375	375	375	350	325	325	325	325	325	325	325	325	325	
P/A Top Up				2		4										1		
HR bpm	125	121	128	123	115	131	112	108	100	95	92	89	99	85	80	85	60	59	66
SAP mmHg	127	120	119	102	94	88	89	80	79	78	78	72	86	103	97	100	95	90	96
DAP mmHg	72	66	64	56	51	52	47	43	47	47	49	49	50	58	56	55	60	55	50
MAP mmHg	90	83	80	72	62	65	58	55	56	55	57	55	60	70	67	65	73	68	65
Temp °C																		
SPO_2	96	99	97	98		98	96	96	98	98	98	98	98	98	98	98	98	98
ET CO_2	26	49	51	53		48	45	44	41	40	40	39	39	39	39	38	36	42
RR	15	26	22	8		11	10	10	10	10	10	10	10	10	10	10	12	12
LiDCO	4:7.1			2.26/CI:2.81													1.53/CI:2.16	
PulseCO	0:6.2	7.4	6.5	5.8	5.3	4.8											1.6	1.6	2.2
PulseCO IND	1:7.1	2:7.3	3:7.3																
Anesth score	1	1	1	1		1	3	0	0	0	0	0	0	0	0	0	1	0	

Baby Oct/17/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1502	1506	1511	1516	1521	1536	1551	1606		
Score		R0	R0	R0	P1	P1	P0	P0		
Other					1519 sternal		1545 stand			
PlasmaSample										

Baby Oct/17/13	Before premed	Before IPPV	Out of MRI
Na+	148	150	147
Cl -	119	119	118
K+	3.6	3.2	3.9
Hb	19	16.3	15
pH	7.379	7.256	7.381
PCO2	35.6	52	36.6
PaO2	100	539	496
HCO3-	22.0		
ABE	-3.9	-3.8	-3.0
Lactate	1.1	1.1	0.5
PCV (%)	54	46	44
TP (mg/dL)	6.2	5.8	5.4
BUN	5-15		

	HR	RR	TEMP	Attitude	**Date:_____Oct 31_2013_____**
Before Instrumentation	150	panting		calm	Randomization Dog number: _____tx2_____
	Time	Response		Attempts	Dog ID#: _____
EMLA application	0730				Dog Name: _____Baby_____
Cephalic vein	0745	No		1	
Meloxicam	0810				**Dog Weight:_____20_____KG**
Dorsal pedal artery	0820	mild		4	

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____0825____									
Blood Gas:_____	174	panting	170	145	126	NA	6.4		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0826_____	2.8	Yes	No	No	1

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:									
Blood Gas:_____	139	panting	182	132	123	NA	5.4		

Time Starting Induction: __0837_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0838_____

Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume	y	y	y	y	y	y	y	5ml	_____1_____
Attempt to Intubate			y		y		Y(in)		Comments:
Relaxed jaw tone									
Lateral palpebral	N	n	n	n	n	n	n		
Medial palpebral	y	y	y	y	y	Y	y		
Coughing			y		N		y		
Swallowing					Y				
Paddling									
Vocalization									

Baby Oct/31/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	0838			0853		0900	0906									0951	0955	1000		1005	1017	1022
Fluid Rate																						
P or A rate	250/70-275/77	300/84	300/84	325/91-350/98			375/105				400/112	425/119		450/126						stop		
P/A Top Up		1		1							1				1							
HR bpm	127	127	130	132	120	145	125	107	103	104	109	107	116	131	129	127	85	77	73	70	75	113
SAP mmHg	114	117	98	106	94	72	76	80	82	81	83	99	87	113	139	136	96	92	90	85	100	110
DAP mmHg	85	66	56	64	54	51	60	52	55	55	56	65	60	84	106	103	61	59	53	51	61	72
MAP mmHg	97	81	70	77	66	60	69	62	64	64	66	78	70	94	117	113	72	67	64	61	72	83
Temp °C																						
SPO_2	96	98	99	99		99	98	98	97	97	97	96	96	95	95	95	97	97		97		
ET CO_2	0	36	46	50		48	43	44	44	44	44	45	41	43	45	44	40	38				
RR	0	0	33	16		11	11	11	11	11	11	11	11	11	11	11	11	11				
LiDCO		2.72/CI:3.68		3.62/CI:4.89														2.02/CI:2.75				
PulseCO	4.2	2.6	2.7	2.6	4.7	3.6											2.3	2.2	2.1	1.8	2.1	2.6
PulseCO IND	1:6.4	2:6.7	3:																			
Anesth score	1	2	1	2		1	1	1	1	1	2	1	1	1	1	1	1	1		1		

Baby Oct/31/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1005	1017				1047	1102	1117		
Score		R0	R0	R0	P3	P3	P2	P0		
Other							1101 sternal	1117 stand		
PlasmaSample										

Baby Oct/31/13	after premed	Before IPPV	Out of MRI
Na+	147	147	147
Cl -	117	117	116
K+	3.5	3.2	4.1
Hb	21.2	18.3	14.9
pH	7.422	7.259	7.331
PCO2	35.6	53.9	45.2
PaO2	94.6	499	583
HCO3-			
ABE	0.2	-4.4	-1.9
Lactate	1.8	2.3	0.9
PCV (%)	58	53	45
TP (mg/dL)	6.4	6.0	5.8
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	68	panting		BAR

	Time	Response	Attempts
EMLA application	0900		
Cephalic vein		No	1
Meloxicam	0945; 0.4 ml		
Dorsal pedal artery		n	1

Date:_____Nov 12__2014_____

Randomization Dog number: _____tx3_____

Dog ID#: _____

Dog Name: _____Baby_____

Dog Weight:_____20_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____1025____									
Blood Gas:_____	140	16	142	105	99	NA	2.7		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1023_____	2.7	no	No	No	0

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	110		127	108	86		2.1		
Blood Gas:_____	95		184	129	104		2.1		
	100	28	190	137	112	3.63/CI:4.5	2.5		

Time Starting Induction: __1040_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____

Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose
Injectable Volume	Y							
Attempt to Intubate	Y							
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	Y							
Coughing	y							
Swallowing								
Paddling								
Vocalization								

Intubation score:
_____0_____

Comments:

Baby Nov/12/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1041	1046	1051	1056		1100	1110	1115								1155	1204	1209		1213	1221	1226
Fluid Rate																						
P or A rate	250/70-275/77	300/84-325/91	350/98							325/91												
P/A Top Up	2	1					2															
HR bpm	96	115	121	124	125	122	139	138	138	127	127	122	122	111	99	95	62	60	52		75	72
SAP mmHg	136	108	106	105	103	96	69	Line loose	75	66	71	76	79	82	82	85	125	120	115		124	121
DAP mmHg	67	57	58	59	56	54	40		45	39	39	42	45	46	45	46	65	57	53		58	64
MAP mmHg	88	72	72	71	69	67	50		56	48	49	52	55	57	55	57	81	72	71		74	78
Temp °C																	36.4					
SPO_2	99	99	99	99		99	97	97	97	97	98	99	99	99	99	99	97	97				
ET CO_2	4	44	56	54		46		39	35	36	38	35	35	35	35	38	40	37				
RR	0->5	7	4	7		11		7	7	7	7	7	7	7	7	7	8	8				
LiDCO				2.39/2.96														1.57/CI:1.94				
PulseCO	5.3	8.3	8	8.7	2.5	2.4											1.2	1	1.1		2	2.1
PulseCO IND	6.5	6	7.4																			
Anesth score	3	1	1	1		1	3	0	0	0	0	0	0	0	0	0	1	1				

Baby Nov/12/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1213	1221	1226	1231	1236	1251	1306	1321		
Score		R0	R0	R2	P3					
Other						Sternal 1304		Stand 1321		
PlasmaSample										

Baby Nov/12/13	after premed	Before IPPV	Out of MRI
Na+	150	151	150
Cl -	3.7	3.2	3.4
K+	120	121	120
Hb	17.6	16.1	14.2
pH	7.338	7.206	7.339
PCO2	41.6	61.1	39.4
PaO2	77.5	518	607
HCO3-	21.3	23.3	20.9
ABE	-3.3	-5.8	-4.3
Lactate	0.7	0.6	0.5
PCV (%)	48	46	41
TP (mg/dL)	64	58	56
BUN	5-15		

	HR	RR	TEMP	Attitude
Pre-Instrumentation	108	panting	39.4	nervous

	Time	Response	Attempts
EMLA application	0731		
Cephalic vein	0752	minimal	`
Meloxicam	0755		
Dorsal pedal artery	0805		

Date:_____Oct 7 2014_____
Randomization Dog number: _____
Dog ID#: _____
Dog Name: _____Baby_____

Dog Weight:_____23_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____ Blood Gas :_____	181	42	143	128	116		3.0/2.8/2.7		

Fentanyl Admin Time: _____0825_____	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
	3.2	Yes	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	148	panting	186	131	107		4.2/3.9/4.5		
BloodGas:_____	141	panting	201	141	119	4.89/CI 6.07	3.8/3.9/4.1/ 4/4.5/4.4/5. 2/5.3		

Time Starting Induction: _____0835_____

P/A Vol: _____	Time: 0835	Time: 0836	Time: 0836	Time:083 7	Time:	Time:	Time Intubation:	___0837_____

Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score: _____1_____
Injectable Volume								
Attempt to Intubate			X					Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Baby Oct/07/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	0837	0842	0847	0852		0859	0940	0945	0950	0955	1000	1005	1010	1015	1020	1025	1031	1036		1039	1050
Fluid Rate																					
P or A rate	250/70	275/77				300/84								325/91							
P/A Top Up#		0843				0901															
HR bpm	151	136	154	162	161	158	111	94	96	95	102	107	125	121	120	125	89	81	90	89	126
SAP mmHg	155	115	104	102	106	100	83	81	78	75	74	76	101	109	110	111	111	93	90	89	107
DAP mmHg	90	62	60	60	60	60	55	51	47	46	44	46	66	73	71	75	56	53	51	53	59
MAP mmHg	109	79	76	76	76	74	66	60	59	55	55	56	78	86	84	87	72	64	63	62	74
Temp °C																					
SPO_2	97	98	98	97		97	96	97	98	97	98	97	97	97	97	97	95	96		96	94
ET CO_2			54	54		46	29	36	37	39	40	41	43	44	43	43	34	36		38	
RR	0	0	0	9		10	16	10	10	10	10	10	10	10	10	10	10	10		10	
LiDCO				3.3/CI 3.76														1.87/CI 2.34			
PulseCO	6.7/6.6/6.2/6.3	6.2/6.3/6.4	6.4/6.5	6.2/6.3	3/2.9	2.5/2.7/2.9											1.4/1.51/1.56/1.61	1.17/1.3	1.8/1.7/1.7	1.7/1.8	2.7/2.8/2.8/2.9
PulsCO IND	6.1/6.2 1min		6.7/6.4/6.5 2min			6.4/6.8/6.6./6.3 3min		6.4/6.3/6.5 4 min													
Anesth score	0	1	0	0		1	0	0	0	0	0	0	0	1	0	0	1	0			

Baby Oct/07/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1039	1045	1050	1055	1100	1115	1130	1145		
Score		R0	R0	R0	P3	P3	P1	P0		
Other							Sternal 1132	Stand 1145		
PlasmaSample										

Baby Oct/07/14	3min after fentanyl	Pre-Vent	End MRI
Na+	150	151	150
Cl -	119	119	118
K+	3.7	3.3	3.9
Hb	20.7	19.3	15.4
pH	7.408	7.230	7.335
PCO2	33.2	55.7	42.4
PaO2	102	362	449
HCO3-	20	22.1	22.3
ABE	-2.0	-6.1	-3.4
Lactate	1.9	3.2	1.5
PCV (%)	61	56	45
TP (mg/dL)	66	64	56
Plasma Sample:			

	HR	RR	TEMP	Attitude	**Date:_____Oct 15_2013_____**
Pre-Instrumentation	144	36	38.6	nervous	Randomization Dog number: _____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	0713				Dog Name: _____Baby_____
Cephalic vein	0728				
Meloxicam	0732				**Dog Weight:_____23_____KG**
Dorsal pedal artery	0740				

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas :_____	187	44	207	134	111		5.3/5.7/4.6		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0754_____	3.2	Yes/No	Yes/No	Yes/No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	141	Panting	201	144	122		3.7/3.8/4		
BloodGas:_____	141	panting	202	144	117	3.87/CI 4.8	4.3/4.2/4.1/ 3.8/3.9/3.7/ 3.6/3.5		

Time Starting Induction: _____0805_____

P/A Vol: _____	Time: 0805	Time: 0806	Time: 0806	Time: 0807	Time:	Time:	Time Intubation:	_____0_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume								_____
Attempt to Intubate				x				Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Baby Oct/15/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	0807	0812	0817	0822		0829	0838	0843	0848	0853	0858	0903	0908	0913	0918	0925	0930		0935	0945
Fluid Rate																				
P or A rate	250/70		275/77				300/84													
P/A Top Up#			0819				0838													
HR bpm	130	125	138	146	135	138	127	120	113	111	110	101	101	101	107	73	70	69	69	134
SAP mmHg	141	114	107	104	104	92	85	79	83	83	84	82	84	84	87	109	100	100	99	107
DAP mmHg	77	63	62	62	60	69	46	48	50	50	50	49	50	50	52	56	53	51	51	64
MAP mmHg	97	82	78	77	75	57	62	58	60	60	60	58	59	59	62	70	66	64	63	77
Temp °C																				
SPO_2	97	97	97	98		98	98	98	98	98	98	98	98	99	99	98	97		97	
ET CO_2	39	41	51	60		53	45	44	44	44	44	43	44	44	44	40	39		37	
RR	0	25	17	6		9	12	12	12	12	12	12	12	12	12	12	12		12	
LiDCO				1.89 CI 2.35													1.81 CI 2.25			
PulseCO	3.7/3.8/3.9	4.9/5/5.1/5.2/5.3	4.7/4.8/4.9/5	4.6/4.7/4.8	1.8/2	1.7/1.8										0.9	0.9/0.7/0.8	1.8/1.6/1.7		2.1
PulsCO IND	3.3/3.4/3.5/3.9 1min		4.1/4.2/4.5/4.7 2min			4.5/4.7/4.8 3min		4.6/4.7/4.9/5 4min												
Anesth score	0	0	1	0		0	1	0	0	0	0	0	0	0	0	1	0			

Baby Oct/15/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	0935	0940	0945	0950	0955	1010	1025	1040		
Score		R0	R0	R0	P3	P2	P1	P0		
Other				paddling		Sternal 1012	Stand 1021			
PlasmaSample										

Baby Oct/15/14	3min after fentanyl	5 min post-intubate	End MRI
Na+	149	149	147
Cl -	117	117	116
K+	3.5	3.4	4.1
Hb	19.8	19.1	14.2
pH	7.384	7.201	7.295
PCO2	38.3	63.5	50.6
PaO2	80.8	442	364
HCO3-	21.7	23.4	23.8
ABE	-1.4	-5.9	-2.7
Lactate	1.7	2.5	0.7
PCV (%)	56	55	41
TP (mg/dL)	64	64	58
Plasma Sample:			

Appendix 2.3: Raw data of dog 3

	HR	RR	TEMP	Attitude
Before Instrumentation	86	panting	38.4	Rowoy/BAR

	Time	Response	Attempts
EMLA application	1202		
Cephalic vein	1230	no	1
Meloxicam 12:38	0.56ml		
Dorsal pedal artery	1234	no	1

Date:_____Oct 16 2013_____
Randomization Dog number: _____no.4_____
Dog ID#: _____
Dog Name: _____Baron_____

Dog Weight:_____28_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____			131	97	87	5.43/CI6.5	Event 8		
Blood Gas:_1235_	108	30	139	90	81	7	5.4	147	15.9

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1255_____	3.9	No	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:									
Blood Gas:_1257__	68	9	166	109	88		5.0		

Time Starting Induction: _____1300_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____1301_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose 5.6ml	Intubation score:
Injectable Volume	y	y	y					_____2_____
Attempt to Intubate	Y							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	Y							
Medial palpebral	Y							
Coughing	y	y						
Swallowing	N							
Paddling	N							
Vocalization	n							

Baron Oct/16/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	Out of MRI	Pre-Recovery	TIVA OFF
TIME	1301												1405	1410	1413				1420	1428	
Fluid Rate						140	140	140	140	140	140	140	140	140	140						
P or A rate	250	275	300	300	300	325	325	325	325	325	300	300	300	300	300				300	300	
P/A Top Up	1	1	1																3		
HR bpm	70	72	73	75	75	86	90	83	83	94	98	96	96	96	96				56	56	55
SAP mmHg	155	139	115	94	97	91	82	90	90	83	84	80	83	77	81	87			123	119	106
DAP mmHg	64	76	59	51	56	55	55	56	55	52	51	48	50	46	48	52			58	56	55
MAP mmHg	93	91	76	64	68	66	63	66	63	60	60	57	60	55	58	62			73	69	70
Temp °C																					
SPO_2	95	95	96	96	96	97	98	98	97	96	95	98	100	100	96				98	97	
ET CO_2	41	41	42	53	44	35	34	36	39	41	41	43	42	42	42				39	37	
RR	0	27	0	22	14	12	12	12	12	12	12	12	12	12	12				13	13	
LiDCO				3.222/ CI 3.9																2.21/CI 2.67	
PulseCO	6.5	4.7;3.9 ;4.2;5; 5	5.6	4.3	4.3														3.4	3.4	
Anesth score	1	0	0	0	1	1	0	0	1	0	0	0	0	0	0				2	1	

Baron Oct/16/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1431	1436	1441	1446	1451	1506	1521	1536		
Score		R0	R0	R0	P0-1	P0	P0			
Other					1455 sternal	1502 stand	Retrun to normal			
PlasmaSample										

Baron Oct/16/13	Before premed	Before IPPV	Extubation
Na+	147	148	147
Cl -	118	116	115
K+	4.3	3.6	3.9
Hb	15.9	14.9	13
pH	7.431	7.252	7.331
PCO2	31.4	53.8	42.1
PaO2	93.4	580	563
HCO3-	22.8		
ABE	-3.1	0.5	-3.2
Lactate	0.7	-2.8	0.4
PCV (%)	45	45	38
TP (mg/dL)	6.0	5.6	5.6
Plasma Sample:			

	HR	RR	TEMP	Attitude	**Date:_____Oct 30_2013_____**
Before Instrumentation	108	48	38.6	excited	Randomization Dog number: _____tx2_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	0822				Dog Name: _____Baron_____
Cephalic vein	0832	no	1		
Meloxicam	0.68ml/0845				**Dog Weight:_____26_____KG**
Dorsal pedal artery	0842	no	1		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____0846_____									
Blood Gas:_____	93	42	160	127	110	NA	NA	NA	NA

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: ____0850_____	3.8	No	No	Yes	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	75		177	111	87	3.33/CI:3.6	3.2		
Blood Gas:_____	105	42	166	106	86	1	3.1		

Time Starting Induction: _____0907_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0909_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	y	y	y				2.4	_____1_____
Attempt to Intubate	n	y	Y(in)					Comments:
Relaxed jaw tone								
Lateral palpebral	n	n	N					
Medial palpebral	y	y	y					
Coughing		y						
Swallowing		y						
Paddling								
Vocalization								

Baron Oct/30/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	Out of MRI	Pre-Recovery		TIVA off	extubation	5min post
TIME	0910			0925		0929	0937	0942						1012	1019	1027		1029	1038	1043
Fluid Rate																				
P or A rate	250/70-275/77	300/84	325/91-350/98	375/105400/112		425/119	450/126	450/126	450/126	450/126	475/133	500/140	500/140	500/140	500/140	500/140				
P/A Top Up	3	1	1	1			1					1								
HR bpm	140	110	96	122	94	111	90	111	106	105	103	103	104	104	88	79	79	71	83	144
SAP mmHg	132	118	107	111	106	101	102	107	95	99	102	103	101	99	91	95	96	96	99	100
DAP mmHg	74	66	60	64	61	58	61	61	56	57	60	62	60	59	61	58	59	56	55	64
MAP mmHg	93	76	75	77	70	70	74	74	68	70	72	73	71	71	69	68	66	66	67	86
Temp °C																				
SPO_2	96	98	98	98		98	98	96	96	96	96	99	99	99	99	95		97		
ET CO_2	0	41	49	46		43	41	42	45	45	43	43	43	43	42	42				
RR	0	7	11	13		11	11	10	11	11	11	11	11	11	11	11				
LiDCO																2.6/CI:2.82				
PulseCO	5.8	4.7	4.1	4.4	3.2										2.1	1.9	2.4	2.1	2.6	3.3
PulseCO IND	1:4.8	2:4.4	3:4.6																	
Anesth score	2	2	2	2		1	2	1	1	1	1	2	1	1	1	1		1		

Baron Oct/30/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1029	1038	1043	1048	1053	1108	1123	1138		
Score		R0	R1	R1	P3	P2	P0	P0		
Other						Sternal 1112 Stand 1115				
PlasmaSample										

Baron Oct/30/13	after premed	Before IPPV	Out of MRI
Na+	145	148	147
Cl -	118	118	115
K+	3.7	3.2	3.8
Hb	16.9	15.2	13.6
pH	7.360	7.280	7.326
PCO2	39.4	50.7	46.1
PaO2	82.8	563	589
HCO3-	21.2		
ABE	-2.7	-2.7	-2.3
Lactate	0.8	0.9	0.5
PCV (%)			
TP (mg/dL)			
BUN			

	HR	RR	TEMP	Attitude	**Date:_____Nov 11 2013_____**
Before Instrumentation	86	40	38.4	BAR	Randomization Dog number: _____tx3_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	0720				Dog Name: _____Baron_____
Cephalic vein		no	1		
Meloxicam	0.56ml				**Dog Weight:_____28_____KG**
Dorsal pedal artery					

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____ _____									
Blood Gas:_____	130	40	148	111	96		6.8		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: ____0835_____	3.9	No	No	No	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	80		141	99	84		4		
Blood Gas:_____	72		153	91	76		3.9		
	83	pant	153	101	83	3.8/4.11	3.5		

Time Starting Induction: _____0856_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0857_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	y	Y					2.8	_____1_____
Attempt to Intubate	y	y						Comments:
Relaxed jaw tone	Y							
Lateral palpebral	y							
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Baron Nov/11/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA off	xtubation	5min post
TIME	0857	0902	0907	0912		0917	0932	0937							1007	1017	1023		1026	1033	1038
Fluid Rate																					
P or A rate	250/70—300/84	325/91	350/98			375/105	400/112			375/105				400/112							
P/A Top Up		1				1	2									1					
HR bpm	120	111	102	110	111	114	127	120	115	113	113	111	110	102	100	69	67	68		66	67
SAP mmHg	133	101	105	93	86	70	63	71	71	70	68	68	71	96	96	113	100	98		96	102
DAP mmHg	70	58	56	53	50	45	46	48	46	46	43	42	43	65	66	69	57	57		56	59
MAP mmHg	89	72	70	66	63	55	54	58	57	56	54	53	53	76	77	81	70	68		65	71
Temp °C			37.2																		
SPO_2	95	99	98	99		99	99	99	99	99	99	99	99	99	99	97	96				
ET CO_2	39	42	53	57		44	34	38	39	39	39	40	40	40	40	43	42				
RR	0->18	115	8	8		12	12	10	10	10	10	10	10	10	10	10	10				
LiDCO				4.96/5.37													3.91/CI:4.23				
PulseCO	4.8	4.2	4.7	4.8	5.5	4.4										2.5	2.5	3.9		5.1	5.9
PulseCO IND	3.7	4.1	4																		
Anesth score	2	1	1	1		1	3	0	0	0	0	0	0	0	0	1	1				

Baron Nov/11/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1026	1033	1038	1043	1048	1103	1118	1133		
Score		R0	R0	R0	P3	P2	P0	P0		
Other					paddling	1101 sternal	1112 stand			
PlasmaSample										

Baron Nov/11/13	after premed	Before IPPV	Out of MRI
Na+	147	148	146
Cl -	3.7	3.3	3.9
K+	117	118	115
Hb	17.1	15	13.9
pH	7.342	7.223	7.297
PCO2	41.6	57.2	45.3
PaO2	76.4	510	614
HCO3-	21.6	22.6	22.1
ABE	-3	-5.6	-4.7
Lactate	1.1	1.1	0.9
PCV (%)	49	48	40
TP (mg/dL)	60	56	58
BUN	5-15		

	HR	RR	TEMP	Attitude
Pre-Instrumentation	120	panting	38.4	calm

	Time	Response	Attempts
EMLA application	0730		
Cephalic vein			
Meloxicam	0752		
Dorsal pedal artery			

Date:_____Oct 8_2014_____

Randomization Dog number: _____

Dog ID#: _____

Dog Name: _____Baron_____

Dog Weight:_____28.4_____KG

After 30 min rest Time:_____ Blood Gas :_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
	111	panting	136	104	95		2.5/2.3/2.4		

Fentanyl Admin Time: _____0804__	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
	4	No	No	Yes	3

3 min after premed Time: BloodGas___0805_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
	68	42	158	102	83		2/1.9/2.1/2.2		
	65		160	105	88	2.07/CI 2.19	1.4		

Time Starting Induction: _____0816_____

P/A Vol: _____	Time:0816	Time:0816	Time:	Time:	Time:	Time:	Time Intubation:	_____0816_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	X							_____0_____
Attempt to Intubate								Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing	X							
Swallowing								
Paddling								
Vocalization	X							

Baron Oct/08/14	POST-Intub	5 min	10min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	816	821	826	0831		0837	0852	0857	0902	0907	0912	0917	0922	0927	0932	0941	0946		0949	0959
Fluid Rate																				
P or A rate	250/70		275/77			300/84	325/91				300/84									
P/A Top Up#			0828			0838														
HR bpm	77	67	83	94	99	102	104	104	103	104	105	103	103	117	99	72	62	62	60	80
SAP mmHg	136	98	92	88	89	90	85	73	71	68	69	69	69	86	96	105	102	105	106	109
DAP mmHg	75	55	53	51	51	52	41	45	44	42	42	42	42	54	64	61	58	59	70	75
MAP mmHg	90	66	63	62	62	64	62	55	53	52	52	51	52	66	73	73	69	71	58	62
Temp °C																				
SPO_2	96	97	96	95		98	98	98	98	98	98	97	97	97	98	98	98		97	95
ET CO_2		19	16	19		47	40	41	40	41	41	40	40	42	41	39	35		34	
RR	0	0	0	0		11	10	10	10	10	10	10	10	10	10	10	10			
LiDCO				3.04/CI 3.22													2.46/CI2.61			
PulseCO	2.1/2.2/2.1	2/2.1	2.3/2.4	3.1/3	3.1/3.2/3.3	3/2.8/2.9										1.7/1.8	1.7/1.8	1.9/2.1/2.2/2.3	2/2.1	3.1/3/3.2/2.9/2.6
PulsCO IND	2.1/2.2 1min		1.7/1.8/1.6 2min			1.7/1.8 3min		1.8/1.9 4 min												
Anesth score	0	0	1	0		1	1	0	0	0	0	0	0	0	0	0	0			

Baron Oct/08/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	0949	0954	0959	1004	1009	1024	1039	1054		
Score		R0	R0	R0	P2	P0	P0	P0		
Other										
PlasmaSample										

Baby Oct/15/14	3min after fentanyl	Pre-Vent	End MRI
Na+	146	147	145
Cl -	117	116	116
K+	4	3.6	4.3
Hb	15.3	15.7	14.5
pH	7.381	7.169	7.312
PCO2	37.6	68.2	45.7
PaO2	80.1	491	479
HCO3-	21.8	23.8	22.9
ABE	-2.4	-6.4	-3.6
Lactate	1.1	1.7	1.1
PCV (%)	44	46	42
TP (mg/dL)	56	54	58
Plasma Sample:			

	HR	RR	TEMP	Attitude	Date:_____OCT 15_2014_____
Pre-Instrumentation	100	24		good	Randomization Dog number: _____
	Time		Response	Attempts	Dog ID#: _____
EMLA application	Y				Dog Name: _____Baron_____
Cephalic vein	Y				
Meloxicam	1150, 0,.5ml				**Dog Weight:_____26.5_____KG**
Dorsal pedal artery					

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas :_____	122	28	136	93	77		3.4/3.5		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1228____	3.6	Yes/No	Yes/No	Yes/No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	73	12	159	90	72		1.9/2		
BloodGas _____	60		189	105	84		1.8		
	60		148	98	74	2.24 CI 2.48	2.3/2.4/2.2		

Time Starting Induction: _____1236_____

P/A Vol: _____	Time: 1236	Time:	Time:	Time:	Time:	Time:	Time Intubation:	___1237_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume								_____1_____
Attempt to Intubate	x							Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Baron Oct/15/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	1237	1242	1247	1252		1256	1302	1307	1312	1317	1322	1327	1332	1337	1242	1348	1352		1355	1404
Fluid Rate																				
P or A rate	250/70-275/77		300/84				325/91													
P/A Top Up#	1240		1247				1302													
HR bpm	98	77	93	102	105	101	130	139	141	140	142	142	142	138	136	76	72	73	72	82
SAP mmHg	140	127	114	103	105	100	101	73	81	91	102	104	108	108	107	108	107	108	106	108
DAP mmHg	76	67	61	59	60	55	59	50	54	61	71	71	74	72	73	65	65	63	61	60
MAP mmHg	94	82	75	70	72	70	73	58	64	70	79	82	84	81	82	74	77	74	73	72
Temp °C																				
SPO_2	97	97	98	98		98	99	99	98	98	98	98	98	98	98	98	98		98	95
ET CO_2	43	43	47	49		41	34	38	39	40	41	42	42	43	43	42	42		41	
RR	7	10	10	7		12	12	12	12	12	12	12	12	12	12	12	12		12	
LiDCO				2.49/ CI 2.75													1.98 CI 2.14			
PulseCO	3.4/3.5/3.6	2.7/2.8	3.5	3.3/3.4/3.5	2.5/2.6/2.9	2.6/2.5/2.8										1.6/1.7	1.6/1.7	1.8/1.9/2	2/2.1	2/2.1
PulsCO IND	1m3.3/3.2in		3/3.12min			2.6/2.7/2.83min		2.6/2.74 min												
Anesth score	1	0	1	0		0	1	0	0	0	0	0	0	0	0	0	0		0	

Baron Oct/15/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1355	1359	1404	1409	1414	1429	1444	1459		
Score		R0	R0	R0	P3	P3	P2	P1		
Other								Sternal/stand 1458		
PlasmaSample										

Baron Oct/15/14	3min after fentanyl	Pre-Vent	End MRI
Na+	146	146	147
Cl -	116	117	115
K+	3.6	3.4	3.6
Hb	14.9	14.7	13.6
pH	7.351	7.315	7.291
PCO2	39.8	42.2	48.6
PaO2	78.9	525	542
HCO3-	21.1	20.9	23.2
ABE	-3.3	-4.7	-3.7
Lactate	0.3	0.3	0.3
PCV (%)	43	42	40
TP (mg/dL)	58	54	54
Plasma Sample:			

Appendix 2.4: Raw data of dog 4

	HR	RR	TEMP	Attitude	**Date:_____OCT/15/2013_____**
Before Instrumentation	60	30		calm	Randomization Dog number: _____
	Time	Response		Attempts	Dog ID#: _____
EMLA application	1230				Dog Name: _____bolt_____
Cephalic vein	1245	calm		1	
Dorsal pedal artery	1400	Calm		1	**Dog Weight:_____KG**

After 30 min rest Time	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	SPO2	Na+	Hgb
Blood Gas Taken t:_1405_	79	12	145/146	94/91	77/68	4.32/CI:4.92			146	13.3
1515	88		150/118	98/85	82/64	4.6				

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1517_____	3.6	No	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	SPO2	Na+	Hgb
Time: 1520			135/185/	74/118/	58/93/8		2.8/6.1/4.09/			
Blood Gas Taken :_____	44/58/67	24	175	107	0		4.66		146	11.9

Time Starting Induction: ____1524_____

P/A Volume : _____	Time:1526	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____ _____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation
Injectable Volume							2.6ml propofol+1.6ml midazolam	score: 1
Attempt to Intubate	Y							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	Y							
Coughing	N							
Swallowing	N							
Paddling	N							
Vocalization	n							

Bolt Oct/15/13	POST-Intub	5 min	10min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	Pre-Recovery		
TIME	1527	1532	1537	1542	1547	1550	1600	1605	1610	1615	1620	1625	1630	1635	1640	1645	1650	1700	1705	1708
Fluid Rate	0	0	0	0	0	0		130	130	130	130	130	130	130	130	130	130	0	0	0
P or A rate	250	250	275	275	275	275		275	275	250	275	275	275	275	275	275	275	275	275	275
P/A Top Up	0	0	1	0	0	0		2	0	0	0	0	0	0	0	0	0	3	0	0
HR bpm	63	62	57	60		75		89	62	64	67	73	72	70	71	73	74	45	41	40
SAP mmHg					121	118	114		135	105	104	99	101	99	100	97	97	98	116	116	118
DAP mmHg					56	56	60		46	60	58	55	55	55	55	54	54	53	65	62	59
MAP mmHg					73	72	74		72	71	68	67	66	66	66	65	65	65	77	72	72
Temp °C						37.6														
SPO_2	96	96	95	99		98		99	99	99	99	99	99	99	99	99	99	96	96	96
ET CO_2	54	53	48	49		41		30	31	31	31	32	32	32	31	31	31	33	33	33
RR		9	12	11		10		10	9	9	9	9	9	9	9	9	9	10	10	10
LiDCO					3.5/CI:3.98															2.4/CI:2.73
PulseCO	5.4		12.1	3.98		3.6												1.5	1.7	1.6
Anesth score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		

Bolt Oct/15/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1711	1718	1723	1728	1733	1748	1803	1818		
Other						sternal	1755 stand			
Score		R0	R0	R0	P2	P1	P1			

Bolt Oct/15/13	Before premed	3 min after fentanyl	Before ventilation	End of MRI
Na+	146	146	147	145
Cl -	115	116	117	115
K+	3.6	3.5	3.2	3.5
Hb	13.3	11.9	13.5	11.6
pH	7.361	7.352	7.262	7.368
PCO2	36.1	35.7	44.2	34.9
PaO2	98.8	98.1	523	533
HCO3-	19.5	18.9	19.1	19.8
ABE	-4.2	-5.1	-7.1	-4.6
Lactate	1.9	1.9	2.4	1.7
PCV (%)	37	35	39	37
TP (mg/dL)	6.2/ BUN 5-15	5.8	5.8	5.8
Plasma Sample:				

	HR	RR	TEMP	Attitude
Before Instrumentation	96	panting	38.6	calm

	Time	Response	Attempts
EMLA application	0940		
Cephalic vein	0950	no	1
Meloxicam	0.52ml,1140		
Dorsal pedal artery	1140	non	5

Date:_____Oct 28_____

Randomization Dog number: _____tx2_____

Dog ID#: _____

Dog Name: _____Bolt_____

Dog Weight:_____26_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas:_____	70	22	130	96	77	NA	3.1/2.3	NA	NA

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1153_____	3.6	No	No	No	1

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 1200	67		185	108	82		1.9/2.4		
Blood Gas:_____	74	30	191	116	94	2.81/3.20	2.7		

Time Starting Induction: _____1204_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____1206_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	y	y	y					_____1_____
Attempt to Intubate		Y(in)						Comments:
Relaxed jaw tone	y	y						
Lateral palpebral	Y	N						
Medial palpebral	Y	y						
Coughing		Y						
Swallowing								
Paddling								
Vocalization								

Bolt Oct/28/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		extubation	5min post
TIME	1206			1221		1225	1235								1315	1321	1328		1335	1349
Fluid Rate																				
P or A rate	250/70-275/77	300/84-325/91	325/91	325/91		325/91	325/91	325/91	325/91	325/91	325/91	325/91	325/91	375/105	375/105	375/105	375/105			
P/A Top Up																				
HR bpm	50	55	62	70	71	84	60	57	60	56	59	67	63	64	61	56	53	51	57	57
SAP mmHg	146	142	124	111	115	113	97	93	97	100	99	101	109	137	137	124	131	111	110	103
DAP mmHg	84	83	58	58	58	58	66	57	71	71	67	67	80	85	86	70	73	65	71	90
MAP mmHg	63	63	72	69	71	69	79	67	80	80	75	76	70	97	96	87	86	79	82	95
Temp °C																				
SPO_2	98	99	99	97		98	98	96	97	96	96	96	96	96	96	97	97		97	
ET CO_2	42	47	49	49		45	44	41	41	40	40	40	40	41	39	38	37		37	
RR	0	9	8	8		11	11	11	11	11	11	11	11	11	11	11	9		11	
LiDCO				2.58/CI:2.94													2.16/CI:2.46			
PulseCO	3.8	2.8	3.0	2.9	3.1	2.3										5.0	1.5	1.5	2.2	2.2
PulseCO IND	1:2.7	2:2.9	3:2.6																	
Anesth score	2	2	1	1		1	2	1	1	1	1	1	1	2	1	1	1			

Bolt Oct/28/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1335	1344				1414		1444		
Score		R0	R0	R0	P3	P1	P0	P0		
Other						1414 sternal 1419 stand				
PlasmaSample										

Bolt Oct/28/13	after premed	Before IPPV	Out of MRI
Na+	144	146	145
Cl -	118	116	114
K+	3.8	3.4	4.0
Hb	12.8	14.1	12.5
pH	7.426	7.227	7.326
PCO2	30.1	53.8	42.5
PaO2	95.4	497	547
HCO3-	19.1	21.3	21.8
ABE	-3.3	-6.2	-3.8
Lactate	1.5	2.2	2.0
PCV (%)	40	40	36
TP (mg/dL)	6.0	6.0	6.0
BUN	5-15		

	HR	RR	TEMP	Attitude	**Date:_____Nov8_2013_____**
Before Instrumentation	72	20	38.4	BAR	Randomization Dog number: _____tx2_____
	Time	Response		Attempts	Dog ID#: _____
EMLA application					Dog Name: _____Bolt_____
Cephalic vein					
Meloxicam					**Dog Weight:_____26_____KG**
Dorsal pedal artery					

After 30 min rest:_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas :__	79	20	122	98	76		2.4		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1051____	3.6	n	n	n	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	70	24	150	93	74		1.9		
Blood Gas Taken :__	95		240	146	97		2.4		
			168	118	90	4.87/5.54	5.2		

Time Starting Induction: __1101_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	____1102_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:2
Injectable Volume Admin	y	y	y	y			2.9	_____
Attempt to Intubate		y	y					Comments:
Relaxed jaw tone	y	y	Y					
Lateral palpebral	y	y	Y					
Medial palpebral	y	y	Y					
Coughing								
Swallowing			y					
Paddling								
Vocalization								

Bolt Nov/08/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1103	1108	1113	1118		1120	1128	1133									1217	1221	1226		1230	1237	1242
Fluid Rate																							
P or A rate	250/70-275/77	300/84-325/91	350/98-375/105			400/112				425/119													
P/A Top Up	2	2				1																	
HR bpm	78	76	89	87	85	106	105	86	82	80	81	78	78	81	79	80	81	66	67	66		72	76
SAP mmHg	156	128	124	113	140	134	112	113	102	107	103	92	90	93	88	84	87	129	133	132		130	105
DAP mmHg	73	55	56	54	55	56	56	47	60	65	59	56	55	58	57	57	58	70	69	65		64	63
MAP mmHg	93	73	73	70	70	72	72	71	72	76	70	65	64	66	64	65	65	82	82	76		73	75
Temp °C	38.2																						
SPO_2	98	96	96	95		99	99	99	99	97	99	99	99	99	99	99	99	98	99				
ET CO_2	35	43	46	43		44	40	40	34	36	36	36	35	35	35	35	35	35	34				
RR	0	12	7	6		8	8	8	8	8	8	8	8	8	8	8	8	11	11				
LiDCO				3.37/3.84															1.97/2.24				
PulseCO	3.3	3.4	4.6	4.3	3.9	3.5												1.5	1.7	1.8		2.5	2.1
PulseCO IND	3.3	3.1	3.1																				
Anesth score	3	3	1	1		1	1	0	0	1	0	0	0	0	0	0	0	1	1				

Bolt Nov/8/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1230	1237	1242	1247	1252	1307	1322	1337		
Score		R0	R0	R0	P3	P2	P1	P0		
Other							1316 sternal1329 stand			
PlasmaSample										

Bolt Nov/8/13	after premed	Before IPPV	Out of MRI
Na+	146	147	146
Cl -	117	116	116
K+	3.6	3.3	3.6
Hb	14.3	13.3	12
pH	7.326	7.203	7.345
PCO2	40.3	55.7	38
PaO2	74.9	561	452
HCO3-	20.1	20.8	20.4
ABE	-4.6	-7.1	-4.6
Lactate	1.1	1.6	1.2
PCV (%)	40	39	35
TP (mg/dL)	60	60	56
BUN	5-15		

	HR	RR	TEMP	Attitude
Pre-Instrumentation	96	18	39.1	calm

	Time	Response	Attempts
EMLA application	0718		
Cephalic vein	0737	none	1
Meloxicam	0738		
Dorsal pedal artery	Lt	none	1

Date:_____Oct 6_2014_____

Randomization Dog number: _____

Dog ID#: _____

Dog Name: _____Bolt_____

Dog Weight:_____29.5_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas:_____	109	22	129	92	77		7.4/7.1/7.5		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0805___	4.1	Yes	No	No	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	99	60	174	108	83		7.6		
BloodGas Taken _____	111		182	116	89		9.4/8.8		
	99		170	112	87	4.19	5.6	147	16.9

Time Starting Induction: _____0822_____

P/A Vol: _____	Time:0822	Time:0823	Time:0823	Time:	Time:	Time:	Time Intubation:	_____0823_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score: _____1_____
Injectable Volume Admin								Comments
Attempt to Intubate			y					
Relaxed jaw tone								
Lateral palpebral	X							
Medial palpebral	x							
Coughing			X					
Swallowing								
Paddling								
Vocalization								

Bolt Oct/06014	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	0824	0829	0834	0839	0842	0903	0908	0913	0918	0923	0928	0933	0938	0943	0948	0956	1004		1009	1017
Fluid Rate						145						dopamine								
P or A rate	250/70->275/77		300/84		325/91			300/84	275/77	250/70						275/77->300/84				
P/A Top Up#	0825		0833		0843	0850										0954/0959				
HR bpm	95	94	110	123	150	125	115	113	113	109	109	92	85	77	96	76	71	75	69	93
SAP mmHg	122	123	110	100	73	74	73	62	61	60	60	60	68	71	71	102	96	95	84	92
DAP mmHg	56	62	57	52	47	58	58	50	51	50	44	43	51	50	49	65	55	57	54	65
MAP mmHg	74	77	72	68	58	65	64	56	55	53	52	50	57	56	57	76	66	67	63	74
Temp °C			38			38.1										37				
SPO_2	97	95	96	97	98	100	100	100	100	100	100	100	99	99	100	97	98		100	96
ET CO_2	42	46	52	57	46	33	39	42	43	44	44	44	45	45	46	35	35			
RR	0	29	11	6	12	12	10	10	10	10	10	10	10	10	10	12	12			
LiDCO				2.25/CI 2.38													1.71/CI 1.81			
PulseCO	4.7	4.4/4.5	5.6/5.7	2.2	1.8/1.7											0.88/0.84/0.79	1.62/1.44/1.4/2.1			1.6/1.8/1.5
PulsCO IND	3.9/4/4.3 1min		4.1/4.2 2min		4.1/4.2, 3min		4.1,4 min													
Anesth score	1	0	1	0	1	1(problem w/ a-line)	0	0	0	0	0	0	0	0	0	2	1			

Baron Oct/06/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1009	1012	1017	1022	1027	1042	1057	1112		
Score		R0	R0	R0	P3	P1	P0	P0		
Other						Sternal:1042 Stand:1045				
PlasmaSample										

Baron Oct/06/14	3min after fentanyl	Pre-Vent	End MRI
Na+	147	149	146
Cl -	117	116	115
K+	3.4	3.2	4
Hb	16.8	15.2	12.9
pH	7.381	7.192	7.312
PCO2	35	54.3	45.3
PaO2	68.2	406	437
HCO3-	20.3	19.1	22.2
ABE	-3.5	-9.3	-3.5
Lactate	2.4	3.2	1.4
PCV (%)	48	49	38
TP (mg/dL)	60	60	60
Plasma Sample:			

	HR	RR	TEMP	Attitude
Pre-Instrumentation	76	20	39	calm

	Time	Response	Attempts
EMLA application	0730		
Cephalic vein	0745		
Meloxicam	0751		
Dorsal pedal artery	Left 2nd		

Date:___Oct 14_2014_____

Randomization Dog number: _____

Dog ID#: _____

Dog Name: _____Bolt_____

Dog Weight:_____29.3_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas :_____	94	22	159	106	85		2.5/2.6		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0844__	4.1	Yes	No	No	

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	99	21	218	139	108		3.2/3.1		
BloodGas Taken	89	19	211	120	89		3.3/3.4		
_____	90	pant	181	116	87	3.39/Ci 3.6	3.1/3		

Time Starting Induction: _____0852_____

P/A Vol: _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score: _____
Injectable Volume Admin								Comments
Attempt to Intubate	x							
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Bolt Oct/14/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	0853	0858	0903	0908		0915	0929	0934	0939	0944	0949	0954	0959	1004	1009					
Fluid Rate																				
P or A rate	250/70-275/77	300/84		325/91								300/84				325/91				
P/A Top Up#		0902																		
HR bpm	108	89	116	127	129	138	135	131	127	122	119	117	116	115	115	80	82	84	85	110
SAP mmHg	133	128	109	119	110	90	80	78	82	76	81	77	78	78	81	100	102	102	100	101
DAP mmHg	69	63	54	54	52	49	51	51	54	48	50	47	48	49	49	64	60	61	59	63
MAP mmHg	87	80	70	72	69	65	61	61	64	58	60	57	58	59	59	76	70	71	69	73
Temp °C																				
SPO_2	95	98	98	96		97	99	97	97	97	98	96	96	96	96	99	99		96	96
ET CO_2	35	47	54	52		48	37	36	37	37	39	40	40	40	45	42	41			
RR	0	17	6	7		11	11	11	11	11	11	9	9	9	9	9	9			
LiDCO				4.31/CI 4.57													1.77/CI 1.88			
PulseCO	3.8/3.9/4/4.3	3.6/3.9/4/4.1	4.7/4.9/5/5.1	6/6.1/5.8/5.9	4.2/4.3/4.4/4.5	3.4/3.7/3.8/4.1										1.5/1.6/1.4/1.6	1.6/1.7	1.8/1.9		2.1/2.2/2.3/2.7/2.6/2.5
PulsCO IND	3.4/3.9/3.1 1min		3.1/3.2/3.4 2min			3m3.4/3.7/3.8 3min		3.7/3.3/2.9/3.2 4 min												
Anesth score	1	1	0	1		0	0	0	0	0	0	0	0	0	0	0	0			

Bolt Oct/14/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1025	1030	1035	1040	1045	1100	1115	1130		
Score		R0	R0	R0	P3	P2	P1	P0		
Other						Sternal 1058		Stand 1124		
PlasmaSample										

Bolt Oct/14/14	3min after fentanyl	Pre-Vent	End MRI
Na+	147	149	147
Cl -	116	115	115
K+	3.5	3.1	3.7
Hb	14.5	13.9	11.2
pH	7.341	7.144	7.266
PCO2	38.1	66.6	47.5
PaO2	83.4	469	447
HCO3-	19.5	21.5	21
ABE	-4.5	-8	-5.6
Lactate	1.8	2.3	1.6
PCV (%)	42	40	43
TP (mg/dL)	60	58	54
Plasma Sample:			

Appendix 2.5: Raw data of dog 5

	HR	RR	TEMP	Attitude
Before Instrumentation	126	36	38.6	excited

	Time	Response	Attempts
EMLA application	0757		
Cephalic vein	0805	Calm	1
Dorsal pedal artery	0815	Calm	1

Date:_____Oct/13/13 _____
Randomization Dog number: ____1-_____
Dog ID#: _____
Dog Name: _____Chance_____

Dog Weight:_____26_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	SPO2	Na+	Hgb
Time:___0855_____										
Blood Gas : 0815	112	24	159	105	85	5.56 (CI:6.31)	NA	NA	144	16.8 g/dL

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: __9:28_____	3.6	Yes	Yes	No	1

2 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	SPO2	Na+	Hgb
Time:										
Blood Gas:_NA__	95	180	142	106	89	5.58 (CI:6.35)	NA	NA	147	14.5

Time Starting Induction: ____0937_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0939_____
Mid/Sal Volume: sal1.6ml	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	Y	Y	Y				1.9	_____3_____
Attempt to Intubate	N	N	Y					Comments:
Relaxed jaw tone	N	Y	Y					
Lateral palpebral	Y	Y	N					
Medial palpebral	Y	Y	Y					
Coughing	N	N	N					
Swallowing	N	N	Y					
Paddling	Y	N	N					
Vocalization	Y	Y	N					

Chance Oct/13/13	POST-Intub	5 min	10 min	15 min	20 min	IPPV Starts	INTO MRI	5 min scan start	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	Pre-Recovery		TIVA OFF
TIME	0940	0945	0950	0955	1000	1005	1016	1021	1026	1031	1036	1041	1046	1051	1056	1101	1106	1111	1118	1124	1129
Fluid Rate							130	130	130	130	130	130	130	130	130	130	130	130	0	0	0
P or A rate		70	77	84->91	98->105	112	112	112	105	112	105	105	105	98	98	105	105	105	105	105	0
P/A Top Up	1	0	2	1	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HR bpm	88	77	74	86	78	107	122	97	89	123	113	105	102	96	97	90	90	97	66	54	53
SAP mmHg	139	116	120	116	115	135	67	88	80	86	70	72	74	73	72	76	76	74	118	130	
DAP mmHg	63	53	57	53	54	54	45	53	47	49	43	44	44	45	43	44	43	43	48	49	
MAP mmHg	80	68	67	66	67	68	59	64	57	65	53	55	55	55	54	54	53	55	60	63	
Temp ^{o}C						37.5															
SPO_2	96	97	97	97	96	97	98	98	98	97	99	99	99	98	98	98	99	99	99	98	
ET CO_2		57	50	51	49	40	35	38	42	40	41	41	41	41	41	40	40	40	41	39	
RR	0	0	10	7	6	17	14	10	11	11	12	12	12	12	12	12	12	12	10	10	
LiDCO (CO/CI)						2.55/2.91														1.85/2.11	
PulseCO																					
Anesth score	3 poor	3 poor	2poor	2 poor	poor	poor		0 stable	0 dorsal	0	0	0	0	0 2 buckin g @ 1055	0	0			0		0

Chance Oct/13/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1129	1137	1142	1147	1152	1207	1222	1237	1307	
other							Return to normal		Normal walking	
Score		R3	R3	R3	P0	P0	P0	P0	P0	
PlasmaSample										

Chance Oct/13/13	Before premed	Before ventilation	End of MRI
Na+	144	147	146
Cl -	115	117	115
K+	3.9	3.3	4.0
Hb	16.8	14.5	12.7
pH	7.398	7.218	7.307
PCO2	33.6	53	45.7
PaO2	89.1	533	514
HCO3-	21.9	20.2	21.4
ABE	-3.7	-7.0	-4.6
Lactate	1.7	1.5	1.2
PCV (%)	50	43	37
TP (mg/dL)	6.0/ BUN 5-15	5.4	5.2
Plasma Sample:			

	HR	RR	TEMP	Attitude
Before Instrumentation	108	30	38.7	calm

	Time	Response	Attempts
EMLA application	0729		
Cephalic vein	0750	no	2
Meloxicam	0.52/0751		
Dorsal pedal artery	0810		

Date:_____Oct 28_2013_____

Randomization Dog number: _____

Dog ID#: _____tx2_____

Dog Name: _____Chance_____

Dog Weight:_____26_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas:_____	120	30	116	94	82	NA	4		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0818__	3.6	No	No	No	0

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	78		152	106	84		3.4		
Blood Gas:_____	139	18	182	135	106	13.1/11			

Time Starting Induction: _____0830_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0832_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	y						_____1_____
Attempt to Intubate	Y(in)							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	N							
Coughing	N							
Swallowing	N							
Paddling	N							
Vocalization	n							

Chance Oct/28/13	POST-Intub	5 min		10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	55 min	60 min	Out of MRI	Pre-Recovery		extubation	5min post
TIME	0832				0847		0855	0905												1005	1012	1020		1034	
Fluid Rate																									
P or A rate	250/70	275/77			300/84			325/91			350/98	375/105				400/112	425/119		450/126						
P/A Top Up		1			1													2	1						
HR bpm	91	80	93	96	101	128	134	80	79	77	76	69	69	72	75	79	86	137	143	150	107	75	90	97	91
SAP mmHg	110	97	113	113	118	104	78	85	88	87	95	96	98	99	98	100	132	151	160	168	103	103	89	97	91
DAP mmHg	60	61	58	58	57	53	50	59	59	55	60	58	58	60	61	64	85	98	107	107	65	58	53	60	60
MAP mmHg	71	73	72	72	73	69	60	66	62	64	70	68	69	70	71	74	100	116	126	124	77	70	64	71	70
Temp °C																									
SPO_2	95	97		97	97		97	99	99	96	97	95	97	95	96	96	96	95	96	96	99	99			
ET CO_2		15		27	22		55	43	45	45	42	41	40	39	39	39	42	42	42	33	38	38			
RR	0	0		0	0		11	10	10	10	10	10	10	10	10	10	10	10	10	10	11	11			
LiDCO		3.15/CI: 3.59			3.22/CI: 3.66																	2.69/CI:			
PulseCO	7.8	4.6	8.0	9.2	5.4	5.9	2.4														1.6	1.5	2.2	2.6	2.5
PulseCO IND	1:7.7	2:2.6		3:4.7																					
Anesth score	1	2		1	1		1	1	1	1	1	1	1	1	1	1	1	2	2	1	1	1			

Chance Oct/28/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1023	1034				1104		1134		
Score		R0	R0	R2	Very dyphoric	Very dysphoric	1115 stop whinning	1134 sternal	1140 stand/ambulate	
Other										
PlasmaSample										

Chance Oct/28/13	after premed	5 min post-intubation	Before IPPV	Out of MRI
Na+	144	145	146	144
Cl -	117	117	117	118
K+	4.1	3.5	3.6	4.2
Hb	16.4	17.7	15.2	14.6
pH	7.333	7.255	7.142	7.332
PCO2	39.7	46.6	67.5	37.7
PaO2	89.4	247	480	610
HCO3-	20.1	20.7	22.6	19.6
ABE	-4.3	-6.2	-7.7	-5.6
Lactate	1.0	1.4	1.1	1.1
PCV (%)	48		45	43
TP (mg/dL)	6.0		5.6	5.4
BUN	5-15			

	HR	RR	TEMP	Attitude
Before Instrumentation	114	18	38.2	

	Time	Response	Attempts
EMLA application	0730		
Cephalic vein	0740		
Meloxicam	0810		
Dorsal pedal artery	0800		1

Date:_____Nov8_2013_____

Randomization Dog number: _____tx3_____

Dog ID#: _____

Dog Name: _____Chance_____

Dog Weight:_____26_____KG

After 30 min rest:	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas :__	80	18	145	112	97		6.1		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0834____	3.6	y	n	n	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	98	24	148	98	83		5.7		
Blood Gas Taken :__	92	20	181	104	89	4.2/4.79	4.7		
	92	pant	180	113	91				

Time Starting Induction: __0844_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0848_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume	y	y	y	y	Y		6.8	_____3_____
Attempt to Intubate					Y			Comments:
Relaxed jaw tone								
Lateral palpebral					N			
Medial palpebral					y			
Coughing								
Swallowing								
Paddling								
Vocalization								

Chance Nov/08/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	Out of MRI	Pre-Recovery	TIVA stop	extubation	5min post
TIME	0848	0853	0858	0903	0906	0915	0920								1000		1010	1018	1022	1032	1037
Fluid Rate									Dopa: 5	7	7	5	5		3						
P or A rate	250/70		275/77-300/87			275/77															
P/A Top Up	1		1		1	1															
HR bpm	71	62	70	74	77	98	105	96	92	92	93	85	75	66	63	76		58	54	55	81	89
SAP mmHg	111	100	96	94	95	72	69	70	68	68	71	72	84	98	89	80		98	88	81	105	116
DAP mmHg	51	48	46	46	46	40	35	40	34	38	39	38	45	47	41	40		49	45	41	53	62
MAP mmHg	67	61	59	57	58	52	44	50	49	47	47	48	54	58	51	49		62	57	52	67	77
Temp °C	37.1																	35.6				
SPO_2	97	97	97	97		97	97	96	96	96	96	96	96	98	98	98		98	98			
ET CO_2	33	37			59	33	334	34	38	38	37	38	39	40	39			38	38			
RR	0	0	0	0		12	10	10	8	8	8	8	8	8	8	8		11	11			
LiDCO				2.47/2.82																		
PulseCO	4.7	3.1	3.7	4.1	2.8	3.1												1.6	1.6	1.9	2.6	3
PulseCO IND	3.4	3.7	3.7																			
Anesth score	1	1	1	1		1	1	0	0	0	0	0	0	0	0	0		1	1			

Chance Nov/08/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1022	1032	1037	1042	1047	1102	1117	1132		
Score		R0	R2	R2	P2	P2	P1			
Other					1047sternal	1115stand				
PlasmaSample										

Chance Nov/08/13	after premed	Before IPPV	Out of MRI
Na+	144	146	144
Cl -	115	116	115
K+	3.8	3.5	3.8
Hb	15.5	15.6	12.6
pH	7.35	7.216	7.308
PCO2	41.6	59.3	41.8
PaO2	77.1	466	610
HCO3-	22	23.1	20.8
ABE	-2.5	-5.5	-5.2
Lactate	0.9	1.1	0.9
PCV (%)	45	45	36
TP (mg/dL)	54	54	50
BUN	5-15		

Appendix 2.6: Raw data of dog 6

	HR	RR	TEMP	Attitude	**Date:_____Oct/16/2013_____**
Before Instrumentation	102	24		nervous	Randomization Dog number: _____no.3_____
	Time	Response		Attempts	Dog ID#: _____
EMLA application	0735				Dog Name: _____Hunter_____
Cephalic vein	0817; 0825	none		3	
Meloxicam	y				**Dog Weight:_____24_____KG**
Dorsal pedal artery	0851	mild		4	

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____0905___			144	99	75	5.26/			
Blood Gas Taken t:0855_	119		151	101	88	CI6.36	5.2	142	18.3

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0914____	3.4	Yes	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 0925			180	120	96	6.94/	6.9		
Blood Gas Taken :__0916_	119	panting	182	119	102	CI:8.40	6.2	145	17.4

Time Starting Induction: _____0932_____

P/A Volume : __1.5____	Time:0933	Time:0933	Time:	Time:	Time:	Time:	Time Intubation:	_____0933_____
Mid/Sal Volume:___1.4___	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	y					1.8ml	_____2_____
Attempt to Intubate	Y							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	Y							
Coughing	Y							
Swallowing	N							
Paddling	N							
Vocalization	n							

Hunter Oct/16/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery	
TIME	0935	0940	0945	0950		0953	1000	1008	1013	1018	1023	1028	1033	1038	1043	1048	1054	1054	1106
Fluid Rate	0	0	0	0		0	120	120	120	120	120	120	120	120	120	120	120		
P or A rate	70	77	84->91	91		91		84	84	84	84	84	84	84	84	84	84		
P/A Top Up			1				2												
HR bpm	120	107	101	99	115	124		109	88	104	89	89	83	86	84	93	61	61	58
SAP mmHg	109	116	108	103	93	85		78	86	85	80	88	84	82	81	86	105	102	101
DAP mmHg	60	66	59	58	53	52		53	57	51	52	56	55	53	54	53	63	62	59
MAP mmHg	75	81	73	72	68	68		62	67	63	60	65	63	61	65	63	76	72	65
Temp °C																			
SPO_2	96	95	95	97		97	97		100	100	100	100	100	100	100	100	100	100	
ET CO_2	29	43	39	47		44		37	43	31	32	35	33	34	34	34	35	34	34
RR	panting	28	21	17		10		8	8	8	8	8	8	8	7	7	13	13	13
LiDCO				3.39/ CI:4.1														1.88/CI:2.28	
PulseCO	6.1	5.9	5.4	5.3	3.2	3.6												1.5	1.4
Anesth score	0	0	2	1		1	1	0	0	0	0	0	1	0	0	0	0		

Hunter Oct/16/13		Stop TIVA	Extub Time 0	E 5	E 10	E 15	E 30	E 45	E 60	E90	E 120
Time		1110	1112	1117	1122	1127	1142	1157	1212		
Score	**Ben**		R2	R3	R3	P0	P0	P0	P0		
	Melissa		0	2	3	1	0	0	0		
Other							Calm between 30-45	Ambulate			
PlasmaSample											

Hunter)ct/16/13	Before premed	3 min after fentanyl	Before IPPV	Extubation
Na+	142	145	146	146
Cl -	114	116	115	115
K+	3.9	3.8	3.5	3.8
Hb	18.3	17.4	16.5	13.6
pH	7.398	7.386	7.292	7.371
PCO2	35	37.3	47.9	38.8
PaO2	103	79.8	527	563
HCO3-	20.7	22.9		
ABE	-2.1	-2.5	-3.2	-2.5
Lactate	0.9	0.7	1.2	0.5
PCV (%)	53	50	47	40
TP (mg/dL)	6.0	5.6	5.6	5.0
BUN	5-15			
Plasma Sample:				

	HR	RR	TEMP	Attitude
Before Instrumentation		panting	38.6	calm

	Time	Response	Attempts
EMLA application	0720		
Cephalic vein	0730	no	1
Meloxicam	0741/0.48ml		
Dorsal pedal artery	0749	no	1

Date:_____Oct 30_2013_____

Randomization Dog number: _____tx2_____

Dog ID#: _____

Dog Name: _____Hunter_____

Dog Weight:_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas:_____	60	panting	118	94	76	NA	1.9	NA	NA

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: ___1103_____	3.4	No	No	No	0

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:									
Blood Gas:_____	115	panting							

Time Starting Induction: _____1112_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____1114_____

Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume Admin	y	y	y	y	y	y	y	4.2	_____3_____
Attempt to Intubate					Y(in)				Comments:
Relaxed jaw tone									
Lateral palpebral	y	y	Y	n	N				
Medial palpebral	y	y	y	y	Y				
Coughing					y				
Swallowing									
Paddling									
Vocalization									

Hunter Oct/30/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1114			1129		1132	1145								1225	1228	1236			1238	1258
Fluid Rate																					
P or A rate	250/70	300/84	325/91-350/98	375/105		400/112				425/119		400/112				400/112					
P/A Top Up																					
HR bpm	105	100	94	86	87	105	86	87	91	98	102	105	105	103	108	86	70	70	83	121	141
SAP mmHg	124	124	116	112	109	105	95	94	97	98	107	108	123	163	163	106	102	100	93	108	128
DAP mmHg	68	65	59	56	57	57	50	60	59	60	66	68	81	97	95	58	55	53	52	64	79
MAP mmHg	84	80	74	71	69	69	69	70	69	71	77	79	92	115	113	71	67	68	66	78	96
Temp ^{o}C																					
SPO_2	98	98	98	99		96	96	97	96	96	96	98	97	97	97	98	97				
ET CO_2	0	33	48	46		41	41	42	42	42	42	42	43	43	42	38	36				
RR	0	0	15	23		11	11	11	11	11	11	11	11	11	11	11	11				
LiDCO				3.05/CI: 3.7													2.37/CI:2.87				
PulseCO	4.3	4.4	4.3	4.1	3.1	3.0										2.3	1.5	2.1	3.0	3.0	5.8
PulseCO IND	1:3.8	2:4.5	3:4.0																		
Anesth score	1	2	2	1		1	1	1	1	1	1	1	1	1	1	1	1				

Hunter Oct/30/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1238	1257			1312	1327		1357		
Score		R2	R3	R3	dysphoric	dysphoric	P0	P0		
Other					1314 sternal	1327 stand				
PlasmaSample										

Hunter Oct/30/13	after premed	Before IPPV	Out of MRI
Na+	147	147	146
Cl -	119	118	118
K+	3.6	3.4	3.6
Hb	16.8	16.5	14.4
pH	7.382	7.274	7.348
PCO2	37.9	49.8	40.5
PaO2	79.8	556	575
HCO3-	22.8	22.0	21.6
ABE	-2.4	-4.6	-3.2
Lactate	0.5	0.9	0.5
PCV (%)	48	47	40
TP (mg/dL)	5.4	5.4	4.8
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	90	pant	38..9	calm

	Time	Response	Attempts
EMLA application	0740		
Cephalic vein		n	
Meloxicam	1140		
Dorsal pedal artery			

Date:_____Nov11_2013_____

Randomization Dog number: _____tx3_____

Dog ID#: _____

Dog Name: _____Hunter_____

Dog Weight:_____24.5_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____ _____									
Blood Gas Taken t:__	110	20	169	127	107		7.9		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1140_____	3.6	y	n	n	0

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	104	pant	215	151	112		7.3		
Blood Gas Taken :__	128		133	122	119	5.57/6.04	6.3		

Time Starting Induction: __1145_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:		Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume Admin	y	y	y	y	y	y	Y	6.7	_____2_____
Attempt to Intubate					y		Y		Comments:
Relaxed jaw tone									
Lateral palpebral	y	y	y	y	y	N	n		
Medial palpebral	y	y	y	y	y	y	Y		
Coughing							y		
Swallowing					y				
Paddling									
Vocalization									

Hunter Nov/11/13	POST-Intub	5 min	10 min	15 min		IPPV Starts		INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1152	1157	1202	1207	1220		1224	1233	1238	1243	1248	1253	1258	1303	1308	1313	1318	1323	1330		1334	1337	1342
Fluid Rate																							
P or A rate	250/70-275/77	300/84-325/91-350/98				375/105																	
P/A Top Up	1					1		1															
HR bpm	88	89	92	92	88	86	87	85	74	78	84	86	74	67	69	59	82	58	59	59		74	64
SAP mmHg	139	142	125	114	105	109	100	94	90	86	85	85	88	98	114	113	100	137	138	135		124	126
DAP mmHg	60	56	52	53	48	47	44	48	46	42	43	42	43	44	45	47	45	52	56	55		57	55
MAP mmHg	81	74	69	67	60	61	59	62	57	56	55	54	54	58	62	63	60	69	72	70		71	73
Temp °C			38.3																				
SPO_2	97	96	97	98		98		98	96	99	99	99	99	99	99	99	99	97	97				
ET CO_2	35	36	49	54		54		46	37	39	38	38	37	37	37	37	39	41	40				
RR	0	35	15	6		9		10	10	10	10	10	10	10	10	10	10	9	10				
LiDCO																			1.85/2.18				
PulseCO	9.1	7.3	8.1	8.2	6.7	3.4	3.2											1.9	1.6	1.8		2.1	1.8
Anesth score	2	2	1	1		1		1	0	0	0	0	0	0	0	0	0	1	1				

Hunter Nov/11/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1334	1337	1342	1347	1352	1407	1422	1437		
Score		R0	R0	R2	P1	P1	P1			
Other				1345 sternal			1421 stand			
PlasmaSample										

Hunter Nov/11/13	after premed	Before IPPV	Out of MRI
Na+	147	147	145
Cl -	118	118	116
K+	3.7	3.5	4.2
Hb	17.2	16.3	14.1
pH	7.366	7.209	7.264
PCO2	37.9	58.5	50.5
PaO2	92.7	551	497
HCO3-	22.1	22	22.2
ABE	-3.4	-6.2	-4.8
Lactate	1.1	1.7	0.6
PCV (%)	50	47	40
TP (mg/dL)	58	58	52
BUN	5-15		

Appendix 2.7: Raw data of dog 7

	HR	RR	TEMP	Attitude
Before Instrumentation	120	36		calm

	Time	Response	Attempts
EMLA application	0720		
Cephalic vein	0740	no	1
Meloxicam	0755, 0.5ml		
Dorsal pedal artery	0750	no	1

Date:____Oct 23 2013_____
Randomization Dog number: _____9_____
Dog ID#: _____
Dog Name: _____Lucky_____

Dog Weight:_____25.5_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:____0805_____									
Blood Gas Taken t:_____	96	24	147	118	99	na	na	Na	na

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0815_____	3.6	Yes	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 0827	55		181	125	108	2.33/CI:2.7			
Blood Gas Taken :__0817_	59	48	152	119	106	5	3.1; 2.3	144	15.4

Time Starting Induction: _____0835_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:		Time Intubation:	_____0838_____
Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume Admin	y	y	y	y	y	y	y	6.8ml	_____3_____
Attempt to Intubate				y					Comments:
Relaxed jaw tone									
Lateral palpebral									
Medial palpebral									
Coughing									
Swallowing									
Paddling									
Vocalization									

Lucky Oct/23/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	Out of MRI	Pre-Recovery
TIME	0838	0843	0848	0853	0901	0910	0915	0920	0925	0930	0935	0940	0945	0950	0955		1007	1012
Fluid Rate						130	130	130	130	130	130	130	130	130	130			
P or A rate	250	275	300	300	300	300	300	300	300/ D:4.5	275/ D:4.5	275/ D:7	275/ D:10	275/ D:10	275/ D:7	275/ D:7			
P/A Top Up		1	1			2												
HR bpm	81	81	85	96	96	80	92	92	88	86	72	75	65	60	50		68	70 72
SAP mmHg	105	104	99	97	93	61	68	71	73	68	60	75	81	101	104		117	98 101
DAP mmHg	68	63	59	60	54	36	42	45	45	42	35	43	42	45	48		63	57 63
MAP mmHg	74	75	71	71	68	43	50	53	53	49	41	50	51	56	62		75	68 73
Temp °C																		
SPO_2	95	96	97	97	99	96	98	98	98	98	98	99	99	99	99		98	98
ET CO_2	42	47	46	49	40	32	34	35	35	35	35	35	35	35	37		45	37
RR	0	6	6	4	10	10	10	10	10	10	10	10	10	10	10		10	10
LiDCO		3.42/ CI:4.04		2.85/CI: 3.37														3.63/CI:4.28
PulseCO				4.7;5.5; 5.4														2.5
Anesth score	0	1	1	1	2	1	1	1	1	1	1	1	1	1	1		2	1

Lucky Oct/23/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1019	1022	1027	1032	1037	1052	1107	1122		
Score		R0	R0	R0	P3	P3	P1	P1		
Other							Sternal and atand and ambulate on 1110			
PlasmaSample										

Lucky Oct/23/13	5 min pot-fentanyl	5 min post-intubation	Before IPPV	Out of MRI
Na+	144	145	146	145
Cl -	116	116	116	3.6
K+	4.1	3.7	3.5	116
Hb	15.4	16.7	14.2	13.1
pH	7.394	7.262	7.222	7.283
PCO2	32.6	46.1	50.6	42.8
PaO2	90.6	180	521	511
HCO3-	19.2	19.8	20	20.1
ABE	-3.8	-6.7	-7.6	-6.5
Lactate	1	1.8	1.6	1.3
PCV (%)	46	47	40	38
TP (mg/dL)	6.4	6.2	6.0	5.8
BUN	5-15			

	HR	RR	TEMP	Attitude
Before Instrumentation	108	24	38.6	calm

	Time	Response	Attempts
EMLA application	0730		
Cephalic vein	0748	no	2
Meloxicam	0750		
Dorsal pedal artery	0800		1

Date:_____Nov5_2013_____

Randomization Dog number: _____tx2_____

Dog ID#: _____

Dog Name: _____lucky_____

Dog Weight:_____26_____KG

After 30 min rest:0810	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__0822	85	24	138	105	92		4.3		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0820___	3.6	No	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	78	30	147	107	96	1.6	2.3		
Blood Gas Taken :__0822	55	26	154	110	100	1.18	1.7		
	70		159	116	101	1.34	1.6		

Time Starting Induction: ____0838_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	Y						_____
Attempt to Intubate		Y						Comments:
Relaxed jaw tone								
Lateral palpebral	N	n						
Medial palpebral	y	y						
Coughing								
Swallowing								
Paddling								
Vocalization								

Lucky Nov/05/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	Out of MRI	Pre-Recovery	TIVA stop	extubation	5min post
TIME	0839			0854	0859	0905	0910		0920 needle	0928 injection					0950	0953	1000	1005	1012	1017
Fluid Rate																				
P or A rate	250/70-	275/77-300/84																		
P/A Top Up		1				1														
HR bpm	80	77	83	98 97	96	83	83	84	82	79	79	81	80	86	86	75	60 63	53	57	63
SAP mmHg	114	105	91	87 81	71	74	73	74	74	72	71	72	71	74	78	79	80 87	87	95	94
DAP mmHg	85	74	64	62 58	52	59	56	57	49	56	54	55	54	57	60	62	59 60	61	67	64
MAP mmHg	85	74	64	62 58	52	59	56	57	49	56	54	55	54	57	60	62	59 60	61	67	64
Temp °C			37.4													35.4				
SPO_2	96	97	99	98	97	98	98	98	97	97	99	99	98	98	98	97	97	97		
ET CO_2	0-46	47	52	53	44	40	42	42	42	42	42	42	42	42	42	40	37	37		
RR	0-6	11	6	15	11	11	11	11	11	11	11	11	11	11	11	11	11	11		
LiDCO				2.64/3.01													1.68/1.91			
PulseCO	1.8	2.6	3.3	4.3 3.2	3											1.7	1.5 1.6	1.7	1.8	1.7
Anesth score	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	1			

Lucky Nov/05/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1005	1012								
Score		R0	R0	R0	P3	P2	P1			
Other						Sternal 1042		1104 stand		
PlasmaSample										

Lucky Nov/05/13	after premed	Before IPPV	Out of MRI
Na+	144	146	153
Cl -	117	117	113
K+	4.1	3.6	4.4
Hb	15.1	15.5	13.1
pH	7.336	7.165	7.264
PCO2	39.6	61.1	44.3
PaO2	78.1	547	606
HCO3-	20.2	21.1	
ABE	-4.2	-8.5	-602
Lactate	1.9	2.6	1.2
PCV (%)	43	45	39
TP (mg/dL)	66	64	60
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	72	28	38.4	calm

	Time	Response	Attempts
EMLA application	0720		
Cephalic vein	0735	no	1
Meloxicam	0735;0.5 ml		
Dorsal pedal artery			1

Date:_____Nov19_2013_____

Randomization Dog number: _____tx3_____

Dog ID#: _____

Dog Name: _____lucky_____

Dog Weight:_____26_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__	72	28	139	111	97		2.5		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0820___	3.6	No	No	No	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	51	24	117	89	76		1.9		
Blood Gas Taken :__0824			164	120	104		1.5		
			155	116	102	1.94	1.3		

Time Starting Induction: ____0833_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	Y					1.7	_____0_____
Attempt to Intubate	Y							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	Y	y	y					
Coughing	Y							
Swallowing	N							
Paddling	N							
Vocalization	n							

Lucky Nov/19/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	50 min	Out of MRI	Pre-Recovery	TIVA stop	extubation	5min post
TIME	0830	0835	0840	0845	0850	0855	0900	0905	0910							0945	0953	1000	1006	1012	1017
Fluid Rate																					
P or A rate	70	70-77	84	91	98-115						98										
P/A Top Up		1	2																		
HR bpm	81	89	81	86 / 107	113	109	98	96	93	92	91	89	90	90	67	68	66	68 / 73		75	72
SAP mmHg	115	115	119	97 / 96	89	66	62	62	64	63	62	63	62	69	86	82	94	79 / 75		91	94
DAP mmHg	67	67	70	59 / 58	53	43	42	42	47	46	42	48	47	53	60	55	54	49 / 48		56	60
MAP mmHg	80	80	83	69 / 69	64	52	51	51	52	52	51	52	53	58	67	63	66	58 / 55		66	70
Temp °C	38.6				37.8												35.4				
SPO_2	99	99	99	99	99	99	97	98	98	97	98	97	97	97	97	98	99	98			
ET CO_2	45	47	47	51	55	51	38	38	37	37	36	33	35	36	36	38	40	37			
RR	0	1	1	1	12	10	9	9	9	9	8	8	8	8	8	8	10	10			
LiDCO				2.8/CI:2.9														2.1/CI:2.39			
PulseCO	1.4	2.1	2.6	2.9	2.9												1.3	1.2 / 1.6		2.9	2.1
Anesth score	0	2	3	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0			

Lucky Nov/19/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1006	1012	1017	1022	1027	1042	1057	1112		
Score		R0	R0	R0	P3	P3	2	1		
Other							1103 sternal	1114 stand		
PlasmaSample										

Lucky Nov/19/13	after premed	Before IPPV	Out of MRI
Na+	140	246	145
Cl -	4.2	3.6	3.9
K+	121	118	114
Hb	15.7	15.2	12.9
pH	7.362	7.134	7.252
PCO2	34.8	51.8	46.5
PaO2	86.3	536	560
HCO3-	15.7	16.6	20.3
ABE	-4.6	-12.9	-7
Lactate	1.8	2.8	2
PCV (%)	46	45	37
TP (mg/dL)	68	62	60
BUN	5-15		

Appendix 2.8: Raw data of dog 8

	HR	RR	TEMP	Attitude
Before Instrumentation	120	30		calm

	Time	Response	Attempts
EMLA application	0723		
Cephalic vein	0738	no	1
Meloxicam	0749 (0.46ml)		
Dorsal pedal artery	0748	no	2

Date:_____Oct 17 2013_____

Randomization Dog number: ____5_____

Dog ID#: _____

Dog Name: _____Major_____

Dog Weight:_____23_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____0755_____	136		108	88	77		4.6		
Blood Gas Taken t:_0750_	146	36	131	96	75	7.49	7.4	146	17.6

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0816___	3.2	Yes	No	Yes	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time: 0819									
Blood Gas Taken :_____	144	panting	163	110	88	NA	8.6	NA	NA

Time Starting Induction: _____0821_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0822_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	Y	Y					2.9ml	_____2_____
Attempt to Intubate	Y							Comments:
Relaxed jaw tone	N							
Lateral palpebral	Y							
Medial palpebral	Y							
Coughing	Y							
Swallowing	N							
Paddling	N							
Vocalization	N							

Major Oct/17/13	POST-Intub	5 min	10 min	15 min	IPPV Starts		INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery	
TIME	0822	0827	0832	0837	0842	0847													
Fluid Rate								115	115	115	115	115	115	115	115	115			
P or A rate	250	250	250	250	250	250	225	200	200	200 dopa	200 dopa	200 dopa	200	200	200	200	200	200	
P/A Top Up																			
HR bpm	99	83	92	102	111	137	85	95	98	98	98	95	113	117	115	107	113	65	57	57
SAP mmHg	132	113	97	95	97	84	99	72	66	68	71	68	78	85	84	98	100	103	101	101
DAP mmHg	71	69	51	49	50	56	56	39	38	40	40	38	44	47	46	56	56	64	50	52
MAP mmHg	90	79	68	66	68	71	69	49	47	50	50	48	56	60	59	68	70	76	65	66
Temp °C				37.7															36.4	
SPO_2	98	99	98	98		99	99	99	99	99	99	99	99	99	99	99	99	100	100	
ET CO_2	28		49	55		66	41	39	39	38	37	37	38	38	39	38	38	36	36	
RR	0	0	0	0		13	13	12	12	12	12	12	12	12	12	12	12	13	13	
LiDCO				3.94/ CI:4.89															1.66/CI:2.06	
PulseCO	6.1;4.2; 4.3;4.4	4.4	5.1	5.8	6.6	6.4	4.2											2.4	2.7	3.3
Anesth score	1	1	0	0		0	0	0	0	0	0	0	0	0	0	0	0	1		

Major Oct/17/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1001	1005	1010	1015	1020	1035	1050	1105		
Score		R0	R1	R0	P1	P0	P0	P0		
Other		1012 sternal			1025stand		1055 return to normal			
PlasmaSample										

Major Oct/17/13	Before premed	Before IPPV	Out of MRI
Na+	146	147	146
Cl -	118	117	116
K+	3.7	3.2	3.7
Hb	17.6	16.6	13.2
pH	7.393	7.194	7.343
PCO2	31.1	58.9	37.6
PaO2	76.6	514	567
HCO3-	19.6	21.6	
ABE	-3.2	-7.3	-4.3
Lactate	0.8	20	0.5
PCV (%)	49	46	38
TP (mg/dL)	6.0	5.6	5.3
Bun	5-15		

	HR	RR	TEMP	Attitude	**Date:_____Oct 30_2013_____**
Before Instrumentation	80	48	38.7	BAR	Randomization Dog number: _____tx2_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	1230				Dog Name: _____Major_____
Cephalic vein		no	1		
Meloxicam	1250,0.5ml				**Dog Weight:_____23_____KG**
Dorsal pedal artery		no	2		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas Taken t:_____	80	48	164	112	93		6.1		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: 1350_____	3.2	No	No	Yes	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	138		159	99	80		9.6		
Blood Gas Taken :_____	133	panting	154	101	73	4.4/CI:5.46	4.2		

Time Starting Induction: _____1359_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____1400_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	y					1.5	_____0_____
Attempt to Intubate	Y(in)							_
Relaxed jaw tone	Y							Comments:
Lateral palpebral	N							
Medial palpebral	y							
Coughing	N							
Swallowing	N							
Paddling	N							
Vocalization	N							

Major Oct/30/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1400			1415		1418	1428									1508	1511	1520		1521		
Fluid Rate																						
P or A rate	250/70	275/77	300/84	325/91						350/98	375/105											
P/A Top Up		1								1												
HR bpm	119	105	116	125	131	152	94	91	98	85	97	98	94	92	91	92	88	86	8	81	122	136
SAP mmHg	113	115	94	91	95	92	116	109	105	111	107	108	107	106	107	110	96	100	9	99	102	109
DAP mmHg	56	61	48	49	49	56	76	72	67	74	67	67	67	66	67	69	61	57	54	56	68	63
MAP mmHg	77	79	64	64	64	70	86	81	77	83	79	79	78	77	77	80	69	68	66	67	82	78
Temp °C																						
SPO_2	97	98	98	98		98	97	98	98	99	98	98	98	98	98	98	97	97		97		
ET CO_2	0	0	0	50		51	38	39	40	39	39	39	39	39	39	38	36	39				
RR	0	0	0	7		11	11	11	11	11	11	11	11	11	11	11	11	11				
LiDCO				3.98/CI:4.93														2.09/CI:2.59				
PulseCO	3.5	2.6	2.7	3.1	3.9	4.1											2.1	2.5	2.3	2.3	3.3	3.1
PulseCO IND	1:2.2	2:2.5	3:2.7																			
Anesth score	1	1	1	1		1	1	0	0	2	1	0	0	0	0	0	1	1				

Major Oct/30/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1521	1532				1602	1617	1632		
Score		R0	R2	R2	P3	O2	P0	P0		
Other						1602 sternal	1617 stand			
PlasmaSample										

Major Oct/30/13	after premed	Before IPPV	Out of MRI
Na+	144	146	145
Cl -	116	117	116
K+	3.6	3.2	3.6
Hb	16.1	16.1	13.4
pH	7.368	7.190	7.355
PCO2	38.6	62.1	40
PaO2	68.9	512	583
HCO3-	21.2	22.4	21.9
ABE	-2.5	-6.6	-3.0
Lactate	0.5	0.7	0.6
PCV (%)	46	46	38
TP (mg/dL)	5.6	5.2	5.0
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	132	24		calm

	Time	Response	Attempts
EMLA application	0730		
Cephalic vein	0740	no	1
Meloxicam	0814		
Dorsal pedal artery	0819	no	4

Date:_____Nov 12__2013_____

Randomization Dog number: _____tx3_____

Dog ID#: _____

Dog Name: _____Major_____

Dog Weight:_____23_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas Taken t:_____	98	18	130	101	86		3.1		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: __0825_____	2.2	No	No	Yes(after taking temp)	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	110		212	115	85		5.2		
Blood Gas Taken :_____	103	24	202	109	81	3.2/CI:3.96	2.9		

Time Starting Induction: _____0835_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0835_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	y					1.5	_____1_____
Attempt to Intubate	Y(in)							Comments:
Relaxed jaw tone	Y							
Lateral palpebral	N							
Medial palpebral	y							
Coughing	y							
Swallowing	N							
Paddling	N							
Vocalization	N							

Major Nov/12/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	0836	0841	0846	0851		0855	0904	0909							0944	0947	0952	0959		1001	1009	1014
Fluid Rate																						
P or A rate	250/70-275/77	300/84-325/91	350/98-375/105									350/98										
P/A Top Up	1	1	1				2															
HR bpm	118	103	125	140	138	141	150	146	128	124	115	114	115	117	116	117	65	56	60		153	111
SAP mmHg	165	131	108	98	99	99	70	73	79	83	78	77	80	87	87	86	136	116	104		101	83
DAP mmHg	68	58	50	49	49	50	46	47	47	46	43	42	44	49	47	48	60	56	51		50	40
MAP mmHg	89	77	70	66	67	67	54	58	58	60	56	53	56	61	61	61	75	71	65		63	54
Temp °C		37.5	36.9															35.7				
SPO_2	99	97	99	99		99	99	99	99	99	99	99	99	99	99	99	99	99				
ET CO_2	42	45	59	61		49	37	36	36	37	37	37	37	38	38	38	36	42				
RR	0	0	8	8		12	7	7	7	7	7	7	7	7	7	7	12	11				
LiDCO				5.78/7.17														2.09/2.6				
PulseCO	4.9	4.2	4.9	4.8	5.1	5.7											2.2	2.1	2.2		3.7	4
PulseCO IND	3.9	4.3	4.8																			
Anesth score	2	1	1	1			3	0	0	0	0	0	0	0	0	0	1	1				

Major Nov/12/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1001	1009	1014	1019	1024	1039	1054	1109		
Score		R0	R0	R2	P3	P3	P1	P0		
Other							1044 sternal	1104 stand		
PlasmaSample										

Major Nov/12/13	after premed	Before IPPV	Out of MRI
Na+	146	147	147
Cl -	118	118	117
K+	3.6	3.2	3.6
Hb	20.4	17.3	13.4
pH	7.345	7.186	7.333
PCO2	39.1	58.6	40
PaO2	71.8	537	592
HCO3-	20.4	21.4	21
ABE	-3.8	-8.1	-4.5
Lactate	0.9	1.6	0.8
PCV (%)	46	49	38
TP (mg/dL)	56	56	50
BUN	5-15		

	HR	RR	TEMP	Attitude
Pre-Instrumentation				

	Time	Response	Attempts
EMLA application			
Cephalic vein			
Meloxicam	1102		
Dorsal pedal artery			

Date:_____Oct 7_2014_____

Randomization Dog number: _____

Dog ID#: _____

Dog Name: _____Major_____

Dog Weight:_____23.7_____KG

After 30 min rest Time:_____	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:___	120	panting	128	105	91		2.2/2/2.1/2.3/2.4/2.2		

Fentanyl Admin Time: ____1109_____	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
	3.2	No	No	No	3

3 min after premed Time:	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
	82	30	162	107	87		2.4		
BloodGas Taken _____	94		152	98	75	4.01/CI 4.97	4.1/4.2/4.2/3.9		

Time Starting Induction: _____1121_____

P/A Vol: _____	Time: 1121	Time: 1122	Time:	Time:	Time:	Time:	Time Intubation:	_____1122_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score: _____0_____
Injectable Volume	X							
Attempt to Intubate								Comments
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing	x							
Swallowing								
Paddling								
Vocalization								

Major Oct/07/14	POST-Intub	5 min	10min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	1122	1127	1132	1137		1145	1153	1158	1203	1208	1213	1218	1223	1228	1233	1236	1243		1247	1256
Fluid Rate																				
P or A rate	250/70-275/77		300/84			325/91	350/98													
P/A Top Up#	1123 1125		1133			1145	1151													
HR bpm	84	71	89	97	93	112	104	111	111	113	117	114	116	114	122	80	61	65	59	68
SAP mmHg	129	120	117	101	98	106	92	87	90	90	91	95	102	103	100	120	111	109	108	126
DAP mmHg	66	56	59	54	52	60	59	54	57	54	54	57	62	64	62	64	56	56	55	63
MAP mmHg	85	76	73	67	65	74	71	66	70	67	68	70	77	79	76	79	71	71	71	78
Temp °C																				
SPO_2	95		99	98		99	98	99	99	99	99	99	99	99	99	95	95			96
ET CO_2		46	44	50		41	40	41	41	42	43	43	44	45	45	40	38			
RR	0	13	13	11		10	10	10	10	10	10	10	10	10	10	10	10			
LiDCO				3.24/CI 4.02																
PulseCO	4	3.1/3.2	4.5/4.4	4.3/4.4	3.1/3.3/3.3/3.4	3.1/3										2/1.9/1.8				
PulsCO IND	3.4/3.3 1min		3.2 2min			3.1/3.2 3min		3.2/3.3/3.4 4 min												
Anesth score	1	0	1	0		1	1	0	0	0	0	0	0	0	0	0	0			

Major Oct/07/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1247	1251	1256	1301	1306	1321	1336	1351		
Score		R0	R0	R0	P3	P2	P0	P0		
Other					Sternal 1215		Stand 1314			
PlasmaSample										

Major Oct/07/14	3min after fentanyl	Pre-Vent	End MRI
Na+	147	148	148
Cl -	119	118	117
K+	3.2	3	3.4
Hb	16.8	15.1	13.3
pH	7.402	7.244	7.311
PCO2	32.5	51.7	44.4
PaO2	105	481	577
HCO3-	19.5	21.5	22.1
ABE	-3.2	-5.9	-4
Lactate	0.7	0.7	0.7
PCV (%)	48	44	38
TP (mg/dL)	60	60	58
Plasma Sample:			

	HR	RR	TEMP	Attitude	**Date:_____Oct 15_2014_____**
Pre-Instrumentation	96	20	38.2	Good	Randomization Dog number: _____
	Time	Response		Attempts	Dog ID#: _____
EMLA application	900				Dog Name: _____Major_____
Cephalic vein					
Meloxicam	950				**Dog Weight:_____23.5_____KG**
Dorsal pedal artery	Rt. Poor, 24G				

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:_____									
Blood Gas Taken t:_____	126	36	123	99	88		2.5/2.6		

Fentanyl Admin	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1027_____	3.3	Yes/No	Yes/No	Yes/No	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	89	16	170	111	84		3.1/2.8		
BloodGas Taken _____	91	17	173	118	93		2.6/2.5		
	91		172	111	84	3.29 CI 4.08	3.1/3.2/3.4		

Time Starting Induction: ____1037_____

P/A Vol: _____	Time: 1037	Time: 1037	Time:	Time:	Time:	Time:	Time Intubation:	_____1037_____
Mid/Sal Vol :_____	1	2	3	4	5	6	Total dose	Intubation score: _____2_____
Injectable Volume								Comments
Attempt to Intubate		x						
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Major Oct/15/14	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		TIVA OFF	5 min post extubation
TIME	1037	1042	1047	1052		1158	1108	1113	1118	1123	1128	1133	1138	1143	1148	1155	1203		1205	1216
Fluid Rate																				
P or A rate	250/70-275/77																			
P/A Top Up#	1039																			
HR bpm	93	56	71	86	89	101	99	113	107	100	92	95	89	102	104	61	55	58	57	70
SAP mmHg	128	112	106	109	103	97	105	82	89	86	82	82	84	83	89	118	105	103	111	98
DAP mmHg	66	58	58	59	56	51	48	54	61	60	57	56	59	57	60	52	47	48	50	51
MAP mmHg	89	74	72	72	72	69	67	65	70	69	65	65	67	67	71	68	61	63	65	64
Temp °C																				
SPO_2	96	96	95	96		97	98	98	99	100	100	100	100	100	100	97	96		96	95
ET CO_2	30	20	19	20		50	37	38	38	393	9	39	40	40	40	40	38		38	
RR	0	0	0	0		11	12	12	12	12	12	12	12	12	12	12	12		12	
LiDCO				4.57 CI 5.6													1.83 CI 2.27			
PulseCO	2.9/3	1.7/1.8/1.9	2.5/2.7/2.8	3.5/3.6/3.8	4.5/4.6/4.7/4.8	5/5.2/5.6/5.7										2.3/2.4/2.5/2.6	2.2/2.3/2.4	1.7/1.9/2	1.8/1.9/2	2/2.1/2.2/2.3
PulsCO IND	1.7/1.8 1min		1.7/1.8 2min			1.7/1.8/1.9 3min		1.6/1.7/1.9 4 min												
Anesth score	10	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0			

Major Oct/15/14	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**/14E 45**	**E 60**	**E90**	**E 120**
Time	1205	1211	1216	1221	1226	1256	1311		
Score		R0	R0	R0	P3	P0	P0		
Other						Stand 1254			
PlasmaSample									

Major Oct/15/14	3min after fentanyl	Pre-Vent	End MRI
Na+	147	148	146
Cl -	118	120	116
K+	3.2	2.8	3.6
Hb	17	15	13
pH	7.379	7.183	7.274
PCO2	33.2	53.6	46
PaO2	76.7	399	533
HCO3-	19.2	19.4	21
ABE	-4.5	-9.3	-5.8
Lactate	0.6	0.8	0.4
PCV (%)	48	43	38
TP (mg/dL)	60	54	54
Plasma Sample:			

Appendix 2.9: Raw data of dog 9

	HR	RR	TEMP	Attitude	**Date:____Oct 23 2013 p.m._____**
Before Instrumentation	90	18	38.5	calm	Randomization Dog number: _____10_____
	Time		Response	Attempts	Dog ID#: _____
EMLA application	1000				Dog Name: _____Mystique_____
Cephalic vein	1		no	5, Lt cephalic	
Meloxicam	1114, 0.51ml				**Dog Weight:_____25_____KG**
Dorsal pedal artery	1135				

After 30 min rest1205	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas :_____	69	18	127	100	86	NA	3.2/2.9		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1214____	3.6ml	No	No	No	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	46	13	143	93	92		1.7/1.6		
Blood Gas Taken :_____	56		163	100	80		2.4/2.6		
	72	42	155	109	88	3.05/CI:3.6	3.1/3/3	148	15.4

Time Starting Induction: _____1225_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____1227__
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score: 2
Injectable Volume	y	y	y				2.1ml	_____
Attempt to Intubate	Y	y						Comments:
Relaxed jaw tone	y	Y						
Lateral palpebral	y	N						
Medial palpebral		y						
Coughing	N	n						
Swallowing	y	Y						
Paddling	N	N						
Vocalization	n	n						

Mystique Oct/23/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery	
TIME	1227	1232	1237	1242		1246	1255	1300	1305	1310	1315	1300	1325	1330	1335	1340	1343	1349	
Fluid Rate							130	130	130	130	130	130	130	130	130	130			
P or A rate	70	77	84	84		91	91	91	98	98 D:5	98 D:5	98 D:10	98 D:10	98 D:10	98	98	98	98	
P/A Top Up		2					2										1346		
HR bpm	109	109	144	145	147	141	153	121	113	107	106	106	101	90	78	60	65	69	71
SAP mmHg	112	116	105	100	100	93	81	75	74	75	75	75	76	84	92	97	98	99	97
DAP mmHg	65	64	61	59	64	55	51	48	46	47	47	47	45	49	49	47	52	58	58
MAP mmHg	80	77	75	71	71	71	60	56	54	56	55	55	54	59	60	60	60	70	66
Temp °C																			
SPO_2	95	97	97	97		98	98	98	98	99	99	99	99	99	99	98	99	97	
ET CO_2	38	43	50	58		53	42	41	40	39	39	39	39	39	39	39	45	43	
RR	0	0	0	9		10	10	10	10	10	10	10	10	10	10	10	10	10	
LiDCO				3.82/4.51															
PulseCO	4.2	4.3	5.5	3.1	3.2	3.9/4													
Anesth score	1	3	1	1		3	2	1	0	0	0	0	0	0	0	0	2	1	

Mystique Oct/23/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1353	1359	1404	1409	1414	1429	1444	1459		
Score		R0	R2	R2	R2	P3	P1	P0		
Other							1441 sternal	1454 standing/ambulate		
PlasmaSample										

Mystique Oct/23/13	Post-fentanyl	Before IPPV	Out of MRI
Na+	148	149	148
Cl -	117	3.2	3.7
K+	3.5	117	116
Hb	15.4	16.7	13.1
pH	7.311	7.165	7.278
PCO2	40.5	62.1	47.6
PaO2	68	452	524
HCO3-	19.4	21.2	
ABE	-5.5	-8.4	-4.2
Lactate	0.5	1.1	0.4
PCV (%)	45	46	38
TP (mg/dL)	6.2	6.2	5.8
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	92	16	38.4	

	Time	Response	Attempts
EMLA application	0910		
Cephalic vein	0920	n	1
Meloxicam	1030		
Dorsal pedal artery	0930		1

Date:_____Nov5_____

Randomization Dog number: _____tx2_____

Dog ID#: _____

Dog Name: _____Mystique_____

Dog Weight:_____25_____KG

After 30 min :1030	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__	72	20	120	95	81		1.5		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____1043___	3.5	No	No	No	2

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	62	18	124	93	78		1.4		
Blood Gas Taken :__	99	18	158	108	85		2.8		
	84	18	165	113	90	2.88/3.4	2.5		

Time Starting Induction: ___1055_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:2
Injectable Volume Admin	y	y	y	y	y	y		_____
Attempt to Intubate					y			Comments:
Relaxed jaw tone	n	n	n	y	y			
Lateral palpebral	y	y	y	y	n			
Medial palpebral	y	y	y	y	Y			
Coughing					Y			
Swallowing					Y			
Paddling								
Vocalization								

Mystique Nov/05/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	1057			1112		1118	1141	1146						1216	1219	1225		1230	1236	1241
Fluid Rate																				
P or A rate	250/70-275/77	300/84-325/91	350/98-375/ 105-400 / 112	425/ 119-450/ 126		475/133-500/ 140	500/140				525/147									
P/A Top Up	2	2	5	1		1					1									
HR bpm	85	87	130	136	133	139	88	77	77	74	95	79	56	61	70	69	68	58	82	69
SAP mmHg	122	105	99	101	105	99	94	84	86	85	120	137	113	112	106	96	96	100	109	113
DAP mmHg	66	55	54	59	63	59	58	52	53	54	84	87	66	65	61	53	54	50	61	60
MAP mmHg	84	70	70	72	71	71	67	62	62	63	96	101	80	78	73	65	66	64	72	74
Temp °C			37.2												35.9					
SPO_2	98	97	99	97		98	98	97	97	97	97	97	97	97	97	97		98		
ET CO_2	0-29	27	39	40		44	36	40	40	40	40	42	37	38	37	35		34		
RR	0-14	11	19	14		11	11	11	11	11	11	10	10	10	10	10		10		
LiDCO				5.55/6.55												2.35/2.78				
PulseCO	3.1	3.8	5.2	6.1	6.6	6.8									2.6	2.5	2.6	2.3	.27	2.6
PulseCO IND	3.5	3.3	3.6																	
Anesth score	3	3	4	2		3	1	0	0	0	1	0	0		1	1				

Mystique Nov/05/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1230	1236	1241	1246	1251	1306	1321	1336		
Score		R0	R2	R2	P2	P0	P0			
Other					Paddling	1300 sternal 1306 stand				
PlasmaSample										

Mystique Nov/05/13	after premed	Before IPPV	Out of MRI
Na+	150	150	146
Cl -	119	118	117
K+	3.6	3.4	3.9
Hb	14.3	16.9	7.309
pH	7.317	7.237	41.7
PCO2	38.1	47.5	608
PaO2	73.2	577	
HCO3-	19.5		
ABE	-6.2	-6.7	-4.7
Lactate	0.6	1.5	0.7
PCV (%)	42	49	37
TP (mg/dL)	60	62	58
BUN	5-15		

	HR	RR	TEMP	Attitude	**Date:_____Nov 18_____**
Before Instrumentation	104	pant	38.2	BAR	Randomization Dog number: _____tx2_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	0900				Dog Name: _____Mystique_____
Cephalic vein		n	1		
Meloxicam	0957;0.5ml				**Dog Weight:_____25_____KG**
Dorsal pedal artery		n	1		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__	104/72	24	130/135	98/91	80/73		3.4/2.6		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0959___	3.5	y	No	No	1

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	95		141	112	89		2.3		
Blood Gas Taken :__	88		159	108	84		3.9		
	93	15	165	107	87	3.5/CI:3.98	3.8		

1043								
P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	y	y				2.3ml	_____1_____
Attempt to Intubate			Y					Comments:
Relaxed jaw tone			Y					
Lateral palpebral	Y	y	Y					
Medial palpebral	y	Y	y					
Coughing								
Swallowing								
Paddling								
Vocalization								

Mystique Nov/19/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45min	50 min	55 min	Out of MRI	Pre-Recovery		extubation	5min post
TIME	1044	1049	1054	1059		1104	1110	1115										1205	1211	1216		1223	1228
Fluid Rate																							
P or A rate	250/70-----325/91	350/98--400/112	425/119	425/119												450/126	450/126		475/133				
P/A Top Up	3	2	1				3												1				
HR bpm	125	139	138	152	139	138	150	131	130	130	122	112	107	106	109	102	85	75	72	60	60	71	70
SAP mmHg	120	105	104	99	101	95	85	88	81	88	82	79	87	81	85	93	101	108	123	100	110	101	103
DAP mmHg	70	53	56	55	56	54	49	55	52	53	51	52	51	54	55	58	63	66	72	70	56	48	57
MAP mmHg	87	71	72	71	71	68	63	67	63	67	62	62	61	62	65	69	72	76	83	54	76	62	74
Temp °C																				35.8			
SPO_2	96	96	96	98		98	99	99	99	99	99	99	99	99	98	98	98	99	98	98			
ET CO_2	39	41	48	47		49	40	37	37	37	37	37	36	36	36	36	36	36	39	41			
RR	0	9	6	8		10	8	8	8	8	8	8	8	8	8	8	8	8	8	8			
LiDCO																				2.2/2,51			
PulseCO	4.7	6.3	5.4	6.2	3.4	3.2													1.07	1.1	2.1	3.8	3.1
PulseCO IND	4.5	5.6	6.2																				
Anesth score	3	3	1	1		1	3	0	0	0	0	0	0	0	0	1	0	0	1	0			

Mystique Nov/19/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1220	1223	1228	1233	1238	1253	1308	1323		
Score		R0	R0	R0	P3	P3	P2	P1		
Other					twitching	twitching	twitching	calm		
PlasmaSample										

Mystique Nov/19/13	after premed	Before IPPV	Out of MRI
Na+	147	148	147
Cl -	3.6	3.2	3.7
K+	118	119	117
Hb	15.3	16.7	12.9
pH	7.303	7.259	7.317
PCO2	40.1	38	40.7
PaO2	79.9	603	554
HCO3-	19.4		
ABE	-6.1	-9.3	-4.7
Lactate	1.2	3.2	1.5
PCV (%)	44	48	37
TP (mg/dL)	60	58	56
BUN	5-15		

Appendix 2.10: Raw data of dog10

	HR	RR	TEMP	Attitude	**Date:_____Oct 24_2013_____**
Before Instrumentation	90	36	38.6	calm	Randomization Dog number: _____11_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	0725				Dog Name: _____Ruby_____
Cephalic vein	0740	no	1		
Meloxicam	0742				**Dog Weight:_____17.5_____KG**
Dorsal pedal artery	0745	no	2		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:_____	102	24	102	91	78	NA	5.5/5.5	NA	NA

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0810____	2.5	Yes	Yes	Yes	1

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	73	54	124	75	64				
Blood Gas Taken :_____	133	Panting	156	103	80				
	121	panting	175	98	79	5.04/7.63	2.8/4.8		

Time Starting Induction: _____0827_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____0829_____
Mid/Sal Volume:_____	1	2	3	4	5	6	7	Total dose	Intubation score:
Injectable Volume Admin	y	y	y	y	y	y	y		_____3_____
Attempt to Intubate				y	Y(in)				Comments:
Relaxed jaw tone									
Lateral palpebral	y	y	Y	n	n				
Medial palpebral	y	y	y	Y	y				
Coughing				y	Y				
Swallowing									
Paddling									
Vocalization									

Ruby Oct/24/13	POST-Intub	5 min	10 min	15 min		IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	Out of MRI	Pre-Recovery		extubation	5min post
TIME	0830					0852	0858								0938	0944	0952			
Fluid Rate																				
P or A rate	70/250-77/275	84/300-91/325	98/350																	
P/A Top Up	2		1				1													
HR bpm	85	88	87	86	80	85	84	85	84	77	74	73	69	72	71	60	54	58	60	56
SAP mmHg	96	94	92	85	85	82	81	74	74	79	80	81	81	80	78	97	95	91	89	93
DAP mmHg	55	56	51	49	47	47	44	48	48	47	48	47	45	45	45	57	51	50	46	52
MAP mmHg	67	66	62	58	56	57	54	55	55	56	56	57	55	55	54	65	63	61	60	61
Temp °C																				
SPO_2	97	97	98	99		99	98	99	99	99	99	99	99	99	99	95	95		95	95
ET CO_2	34	46	46	55		47	36	36	37	36	35	35	35	35	35	32	34			
RR	19	10	12	8		10	10	10	10	10	10	10	10	10	10	10	10			
LiDCO				2.12/3.22																
PulseCO	4.1	3.6	3.8	3.4		3.1/2.4										2.2	2.0	1.6		
PulseCO IND	1:4.0/3.5/3.8	2:3.5	3:3.5																	
Anesth score	2	1	2	1		1	2	1	1	1	1	1	1	1	1	1	1			

Ruby Oct/24/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	0955	1001				1031	1046	1101		
Score		R0	R0	R0	P3	P1	P0	P0		
Other						102 6sternal	1046 standing/ ambulate			
PlasmaSample										

Ruby Oct/24/13	after premed	Before IPPV	Out of MRI
Na+	146	147	146
Cl -	118	119	117
K+	3.6	3.3	3.8
Hb	16.4	16.5	14.0
pH	7.366	7.230	7.351
PCO2	35.9	49.9	37
PaO2	85.2	538	546
HCO3-	19.7	20.2	
ABE	-3.8	-7.6	-4.6
Lactate	1.0	1.9	0.8
PCV (%)	46	47	
TP (mg/dL)	5.6	5.4	
BUN	5-15		

	HR	RR	TEMP	Attitude
Before Instrumentation	126	54	39.2	

	Time	Response	Attempts
EMLA application	0845		
Cephalic vein	0845	n	1
Meloxicam	0920		
Dorsal pedal artery	0934		3

Date:_____Nov6_2013_____

Randomization Dog number: _____tx2_____

Dog ID#: _____

Dog Name: _____Ruby_____

Dog Weight:_____18_____KG

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__	122	24	118	73	59	2			

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____0937__	2.5	n	n	n	

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	79	48	166	98	75		5.4		
Blood Gas Taken :__	89		115	87	71	2.36/3.44	2.2		
	84		122	71	51	1.99/2.89	2.5		

Time Starting Induction: __0951_____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:2
Injectable Volume Admin	y	Y						_____1_____
Attempt to Intubate	Y	y						Comments:
Relaxed jaw tone	Y							
Lateral palpebral	Y	N						
Medial palpebral	y	Y						
Coughing		y						
Swallowing								
Paddling								
Vocalization								

Ruby Nov/05/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	Out of MRI	Pre-Recovery	TIVA stop	extubation	5min post
TIME	0952	0957	1002	1007	1011	1020	1025								1105	1111	1116	1121	1131	1136
Fluid Rate																				
P or A rate	250/70-275/77	300/84				325/91-350/98					375/105	400/112								
P/A Top Up	1											1				1				
HR bpm	120	84	87	87 92	89	74	88	83	86	90	89	94	106	110	107	62	61 58		75	70
SAP mmHg	105	102	93	92 90	85	68	86	87	88	92	105	124	140	140	142	112	111 105		104	100
DAP mmHg	55	55	51	51 50	52	52	59	59	62	65	72	85	92	94	95	67	65 62		61	59
MAP mmHg	70	68	62	63 60	60	58	68	68	69	73	82	96	104	107	110	81	75 75		74	71
Temp °C			37.5																	
SPO_2	95	98	98	99	98	98	98	98	98	97	97	97	97	97	97	98	98			
ET CO_2	38	50	53	54	40	40	41	40	40	42	43	44	40	39	39	33	34			
RR	20	9	6	6	10	10	10	10	9	9	10	10	10	10	10	10	10			
LiDCO				2.18/3.17													1.36/1.97			
PulseCO	4.1	2.0	2.3	2.4 2.4	1..6											1	0.96 1.07		1.91	1.6
PulseCO IND	3.1	2.4	2.3																	
Anesth score	2	1	1	1	1	1	0	0	0	0	1	1	0	0	0	1				

Ruby Nov/05/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	1121	1131	1136	1141	1146	1201	1216	1231		
Score		R0	R0	R0	P3	P3	P3			
Other								1231sternal	1247 stand	
PlasmaSample										

Ruby Nov/05/13	after premed	Before IPPV	Out of MRI
Na+	146	147	146
Cl -	117	118	117
K+	3.6	3.2	3.6
Hb	15.3	14.6	14.9
pH	7.352	7.201	7.358
PCO2	37.9	56.8	34.6
PaO2	67.5	497	600
HCO3-			
ABE	-3.9	-7.1	-5.4
Lactate	0.7	0.7	0.9
PCV (%)	43	40	42
TP (mg/dL)	54	50	48
BUN	5-15		

	HR	RR	TEMP	Attitude	**Date:_____Nov19_2013_____**
Before Instrumentation	130	20	38.8	QAR	Randomization Dog number: _____tx3_____
	Time	Response	Attempts		Dog ID#: _____
EMLA application	1130				Dog Name: _____Ruby_____
Cephalic vein		n	1		
Meloxicam	1230; 0.35ml				**Dog Weight:_____18_____KG**
Dorsal pedal artery		n	2		

After 30 min rest	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Blood Gas Taken t:__	112	20	119	97	84		2.9		

Fentanyl Administration	Volume (mls)	Salivation	Nausea	Defecation	Sedation Score
Time: _____	2.5	n	n	n	3

3 min after premed	HR	RR	SAP	MAP	DAP	LiDCO	PulseCO	Na+	Hgb
Time:	58	24	123	99	78	3.27	2.6		
Blood Gas Taken :__	81		121	99	76	4.76	2.2		
	108		125	86	66	4.5	4.2		

Time Starting Induction: _____

P/A Volume : _____	Time:	Time:	Time:	Time:	Time:	Time:	Time Intubation:	_____
Mid/Sal Volume:_____	1	2	3	4	5	6	Total dose	Intubation score:
Injectable Volume Admin	y	Y					2.8ml	_____1____
Attempt to Intubate		y						Comments:
Relaxed jaw tone								
Lateral palpebral								
Medial palpebral								
Coughing								
Swallowing								
Paddling								
Vocalization								

Ruby Nov/19/13	POST-Intub	5 min	10 min	15 min	IPPV Starts	INTO MRI	5 min	10 min	15 min	20 min	25 min	30 min	35 min	40 min	45 min	50 min	Out of MRI	Pre-Recovery		TIVA stop	extubation	5min post
TIME	0150	0155	0200	0205	0210	0215	0220									0303	0310	0313		0318	0323	0328
Fluid Rate																						
P or A rate	250			275																		
P/A Top Up	1																					
HR bpm	67	67	62	71	80		60	66	69	61	60	64	67	65	66	64	55	57	58		77	
SAP mmHg		106	96	91	83		96	95	96	100	104	102	102	102	102	101	103	102	100		97	136
DAP mmHg		57	61	48	46		46	58	61	63	62	62	61	61	60	61	59	58	56		52	71
MAP mmHg		70	70	62	56		67	68	70	72	73	71	70	70	71	70	71	69	67		64	88
Temp °C	38		37.6	37.6																		
SPO_2	99	99	99	99	99		99	99	99	97	99	99	99	99	99	99	98	98				
ET CO_2	38	38	39	52	47		37	37	34	31	34	35	36	36	36	36	43	46				
RR	1	2		8	8		8	8	7	7	10	10	10	10	10	10	10	10				
LiDCO				1.9/2.77																		
PulseCO	1.8	1.7	1.7	1.8	2.2												1.2	1.4	1.6		2.3	1.2
PulseCO IND	1.7	2.1																				
Anesth score	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1				

Ruby Nov/19/13	**Stop TIVA**	**Extub Time 0**	**E 5**	**E 10**	**E 15**	**E 30**	**E 45**	**E 60**	**E90**	**E 120**
Time	0318	0323	0328	0333	0338	0353	1608	1623		
Score		R0	R2	R0	P3	P3				
Other						1557 sternal				
PlasmaSample										

Ruby Nov/19/13	after premed	Before IPPV	Out of MRI
Na+	147	147	146
Cl -	3.2	119	3.3
K+	117	2.9	116
Hb	15.1	15.3	13
pH	7.323	7.266	7.25
PCO2	35.8	40.1	47.1
PaO2	72.8	586	568
HCO3-	19.1		
ABE	-6.9	-8	-5.7
Lactate	0.5	0.5	0.4
PCV (%)	42	44	38
TP (mg/dL)	54	50	48
BUN	5-15		

Appendix 3: Treatments assignment

Dog	Name	Date	Imaging Modalities	Treatment
1	Alonzo	101414	MRI	AS
1	Alonzo	100614	CT2	PS
2	Baby	101713	MRI	PS
2	Baby	103113	CT1	PM
2	Baby	111213	MRI	AM
2	Baby	101514	MRI	PM
2	Baby	100714	CT2	AM
3	Baron	101613	MRI	PS
3	Baron	103013	CT1	AS
3	Baron	111113	MRI	PM
3	Baron	101514	MRI	AS
3	Baron	100814	CT2	PM
4	Bolt	101513	MRI	PM
4	Bolt	102813	CT1	PS
4	Bolt	110813	MRI	AS
4	Bolt	101414	MRI	AM
4	Bolt	100614	CT2	PM
5	Chance	101513	MRI	AS
5	Chance	102813	CT1	AM
5	Chance	110813	MRI	PS
6	Hunter	101613	MRI	AM
6	Hunter	103013	CT1	AS
6	Hunter	111113	MRI	PS
7	Lucky	102313	MRI	AS
7	Lucky	110513	CT1	PM
7	Lucky	111913	MRI	AM
8	Major	101713	MRI	PM
8	Major	103013	CT1	AM
8	Major	111213	MRI	AS

8	Major	101514	MRI	PS
8	Major	100714	CT2	AS
9	Mystique	102313	MRI	AM
9	Mystique	110513	CT1	PS
9	Mystique	121813	MRI	AS
10	Ruby	102413	MRI	PS
10	Ruby	110613	CT1	AM
10	Ruby	111913	MRI	PM