DOSE REDUCTION AND CARDIOPULMONARY EFFECTS OF
ANESTHETIC INDUCTION WITH PROPOFOL WITH OR
WITHOUT MIDAZOLAM IN CRITICAL CANINE PATIENTS

by

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ABSTRACT

DOSE REDUCTION AND CARDIOPULMONARY EFFECTS OF ANESTHETIC INDUCTION WITH PROPOFOL WITH OR WITHOUT MIDAZOLAM IN CRITICAL CANINE PATIENTS

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This thesis describes a prospective, randomized, blinded study to investigate the effects of midazolam as a co-induction drug in combination with propofol, in critically ill dogs. Case enrollment included dogs with a weight ≥ 10 kg and age ranging from 1-15 years, requiring an exploratory laparotomy and classified according to the American Society of Anesthesiologist physical status score (ASA) as III or IV. Dogs were also scored for the Survival Prediction Index (SPI2) to predict their surgical risk.

Dogs were allocated to two groups, which included premedication with two separate doses of fentanyl; F1 (2 µg kg⁻¹, IV) and F2 (3 µg kg⁻¹, IV) for instrumentation; then one group was induced with IV propofol, (P: propofol 1 mg kg⁻¹) and the other group with propofol and midazolam (M: propofol 1 mg kg⁻¹, followed by IV midazolam (0.3 mg kg⁻¹), with subsequent propofol (0.25 mg kg⁻¹; q6 seconds) as required to achieve endotracheal intubation. Both groups had anesthesia maintained with isoflurane. Sedation and induction quality was assessed, and dose requirements for induction with propofol were measured and compared between the groups. Selected cardiopulmonary parameters were assessed after F1 and F2, induction, and maintenance with isoflurane with spontaneous and mechanical ventilation during surgical preparation. Measurement times were defined as follows: T0, patients transferred—from the intensive care unit (ICU) to
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There was no difference in age or weight. Dogs in the M group had a significantly lower propofol induction dose requirement than the P group, associated with similar sedation scores between groups, but a significantly better intubation/induction score in the M group. However, heart rate, arterial blood pressure, respiratory rate, cardiac index, systemic vascular resistance, end-tidal isoflurane concentration and end-tidal carbon dioxide concentration, were similar between groups at all time intervals. The distribution of ASA and SPI2 scores for the dogs was similar in both groups, but there was no correlation between ASA and SPI2 scores.

In conclusion, this study demonstrates that co-induction with midazolam improves endotracheal intubation and the induction phase. Despite a reduction in the induction dose of propofol, midazolam co-induction did not improve cardiopulmonary function in critically ill dogs, when compared to a higher dose of propofol alone.
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DECLARATION OF WORK PERFORMED

I declare that the work reported in this thesis was performed by myself and the contributing authors as stated.

The authors’ contribution is as follows:

**Rodrigo Aguilera:** Acquisition of owners consent, anesthetic monitoring, data collection, statistical analyses, and manuscript and thesis preparation. **Melissa Sinclair:** Study design and funding application, data collection, statistical analyses, manuscript and thesis preparation, thesis review and revision. **Shane Bateman:** Thesis and manuscript revision.

**Alexander Valverde:** Data collection, manuscript and thesis preparation, thesis review and revision. **Brad Hanna:** Thesis and manuscript revision.
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CHAPTER 1

GENERAL LITERATURE REVIEW
1.1 INTRODUCTION

The term anesthesia, derived from the Greek word *anaisthēsía*, meaning “insensibility” is used to describe the loss of sensation to the entire or any part of the body. Anesthesia is induced by drugs that depress the activity of nervous tissue locally, regionally, or within the CNS (Tranquilli et al. 2007). Anesthesia is by definition a reversible process of unconsciousness for surgical and/or diagnostic procedures, obtained with the administration of injectable and/or inhalant anesthetics.

All components of anesthesia (sedation, muscle relaxation and analgesia) and phases of anesthesia (premedication, induction, maintenance and recovery) cannot be produced by a single injectable anesthetic without affecting negatively vital organ functions and still providing all desired effects. Therefore, combinations of drugs are often necessary to provide a more balanced surgical anesthesia without depressing organ performance. Intravenous anesthetics are used to induce mental depression and an unconscious state. They can be administered as a single dose or by repeated injection and/or infusion to maintain the state of general anesthesia, but more often additional drugs, such as analgesics, inhaled anesthetics and muscle relaxants are combined with intravenous injectable anesthetics, to maintain all of the components of general anesthesia.

The health status of the patient determines the selection of anesthetic drugs used for the different phases of anesthesia, i.e., premedication, induction, maintenance, and recovery, since patient risk increases with disease. Marked individual variations occur in how a patient may respond to anesthetic drugs, according to the interplay of several factors, such as the patient’s cardiovascular, respiratory and central nervous system (CNS) status, metabolic activity, and pre-existing diseases (Muir 2007). Hence, prior to anesthesia, patient assessment and stabilization of any derangement is necessary for proper anesthetic planning and drug selection.
1.2 MORBIDITY AND MORTALITY IN VETERINARY ANESTHESIA

1.2.1 Anesthetic Risk

Risk is the likelihood of some adverse or undesired outcome and the goal of veterinarians is to reduce anesthetic risk with proper patient pre-anesthetic stabilization, anesthetic induction and maintenance techniques as well as surgical skill and efficiency. It is important that clinicians continue to strive to determine the frequency and understand all of the potential causes or risk factors of anesthetic-related patient morbidities and mortalities (ARMM). By determining the frequency of ARMM in both large referral veterinary clinics and smaller private practices, the benefits of performing a surgical procedure can be considered against the potential for complications or death and baselines for assessing future improvements in case management. Understanding the causes of ARMM also informs the veterinary team and owner about the risks of a particular case’s anesthetic management when their pre-existing problems cannot be corrected and ensures that risk factors are corrected prior to anesthesia if avoidable or modifiable (Senior 2013).

The main objective of ARMM studies is to know how often anesthesia-related adverse events or deaths occur, allowing clinicians to estimate risk and also analyze associations of hypothesized causal factors. The risk may be stated as an overall risk for the study population (e.g. the proportions of animals that suffer ARMM) or an individual animal’s risk (the probability of an animal dying if it is anesthetized). An animal may be exposed to several types of risk at the same time and the risks or risk factors that are present in epidemiological studies may not reflect the true or overall exposure to all risks of an individual undergoing anesthesia. There may also be risks that the individual is exposed to that most of the individual population may not be, and so the population risk does not reflect the risk for that individual (Senior 2013). A risk factor scale
commonly used by anesthetists in human and veterinary medicine is the American Society of Anesthesiologists (ASA) physical status risk classification system.

1.2.2 American Society of Anesthesiologists (ASA) Classification

The American Society of Anesthesiologists Physical Status Classification of the patient (ASA status) is a risk stratification scoring system used to subjectively assess the person or animal’s risk for anesthesia. This classification method was first proposed in 1941. It has a high inter-observer variation using the physical status to categorize patients. It is part of the decision-making process for selecting the optimal pre-anesthetic medication, induction and maintenance drug. Some advantages of its use include that it is simple, easy to understand and commonly used. Some limitations are that it does not consider effective preoperative stabilization of the patient, complications expected from the surgery planned, and proposed postoperative care. This scoring system does not make adjustments in terms of age, sex, or size of the patient based on breed, and does not have relation to the type of surgical procedure, experience or ability of the anesthesiologist or surgeon or the anesthetic technique being used (MacMillan & Brearly 2013).

Despite the widespread use of the ASA classification system, it may not directly relate to the actual morbidity or mortality rate in people or animals, although epidemiologic evidence suggests that prior physical status correlates to anesthetic-related death.

The ASA status is organized as an ordinal rating scale, with a total of six categories for human anesthesia. Only the first five are relevant to veterinary anesthesia. The six categories are as follows:

ASA-I- a normal healthy patient
ASA II- a patient with mild systemic disease without substantive functional limitations: pregnancy, obesity, well controlled diabetes mellitus, mild lung disease

ASA III- a patient with severe systemic disease with substantive functional limitations: poorly controlled diabetes mellitus, overweight, active hepatitis, implanted pacemaker

ASA IV- a patient with severe systemic disease that is a constant threat to life: airway stents, ongoing cardiac ischemia, valve dysfunction, sepsis, DIC, ARD

ASA V- a moribund patient who is not expected to survive without surgery: massive trauma, ischemic bowel, MODS

ASA VI- a declared brain-dead patient whose organs are being removed for donor purposes

1.2.3 Anesthetic-Related Mortality in Animals

The risk of anesthetic-related death has substantially decreased in small animals over the last twenty years. A prospective, cohort, multicentric study done in the United Kingdom in 2008 reported an overall risk of anesthesia-related death in dogs of 0.17% and 0.24% in cats. This study reported a risk of anesthesia-related death in ASA III-V patients of 1.32 in dogs and 1.51 in cats (Brodbelt et al. 2008). Although the risk of death reported suggests improved standards of anesthesia, the risk of anesthesia-related deaths in human anesthesia appears consistently lower. Retrospective and prospective studies conducted during the last 30 years in human anesthesia reveal a mortality risk of approximately 0.05% to 0.01% where death was considered primarily as a result of anesthesia, and of approximately 0.02% to 0.005% where anesthesia played a contributory role but was not the sole cause of death (Senior 2013). Differences in standards of anesthesia, including level of training of those involved and the facilities available, are more likely
to explain these substantially lower results in human anesthesia than species differences (Brodbelt et al. 2008). Animals undergoing procedures with just sedation may be at lower risk of death than those undergoing general anesthesia. Sick animals remain particularly at risk of perioperative death and should be targeted for close attention to pre-operative stabilization and improvement in anesthetic management and monitoring (Brodbelt et al. 2008).

Three prospective multicenter studies to review small animal anesthetic mortality have been undertaken to address the current rates in veterinary medicine (Senior, 2013). The first study recruited 53 practices in the United Kingdom and recorded data from 41,881 anesthetic events over a 2-year period (1984-1986). The overall mortality risk was 0.23% in dogs. If pre-existing physical status was taken into account the mortality was 0.11% in patients ASA I-II, and 3.13% in patients ASA III-V (Clarke & Hall 1990). A second study recruited 76 practices in Canada and recorded data from 16,789 anesthetic events over a 6-month period (1993). The overall mortality risk was 0.11% in dogs. For healthy dogs ASA I-II mortality risk was 0.07% (Dyson et al. 1998). The most recent study recruited 117 practices in the United Kingdom over a 2-year period (2002-2004) included the analysis of 98,036 canine anesthetic events. The overall anesthetic and sedation mortality risks were estimated to be 0.17% in dogs. In healthy dogs ASA I-II the risks were estimated to be 0.05% and in sick dogs ASA III-V the risks were estimated to be 1.33% (Brodbelt et al. 2008).

Investigation into the causes of anesthetic deaths allows for a more complete evaluation of mortality and, when risk factors are identified, the knowledge of major causes of death can aid to the understanding of potential underlying mechanisms related to these risk factors and prevention. Perioperative death may result from preexisting disease, anesthetic, surgical, procedural causes or a combination of all of these. The underlying physiological cause may also be multifactorial,
involving the failure of a number of body systems, and when classifying a specific cause the primary precipitating etiology has generally been reported. Cardiovascular and respiratory complications represent the major causes of perioperative anesthetic-related deaths in dogs at a combined total of 50% in a recent Confidential Enquiry into Perioperative Death Small Animal Fatalities (CEPSAF), although gastrointestinal, neurological and hepatorenal causes were also reported (Brodbelt 2009).

In the CEPSAF, 23% of perioperative fatalities were cardiovascular causes, including; cardiac pump failure and vascular collapse, resulting in failure of blood delivery to vital tissues (Brodbelt et al. 2008). Cardiac arrest has been reported to result from cardiac arrhythmias associated with increased circulating catecholamines, myocardial hypoxia, specific anesthetic drugs, pre-existing pathology, and specific cardiac procedures. Hypovolemia and circulatory failure were the other major cause of cardiovascular collapse (Brodbelt 2009).

Respiratory complications represented the other main cause of anesthetic-related deaths in dogs in the CEPSAF at 30-40% (Brodbelt et al. 2008). Problems with airway maintenance and inadequate ventilation were the principal factors, although failed endotracheal intubation, trauma to the upper airways, and delivery of hypoxic inspired gas mixtures were also listed.
1.3 VETERINARY SEVERITY SCORES

In addition to ASA classification prior to anesthesia, illness severity scores can be assessed upon admission to the intensive care unit (ICU) as the patient is stabilized and evaluated, and are sometimes used to predict outcome. These prediction factors, are accounted for in the Acute Physiologic And Chronic Health Evaluation (APACHE) in human medicine or the Survival Prediction Index 2 (SPI2), specific for veterinary medicine, to calculate the risk of death (King et al. 2001), and although intended for patients in ICU, they could be useful for anesthetized patients since often critical patients require of general anesthesia to resolve their illness.

1.3.1 Definition and Utilization

An illness score or a severity score system is a value assigned to a patient that correlates with a probability that a specific outcome will follow. This score is computed with varying degrees of complexity from several variables. Scoring systems for illness severity typically are based on a number of clinical variables that predict mortality risk, and provide an objective basis for patient triage and risk stratification for scientific purposes (Hayes et al. 2010). Although several scores have been developed and proposed in recent years and are being used clinically, scoring systems in general have achieved limited adoption in the veterinary clinical research setting (Hayes et al. 2010). Objective methods of assessing severity of disease can provide means to achieve risk stratification, so that groups of patients with similar illness severity can be categorized, treated differently, and if different outcomes result, valid conclusions can be reached to compare therapies and standard of care between and within practices and institutions (King et al. 1994). By
categorizing patients and allocating a numeric value on the degree of illness, a more homogenous group is obtained, allowing for comparisons in the research or clinical setting (King et al. 2001)

1.3.2 Development of a Scoring System

In order to develop a scoring system the researchers have to determine which candidate variables are going to be part of the model and determine their relative importance. An end-point is essential for the scoring system, it can be extreme and simple, such as mortality because it lacks ambiguity and availability of data can be generated from a variety of sources, or it can be morbidity, which is more attractive for analysis because it occurs more frequently than mortality and data can be drawn from smaller populations, but is more difficult to collect and there is little standardization of morbidity definitions (Higgins 1998).

Variables are factors that affect the end-point or outcome, and include demographics of the population (e.g. age, body size), preexisting health problems (e.g. diabetes, renal failure, chronic conditions), measurement of physiologic parameters (e.g. blood pressure, heart rate) or blood values (e.g. hematocrit, albumin), but must be as free as possible from subjectivity and bias (Higgins 1998). Because of the use of several variables in scoring systems, a number of techniques can be used to determine the relative importance of simultaneous risk factors, the most common being multiple logistic regression. Logistic regression allows to assess the relative effect of each significant univariate predictor in the presence of all other variables; however, to avoid making the model too sensitive to the specifics of the study population, it is recommended to limit the number of terms included to $1/10^{th}$ of the number of events observed in that population.

The end result of multivariate analysis will be a logistic regression equation that relates various independent variables to the probability of an outcome (Higgins 1998), and the resulting
score can then be related to risk. The quality of any scoring system is ultimately determined by the quality of the database on which it was developed, whether obtained in a retrospective or prospective study (Higgins 1998).

The next step after obtaining a logistic regression equation on one case population is to assess model performance and determine if it can be transferred to another case population and retain predictive accuracy. Transferability depends heavily on the differences between construction population and end-user population. In general, external validity tends to be better when the construction data set was obtained from multiple locations (King et al. 2001; Hayes et al. 2010). Model performance requires knowledge of how well the model tracks actual observed values across its range (calibration), and how sensitive and specific it is in predicting outcome (discrimination). Calibration is usually determined by the Homer-Lemeshow goodness of fit test, which divides the population in subgroups by deciles of risk and compares observed and expected occurrences of the outcome for each decile by Chi-square. The null hypothesis is that the model does not fit; thus \( p > 0.05 \) indicates a good model. A low chi-squared total, adjusted to the degrees of freedom in the model, also shows good performance (Higgins 1998). Discrimination may be examined using a plot of true positive proportion versus false positive proportion to create a relative operating characteristic curve. The area under this curve (C-statistic) varies between 0 and 1.0. Most models have C-statistics values in the range of 0.70 to 0.85. Prospective application of the model to a data set distinct from its development set is necessary to ensure that the model is stable (Higgins 1998). Both concepts, discrimination and calibration, are not mutually exclusive, they measure different characteristics, but characterization of discrimination may only be truly appropriate if good calibration already has been demonstrated (Higgins 2005).
Finally, the validity of the model is established by three forms of validity, including construct, content and predictive validity. A scoring system will have construct and content validity if it evaluates aspects of disease and illness known by previous research or clinical experience to correlate with severity across all aspects of the disease pathophysiology. Predictive validity refers to the correlation between actual and predicted outcomes of patients whom the score is applied (Kaplan & Sacuzzo 2008). Validity establishes that the score predicts the outcome reliably with actual outcomes (Hayes et al. 2010).

1.3.3 Severity Scoring Systems in Veterinary Medicine

In veterinary medicine, several scores have been developed for emergency or critical cases to predict mortality, to provide an objective basis for patient triage and risk stratification for scientific purposes, and to guide treatment and diagnostic testing. Hoffman et al. (1992) developed a predictive equation identifying and weighing 41 clinico-pathologic variables separated into 4 categories: clinical parameters, venous blood gas, biochemical profile and complete blood count. These prognostic variables for survival were retrospectively obtained from 56 neonatal foals that where admitted to the Ontario Veterinary College between 1983 and 1986. After identification, these parameters were weighed in the formulation of a predictive logistic regression equation (Pn [probability of non-survival] = e^A/1+e^A; where A= -1.46 + -0.107 x PvO₂ (mmHg) + 0.213 x anion gap (mmol L⁻¹). This equation was tested prospectively in neonatal foals that underwent care in the intensive care at OVC for the following period of 3-year (Hoffman et al. 1992).

In 1993, another severity scoring system was developed using a logistic regression equation using variables collected by a single person within the first 24 hours from a group of 200 dogs admitted to the ICU at the Veterinary Hospital of the University of Pennsylvania, the survival
prediction index (SPI) (King et al. 1994). Biased evaluation is possible for a score using the same set of patient data, which was acknowledged by the authors of the SPI, and in response pursued validation of the SPI2 on data collected prospectively at several referral centers (King et al. 2000).

The SPI2 was constructed by a backward elimination procedure, eliminating variables with \( p > 0.10 \) (King et al. 2000). Variables deleted included rectal temperature, body weight, heart rate, \( \text{SaO}_2 \), bicarbonate concentration, neurologic status, WBC count, concentration of total solids, glucose and bilirubin, and chronic versus acute status. The logistic equation was constructed then by weighing 7 different parameters: mean arterial pressure, respiratory rate, creatinine, PCV, albumin, age and medical versus surgical status. The AUC of the estimation sample for this reduced-model SPI2 was 0.76, indicating that there was not an appreciable loss of accuracy.

More recently, Hayes et al. (2010) developed the Acute Patient Physiologic and Laboratory Evaluation (APPLE) score. They constructed 2 models that operate independent of primary diagnosis and was independently validated. Both models \( \text{APPLE}_{\text{full}} \) and \( \text{APPLE}_{\text{fast}} \) have good performance on construction and validation. Both models where constructed from data collected from 598 patients records admitted to the Ontario Veterinary College ICU. The model was prospectively validated in 212 patients admitted subsequently.

Simeonova et al. (2013) developed retrospectively, a scoring system using a small number of patients \( (n = 58) \) that which could serve as a guide for clinicians to predict outcome dogs with acute abdomen treated surgically. They used 14 parameters to develop their scoring system for the prediction of death in acute abdominal disease in dogs treated with exploratory laparotomy. Single predictive variables with \( p < 0.05 \) like hematocrit, temperature, RR received 1 point; those with \( p < 0.01 \) like mucous membrane colour, CRT; all parameters entering to multivariate model received 5 points, like body weight, neoplastic process, ruptured organ. Dogs that received 14 points had
a 50% chance of survival, with a sensitivity of 90.5%, specificity of 97.3%, and positive and negative predictive values of 95% and 94.7%, respectively, at this cut-point. According to the receiver operator curve (ROC) analysis, this scoring system classified 94.8% (Simeonova et al. 2013).

Hall et al, in 2014 determined in a prospective, multicenter, cohort study that for dogs admitted with trauma, the use of an animal trauma triage score (ATT) that assesses perfusion, cardiac rhythm, respiratory function, eye/muscle/integument status, skeletal integrity, and neurological function, and the use of the modified Glasgow coma scale (MGCS) that assesses motor activity, brainstem reflexes, and level of consciousness, were both useful at predicting outcome (death versus survival to hospital discharge).

1.3.4 Severity Scoring Systems in Human Medicine

In human medicine, different scoring systems have been developed to meet different needs. So-called generic scoring systems assess severity of illness in general ICU patients, while others were designed specific situations, such as the Glasgow Coma Scale, the Injury Severity Score, and the Model for End Stage Liver Disease (Vincent & Moreno 2010). Since their introduction some 30 years ago (and adaptations to permit greater ease of use), illness severity scores have become routine practice in many ICU’s and can be divided in two groups: outcome prediction scores and organ dysfunction scores. There are three main outcome scores used in adult critical care medicine include: APACHE, Simplified Acute Physiologic Score (SAPS) and Mortality Prediction Model (MPM) score.

APACHE was the first outcome prediction score to be developed and is the most widely used of these scores. This score was separated in 2 parts, a score related to health status of patient
prior to admission (functional status, chronic diseases) and a score related to actual physiological status (34 physiological variables assessed during the first 32 hours following admission). A patient’s APACHE classification consists of a number (physiological score) and a letter (chronic health status). Validation studies have demonstrated that this score is consistently accurate in predicting mortality in ICUs and hospitals (Vincent & Moreno 2010).

The APACHE score has been updated with new versions, such as in 1985 APACHE II was introduced and was easier to use with just 12 physiological variables and the chronicity score incorporated directly into the model so there is only one overall score ranging from 0-71 (Knaus et al. 1985). In 1991 APACHE III was developed and updated in 1998, but never gained wide support due to the more complex nature of the score and the software was not freely accessible (Vincent & Moreno 2010). Then in 2006, APACHE IV was created using same physiological variables, validated in 131,618 patients and was reported to have an AUROC (discrimination) of 0.88 and a Homer-Lemeshow chi-square (validation) of 16.9 (Zimmerman et al. 2006).

The SAPS was developed and validated in France in 1984 using 13 weighted physiological variables and age to provide an indication of risk of death in ICU patients (Le Gall et al. 1984). In 1993 SAPS II was developed with a larger database (Le Gall et al. 1993) and in 2006 SAPS III was created using complex statistical techniques to select and weight variables, using information from 16,784 patients from 303 ICUs in over 30 countries (Metnitz et al. 2005).

The MPM was developed using data from 1 ICU and published in 1985 (Lemeshow et al, 1985). Unlike APACHE and SAPS, MPM consisted of 2 models: an admission score (7 admission variables) and a 24 h score that reflected 7 variables reflecting treatments and the patient’s condition in ICU. In 1993 MPM II was developed using logistic regression techniques on a database of more than 12,000 patients from 12 countries (Lemeshow et al. 1993). Unlike APACHE
and SAPS systems, in MPM II each variable is designated as present or absent. In 2007 MPM III was updated using 125,000 patients from 135 ICUs in 98 hospitals across North America (Nathanson et al. 2007).
1.4 ABDOMINAL EXPLORATION AS A CLINICAL CASE MODEL TO PERFORM ANESTHETIC RESEARCH

Canine patients requiring exploratory laparotomy may range from ASA II-V, but the most frequent classification is an ASA class III, because they have unresolved volume deficits noted clinically as dehydration, hemoconcentration, azotemia, hypotension, metabolic acidosis and hyperlactatemia. All of these factors may contribute negatively to the cardiopulmonary response of the dog to anesthetic induction and maintenance, as well as preparation for surgery.

Abdominal surgeries are performed in dogs for various reasons including cholecystectomy, enterotomy, gastrotomy and corresponding foreign body removal, intestinal resection and anastomosis, liver tumour removal or biopsy, splenectomy, and or abdominal lavage. Gastrointestinal (GI) foreign bodies are common in dogs and anesthesia and surgery may be performed in private or referral veterinary hospitals, making this an ideal scenario that will require general anesthesia in patients with an altered cardiopulmonary and acid base status, without the risk of acute or ongoing significant blood loss. GI foreign bodies in dogs often represent a diagnostic challenge as they present with a variety of clinical signs, varying gastrointestinal locations of the obstruction with varying onset times of sickness of hours to weeks depending on the location (Boag et al. 2005; Hayes 2009; Hobday et al. 2014). These obstructive GI lesions from foreign bodies develop as dogs ingest a large variety of objects that do not pass through the GI tract and cause a complete or partial obstruction (Boag et al. 2005).

Ingested foreign bodies can obstruct at various potential locations. One retrospective veterinary teaching hospital study recorded the locations of the ingested foreign body in 94.9% of cases to be as follows; 50% in the stomach, 3.6% in the proximal duodenum, 2.9% in the distal duodenum, 27.5% in the jejunum, 2.9% in the ileum, 3.6% in the colon, 2.2% were linear foreign
bodies specifically anchored in the mouth, and 2.2% were multiple foreign bodies located at different sites (Boag et al. 2005). Hayes (2009) reported foreign bodies causing obstruction at all points along the gastrointestinal tract in dogs; however, the jejunum was the most common location of obstructions (55%) with most of them found in mid jejunum (26%), followed by proximal jejunum (23%) and distal jejunum (6%). Most dogs presented to the veterinarian within one day of ingestion of the foreign body and had a gastric foreign body, although some cases had the foreign body already within the mid-jejunum, even on day 1. With increasing duration of clinical signs objects were more likely to be found in proximal and mid-jejunum (Hayes 2009).

Linear foreign bodies, according to some authors, have a higher frequency of postoperative complications and a worse prognosis compared to nonlinear foreign bodies (Hayes 2009). Despite the higher frequency of clinical signs like intestinal necrosis, perforation, peritonitis and longer hospitalization, Hobday et al. (2014) found that the overall short-term outcome of linear foreign bodies was excellent compared with non-linear foreign bodies. Boag et al. (2005) reported that 36.2% of foreign bodies were described as being linear, and in 6% of the cases this type of foreign body was anchored in the mouth, 78% of them in the pylorus, 2% in the duodenum, 8% in the jejunum, and 4% were unrecorded for specific location. In another study, linear foreign bodies accounted for 16% of foreign bodies with the most common anchorage point in the pylorus with the foreign material extending into proximal jejunum. Canine linear foreign bodies are usually fabrics, plastics and textile materials (Hayes 2009).

Experimental studies of GI obstruction in dogs have revealed that, after an obstruction has been present for over 24 hours, there is secretion of sodium, potassium, and water rather than absorption in the bowel proximal to the obstruction. GI function is also abnormal distal to the obstruction. Thus, disturbances in normal GI tract function secondary to complete or partial
obstruction can rapidly result in disturbances of fluid balance, acid-base status and serum electrolyte concentrations. Protracted or profuse vomiting and diarrhea with reluctance to consume adequate volumes of food and fluid can also affect the intravascular volume and hydration status of the dog and therefore, lead to further alterations in acid-base and electrolyte status (Boag et al. 2005). The most common acid-base and electrolyte abnormalities associated with linear foreign bodies include hypochloremia, metabolic alkalosis, hyperlactatemia, hypokalemia, hyponatremia, hemoconcentration, and increased blood urea nitrogen (Boag et al. 2005; Hobday et al. 2014).

In the largest retrospective study to date evaluating the clinical course of linear foreign bodies and non-linear foreign bodies in dogs, linear foreign bodies required significantly more gastrotomies, enterotomies, and intestinal resection and anastomoses than dogs with non-linear foreign bodies (Hobday et al. 2014). In comparison, 64% of non-linear foreign bodies were successfully removed by endoscopy (Hobday et al. 2014).

The reported survival rates in the literature to date for linear foreign bodies are high with reports of 98% (Boag et al. 2005), 96% (Hobday et al. 2014), and 80% (Hayes 2009) survival.

Proper assessment of patients requiring abdominal surgery is important to predict risk and improve survival, by stabilizing the patient before anesthesia. In addition to ASA classification, which helps to guide the anesthetic management or predict cardiopulmonary responses of the affected patient to anesthetic drugs, illness severity scores such as the SPI2 can be assessed upon admission to the intensive care unit (ICU) as the patient is stabilized and evaluated prior to anesthesia. Both scoring systems can predict risk of death and outcome, but have not been used in the same patient that first is admitted to ICU and then undergoes surgery; therefore the correlation of the two is unknown for risk stratification.
1.5 ANESTHESIA OF CRITICALLY ILL PATIENTS

The selection of anesthetic drugs used for the different phases of anesthesia, i.e., premedication, induction, maintenance, and recovery, is very important in the critically ill patient, since patient risk increases with disease. Critically ill patients usually present with specific needs for fluid therapy and pain control, to correct clinical dehydration and electrolyte disturbances, to alleviate discomfort and stress, and to normalize the patient’s cardiopulmonary function. Preoperative assessment and stabilization is recommended and efforts should continue throughout the different phases of anesthesia. However, in many instances, complete stabilization is not only not possible without surgery, but often can also not be completed during anesthesia.

Examples of ASA ≥ III cases in canine patients include gastrointestinal foreign bodies, hemoabdomen, intestinal accidents, septic abdomen, all of which require exploratory laparotomy.

1.5.1 Preanesthetic sedation and analgesia

Premedication is an important part of the anesthetic period. During this phase, the veterinary anesthesiologist must provide analgesia, muscle relaxation, sedation, and amnesia. In order to provide all these beneficial effects, different groups of drugs may need to be combined, to provide the best effects of each individual drug and allow for dose reductions of each drug to avoid adverse side effects. In terms of drugs used in veterinary medicine during the premedication phase, the most commonly used drugs are alpha2-adrenoreceptor agonists, phenothiazines, and opioids. Critically ill canine patients, ASA ≥ III, are commonly premedicated solely with a mu-
 agonist opioid before induction of anesthesia to achieve sedation as well as pre-emptive analgesia, to minimize significant negative cardiovascular effects.

Opioids are fundamental drugs given to provide reduction in the injectable and inhalant anesthetic, as well as analgesia. In terms of physicochemical properties, they are weak bases, most of them highly lipid soluble, with a rapid onset of action, a wide therapeutic margin, which can be administered by multiple routes (intravenous (IV), intramuscular (IM), subcutaneous (SQ), oral (PO), intra-articular (IA), intranasal (IN), neuraxial, transdermal, transmucosal). Opioids have hepatic and extrahepatic metabolism, they have a high volume of distribution (wide and rapid tissue distribution), and the time to peak concentration depends on first pass uptake done by lungs or liver (Miller 2009). Pharmacodynamically, opioids exert their analgesic effects by inhibiting synaptic transmission through different mechanisms, for example, they decrease influx of Ca$$^{++}$$ and decrease neurotransmitter release presynaptically, they increase the efflux of K$$^{+}$$ thereby hyperpolarizing projection neurons, and they inhibit ascending/descending nociceptive pathways. Regarding sedation, opioids elicit their sedative actions by decreasing the release of acetylcholine in the prefrontal region of brain, and also through inhibition of locus coeruleus in the brain (Miller 2009).

1.5.1.1 Fentanyl

One of the most commonly used mu-agonists opioids is the synthetic opioid fentanyl. Fentanyl is a highly lipid soluble substance, with a rapid onset of action and a peak analgesic effect that can occur in 5 minutes and last approximately 30 minutes after a standard dose (Tranquilli et al. 2007). Premedication with fentanyl can also provide sedation and reduce the overall induction dose of propofol dogs (Tranquilli et al. 2007; Liao et al. 2015).
1.5.1.1 Dose

Fentanyl (2 µg kg\(^{-1}\) IV, over 30 seconds), when given as a co-induction drug 2 minutes before the injectable anesthetic propofol, resulted in a reduced dose requirement but did not obviate the hypotension that occurs during induction of anesthesia (Covey-Crump & Murison. 2008). Mutoh (2016) demonstrated that the combination of fentanyl and midazolam, due to the anesthetic sparing effect and/or inhibition of airway reflexes, contributed to a more rapid alveolar sevoflurane concentration during mask induction and improved intubation conditions in dogs, while decreasing the chances of adverse effects elicited by endotracheal intubation, such as coughing.

In conscious dogs, fentanyl has a fast distribution time (\(t_{1/2a}\)) of 4.5 ± 1.5 minutes after a single 10 µg kg\(^{-1}\), IV dose, and achieves plasma concentrations of 5.0 ng mL\(^{-1}\) in the first 2.5 minutes post-administration (Sano et al. 2006), which exceed reported analgesic concentrations of 1-2 ng mL\(^{-1}\) (Sear 1998; Robinson et al. 1999). Fentanyl has a rapid decline in peak plasma concentration, which decreases then below therapeutic concentrations in less than 30 minutes (Sano et al. 2006). The concomitant administration of a constant rate infusion at 10 µg kg\(^{-1}\) hour\(^{-1}\) increases the elimination half-life (\(t_{1/2\beta}\)) of the single IV dose (45.7 ± 8.6 minutes) by 3-4 fold (151.1 ± 61.0 to 182.1 ± 69.1 minutes) and maintain therapeutic concentrations for up to 6 hours (Sano et al. 2006). Other studies have measured longer \(t_{1/2\beta}\) of 199-211 minutes for IV dose ranges of 2.5-640 µg kg\(^{-1}\), under inhalant anesthesia, independent of the dose (Murphy et al. 1979; Murphy et al. 1983). Differences in clearance are probably affecting the shorter \(t_{1/2\beta}\) between studies, since in one study a high clearance of 77.9 mL minute\(^{-1}\) kg\(^{-1}\) (Sano et al. 2006) contrasts with lower clearances of 37 mL minute\(^{-1}\) kg\(^{-1}\) (Murphy et al. 1979; Murphy et al. 1983), in addition to a lower volume of distribution (5 L kg\(^{-1}\)) in one study (Sano et al. 2006) versus higher volumes of distribution in the other studies (9.5-9.8 L kg\(^{-1}\)) (Murphy et al. 1979; Murphy et al. 1983).
Anesthetic drugs and their effects on cardiovascular parameters may also play a role in affecting the disposition of fentanyl, as it has been demonstrated that some drugs like acepromazine can increase fentanyl’s clearance and volume of distribution, whereas dexmedetomidine did not (Keating et al. 2016). Increases in heart rate and consequent improvement in cardiac output have also increased the clearance and volume of distribution of fentanyl in isoflurane-anesthetized dogs (Machado et al. 2019).

1.5.1.1.2 Cardiorespiratory Effects

Intravenous administration of fentanyl (5-20 µg kg⁻¹) to conscious or isoflurane-anesthetized dogs results in a decrease in heart rate and a corresponding decrease in cardiac index and oxygen delivery, despite an increase in stroke volume index (Grimm et al. 2005; Keating et al. 2013; Machado et al. 2019). Systemic vascular resistance also increases initially and then decreases over time, which also results in lower blood pressures (Grimm et al. 2005; Keating et al. 2013; Machado et al. 2019).

Respiratory rate decreases in isoflurane-anesthetized dogs after fentanyl (5 µg kg⁻¹, IV) administration, which results in increases in PaCO₂ and decreases in arterial pH (Keating et al. 2013).

1.5.2 Injectable Induction Drugs

Veterinary patients require a stress free, rapid sequence anesthetic induction for surgery, which ideally occurs without inflicting significant cardiovascular or respiratory compromise, to minimize the impact of anesthesia on their primary disease. The objective for typical canine
anesthetic techniques, is to reduce the potential patient risk of anesthesia by using safer and reduced dosages of anesthetic drugs, and ultimately decrease patient morbidity and mortality.

Common intravenous injectable induction anesthetics include propofol, alfaxalone, etomidate, and ketamine (Ray & Mckeown 2007), and as research shows, all have advantages and disadvantages. In Canada, cases are most commonly managed with opioid premedication, followed by induction with propofol, alfaxalone, or ketamine, with or without co-induction with a benzodiazepine, such as midazolam or diazepam.

Critically ill patients, with less than ideal organ/system function and stability are particularly susceptible to the negative cardiopulmonary effects of anesthetics in all phases of anesthesia, especially the induction and maintenance phases. During the induction phase, injectable anesthetic induction drugs are administered at a relatively high dose to achieve brain concentrations that rapidly produce unconsciousness and inhibit normal neuron function. These rapid injectable anesthetic drug levels could exacerbate inhibited or altered neuron function already present with the patients’ primary disease process. In unhealthy patients, like patients with sepsis from abdominal diseases, induction of anesthesia can be hazardous, because of common concomitant factors, such as hypoxemia, hypotension, volume depletion, and multiple organ impairment.

1.5.2 Propofol
1.5.2.1 Physical and Chemical Properties

Propofol a commonly used induction drug, is a nonbarbiturate sedative/hypnotic formulated in an oil-in-water formulation (pH 7-8.5) that contains propofol (10 mg mL\(^{-1}\)), glycerol (22.5 mg mL\(^{-1}\)), egg lecithin (12 mg mL\(^{-1}\)) and soybean oil (100 mg mL\(^{-1}\)) (Sams et al. 2008). The
best features of this drug include rapid induction, short duration of action, and no significant cumulative effects on repeated administration (Muir & Gadawski 1998), making this drug suitable for induction and maintenance of clinical anesthesia.

1.5.2.1.2 Pharmacology

The drug has a large volume of distribution at steady states, ranging from 2.5 to 9.7 L kg\(^{-1}\), and a clearance of 34.4 to 114 mL kg\(^{-1}\) min\(^{-1}\) (Hughes & Nolan 1999). Total clearance of propofol is greater than hepatic blood flow, suggesting extrahepatic metabolism, and thus enabling it to be a suitable choice in patients with pre-existing liver or kidney disease (Nolan & Reid 1993; Glowaski & Wetmore 1999)

Propofol is mainly metabolized by liver hepatocytes (Posner 2017). There may be significant differences among species in terms of extrahepatic metabolism and it has been shown that in cats metabolism occurs in pulmonary tissue (Posner 2017). Hiraoka et al. (2005) found that in humans, the metabolic clearance of propofol by the kidneys accounts for almost one third of total body clearance and is the major site for extrahepatic elimination.

1.5.2.1.3 CNS Effects

The hypnotic action of propofol is mostly mediated by enhancing \(\gamma\)-aminobutyric acid (GABA)–induced chloride current through its binding to the \(\beta\)-subunit of GABAA receptor. The \(\alpha\)-subunit and \(\gamma\)-subunit subtypes also seem to contribute to modulating the effects of propofol on the GABAA receptor. Propofol through its action on GABAA receptors in the hippocampus inhibits acetylcholine release in the hippocampus and prefrontal cortex. Propofol has a direct depressant effect on neurons of the spinal cord. In acutely dissociated spinal dorsal horn neurons,
propofol acts on GABAA and glycine receptors. The hypnotic action of propofol is pressure reversible, and it adheres to the correlation exhibited by other general anesthetics between anesthetic potency and octanol/water distribution coefficient. (Miller 2009)

1.5.2.1.4 Cardiovascular Effects

The pharmacologic profile allowing for a rapid sequence induction makes propofol an ideal choice in canine patients. However dose-related cardiopulmonary depression does result from its administration. Propofol decreases arterial blood pressure due to a drop in systemic vascular resistance, cardiac contractility, and preload. Arteriolar and venous dilation contributes to hypotension associated with propofol (Robinson et al. 1997, Butt & Ahmed 2013). Induction of anesthesia with propofol is associated with a sudden cessation of sympathetic (vasoconstrictor) nerve activity (Robinson et al. 1997). Propofol causes direct negative inotropic effects that may be more pronounced in a pathological myocardium than those produced by this intravenous anesthetic in a normal myocardium (Pagel et al. 1998). In dogs, propofol decreases mean arterial pressure, left ventricular systolic and end diastolic pressures, end diastolic segment length, rate pressure product, pressure work index, diastolic coronary vascular resistance, and mean aortic blood flow (Pagel et al. 1998).

In healthy research dogs, after premedication with fentanyl, propofol reduces heart rate, mean arterial blood pressure and cardiac index by 10-20% (Liao et al. 2015).

Heart rate does not change significantly after an induction dose of propofol. Propofol either may reset or may inhibit the baroreflex, reducing the tachycardic response to hypotension (Ebert et al. 1992). Propofol also decreases cardiac parasympathetic tone in a dose-dependent manner, has minimal direct effects on sinoatrial node function and normal atrioventricular and accessory
pathway conduction (Miller 2009).

### 1.5.2.1.5 Respiratory Effects

Respiratory depression and apnea are consistent side effects in animals (dogs, cats, pigs, horses), which have received IV propofol for anesthetic induction (Muir & Gadawski 1998). The respiratory rate decreases significantly when compared with baseline values before sedation. After induction and during maintenance with propofol an elevation of PaCO$_2$ and a decrease of arterial pH were observed when compared with normal non-anesthetized values (Suarez et al. 2012). Onset of apnea usually is preceded by a marked tidal volume reduction (Miller 2009).

### 1.5.2.1.6 Induction Dosage and Quality of Induction

Propofol has a wide initial dose range, (2-8 mg kg$^{-1}$, IV) in dogs and induces rapid central nervous system depression followed by a short period of unconsciousness facilitating anesthetic induction within 20-30 seconds after an IV bolus. The IV dose for induction of anesthesia in unpremedicated dogs ranges from 6-8 mg kg$^{-1}$, whereas the dose in sedated animals may be as low as 2-4 mg kg$^{-1}$. Anesthetic doses of propofol and clinical techniques are based on the average normal healthy dog, categorized as ASA classification I or II, since most of the scientific data on doses and cardiopulmonary effects are derived from healthy research dogs.

Adverse induction behavior characterized by paddling of limbs, muscle twitches, and pain on injection have been associated with the use of propofol during induction (Ferreira et al. 2015). Myoclonus has also been described in human and veterinary medicine. Propofol causes a wide range of movement disorders in 30-70% of children at the time of anesthesia and usually when anesthesia wears off. The manufacturer (Astra Zeneca) recognizes that myoclonus is a rare
complication occurring at a rate of less than 1 in 1,000-10,000 patients, and is self-limiting and short-lived with no treatment needed (Dearlove & Dearlove 2002). In a study done by Cattai et al. (2015) the incidence of myoclonus was 1.2% in dogs undergoing TIVA with propofol with or without fentanyl.

The mechanisms by which anesthesia with propofol initiates myoclonus that does not respond to further doses of propofol, is yet to be clarified in both dogs and humans. Propofol exerts its anesthetic effect mainly by increasing the inhibitory action of GABA in the CNS but also possesses some action over other receptors, of particular interest for the genesis of this phenomenon could be its antagonist action of the glycine receptor, an inhibitory neurotransmitter in the CNS, particularly concentrated in the spinal cord and brainstem (Cattai et al. 2015).

Propofol is usually injected as a single bolus for induction of general anesthesia, enabling intubation and initiation of inhalant anesthesia, or due to its pharmacodynamic features continuing with a total intravenous anesthesia protocol (TIVA) (Tranquilli et al. 2007).

Propofol has minimal analgesic properties, which is the reason why is usually used with the concurrent administration of analgesic drugs like opioids or α2-agonists during the premedication phase. Recovery is rapid and free of excitement.
1.6 THE USE OF CO-INDUCTION TECHNIQUES

Co-induction of anesthesia is the use of two or more drugs together (Covey-Crump & Murison 2008). It refers to the administration of a small dose of sedative or other anesthetic drug prior to the primary injectable induction drug (e.g. propofol; alfaxalone). To achieve a beneficial effect from co-induction, the drug selected should not only have a hypnotic dose-sparing action but must have minimal cardiovascular effect of its own (Minghella et al. 2016). The objective of this technique is to improve the ratio of desired versus adverse effects (Butt & Ahmed 2013) from propofol, alfaxalone, or etomidate.

Use of induction anesthetic drugs with co-induction drugs is common in veterinary anesthetic practice (Covey-Crump & Murison 2008; Mair et al. 2009; Robinson et al. 2013; Sanchez et al. 2013; Hopkins et al. 2014; Martinez-Taboada et al. 2014; Liao et al. 2015). Commonly used drugs in co-induction techniques include midazolam, diazepam, lidocaine, and fentanyl.

Co-induction anesthetic drugs are used to lower the injectable intravenous dose of induction anesthetics (e.g. propofol), with the aim of decreasing the possible negative cardiopulmonary effects that result from a sudden high plasma concentration of the induction anesthetic. It has not yet been investigated if the use of co-induction drugs with the primary injectable induction drug will benefit critically ill patients (ASA classification ≥ III). For example, despite dose reductions of up to 25% in the induction dose of propofol in research dogs, premedicated with fentanyl, and co-induced with midazolam, there was no clear benefit in cardiopulmonary function with the use of this combination when compared to the use of propofol alone (Liao et al. 2015). The benefits of co-induction in critically ill patients in reducing the
induction dose of anesthetic drugs and preserving cardiopulmonary function has not been investigated.

1.6.1 Advantages and Disadvantages

The main reasons for using a co-induction technique in a healthy or elective patient is to reduce the primary volume and dose of the injectable anesthetic drug, and to promote a faster and smoother anesthetic induction process during endotracheal intubation. With an improved anesthetic depth the coughing and gagging reflexes during anesthetic induction can be minimized (Whitwam 1995). The use of co-induction anesthesia, in patients with poor hemodynamic stability may result in the administration of lower doses of intravenous induction anesthetics, smoother endotracheal intubation, and potentially fewer cardiorespiratory side effects (Abbasivash et al. 2014; Liao et al. 2015).

The disadvantages of using a co-induction technique, although minor, are important to the veterinary practitioner. The clinical disadvantages with co-induction are mainly two-fold: 1) the potential for excitement which could actually increase the dose of the primary induction drug needed and 2) time for administration of two separate drugs separated by catheter flushing and multiple injections. In addition, the veterinary practitioner needs to have added pharmacological knowledge of the two different drugs vs. only one and potential drug interactions.

1.6.2 Drugs Commonly Used for Co-Induction

1.6.2.1 Benzodiazepines

All benzodiazepines, depending on species, have hypnotic, sedative, anxiolytic, amnesic, anticonvulsant and centrally produced muscle relaxant properties. The chemical structure of each
drug dictates its particular physicochemical properties, pharmacokinetics, and receptor binding characteristics (Miller 2009).

Biotransformation of the benzodiazepines occurs in the liver. The two principal pathways are microsomal oxidation (N-dealkylation or aliphatic hydroxylation) and glucuronide conjugation. The difference in the two pathways is significant because oxidation is susceptible to outside influences and can be impaired by certain population characteristics (e.g. old age), disease states (e.g. hepatic cirrhosis), or the co-administration of other drugs that can impair oxidizing capacity (e.g. cimetidine). Conjugation is less susceptible to these factors. Midazolam and diazepam undergo oxidation reduction. The fused imidazole ring of midazolam is oxidized rapidly by the liver, much more rapidly than the methylene group of the diazepine ring of other benzodiazepines. This fast oxidation accounts for the greater hepatic clearance of midazolam compared with diazepam (Miller 2009).

1.6.2.1.1 Diazepam

Diazepam is the most widely used benzodiazepine in veterinary medicine. It is not soluble in water. The parental formulation contains 40% propylene glycol and 10% ethanol, making the IM route of administration less effective with poor absorption and painful with local tissue irritation. In terms of pharmacokinetics, diazepam is highly lipid soluble and is rapidly distributed throughout the body. In dogs, horses and cats it can cause excitement, dysphoria, and ataxia, or it can trigger aggressive behavior, making the use of benzodiazepines as a single sedative drug of limited value in these species (Tranquilli et al. 2007).
1.6.2.1.2 Midazolam

Midazolam, an imidazobenzodiazepine, became the first water soluble benzodiazepine for human use in 1986. The commercial product has a pH of 3.5, is compatible with 5% dextrose in water, 0.9% sodium chloride, and lactated Ringer’s solution in glass and plastic containers. It is also physicochemically compatible with and can be mixed with meperidine, atropine, glycopyrrolate, sufentanyl, fentanyl, nalbuphine and ketamine in aqueous solution (Roche Technical notes, document number 069-009 to 069-022, 1987). When the pH is greater than 4, as in plasma, the benzene ring opens making midazolam’s structure more stable, highly lipid soluble, and rapidly absorbed after IM injection with an onset time of 15 min for CNS effects (Court & Greenblatt 1991). The onset of CNS effects occurs 1-2 min after IV administration (Brown et al. 1993). Midazolam has a rapid and reliable absorption and peak plasma concentrations in 10 min or less with IM injection, with a bioavailability ranging from 35-73% (Schwartz et al. 2013), and an oral bioavailability of approximately 69% (Court & Greenblatt 1991). After IV administration of 0.5 mg kg\(^{-1}\), the volume of distribution at steady-state is reported to be 0.68 L kg\(^{-1}\), with an accompanying elimination half-life of 63.3 min, and a clearance of 12.1 mL min\(^{-1}\) kg\(^{-1}\) (Brown et al. 1993; Schwartz et al. 2013).

Midazolam is more lipophilic than diazepam and has twice the affinity for the GABA\(_A\) receptor, despite the use of a similar dose in veterinary medicine of 0.1-0.5 mg kg\(^{-1}\). It produces minimal to no effects on the cardiopulmonary function of dogs. It can be used alone or in combination with opioids, phenothiazines or alpha2-agonists to sedate dogs. It can be administered IV as a co-induction drug before induction of anesthesia with ketamine, thiopental, propofol, alfaxalone or etomidate, in order to improve muscle relaxation and to reduce the dose of anesthetic required to induce anesthesia (Anderson & Robb 1998; Jones et al. 2002, Covey-Crump &
Benzodiazepines, by definition, are ideal co-induction drugs due to their lack of cardiopulmonary depression (Lemke 2007).

In dogs, Covey-Crump & Murison (2008) found that propofol-midazolam co-induction was associated with excitement and higher pulse pressure. Also, dogs that received midazolam (0.2 mg kg\(^{-1}\), IV) over 30 seconds, 2 minutes prior to induction exhibited more excitatory phenomena such as limb paddling. In the same study, fentanyl-propofol co-induction (fentanyl 2 \(\mu\)g kg\(^{-1}\), IV) resulted in a reduced dose requirement of propofol, but did not obtund the hypotension caused by propofol (Covey-Crump & Murison 2008). Propofol-benzodiazepine combinations produced a greater decrease in temperature and longer interval to restoration of normothermia than did dogs that received ketamine-benzodiazepine combinations (Bornkamp et al. 2015).

In another study of healthy research dogs induced with propofol or alfaxalone with or without midazolam co-induction after sedation with fentanyl (7 \(\mu\)g kg\(^{-1}\), IV), no differences were observed in cardiovascular or respiratory variables immediately after induction and during maintenance using TIVA with the respective induction drug (Liao et al., 2015). Despite dose reduction for propofol and alfaxalone with midazolam co-induction a benefit in cardiopulmonary function could not be demonstrated (Hopkins et al. 2013; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Liao et al. 2015).

1.6.2.2 Lidocaine

Lidocaine, is a local anesthetic drug and a Class IB antiarrhythmic drug with analgesic and prokinetic properties when administered systemically in humans (Salem et al. 2016). Lidocaine
produces sedation and analgesia in dogs with minimal cardiovascular depression (Braun et al. 2007).

Minghella et al. (2016) reported that the use of lidocaine (2 mg kg\(^{-1}\), IV) 2 minutes before the induction of anesthesia with a propofol target-controlled infusion (plasma target concentration 1 \(\mu\)g mL\(^{-1}\)) did not reduce the total dose of propofol required for loss of jaw tone. Cerasoli et al. (2016) using lidocaine (2 mg kg\(^{-1}\), IV) 2 minutes before induction with propofol (1 mg kg\(^{-1}\), IV, over 40 seconds) did not reduce the induction dose and had no effect on the overall induction quality, compared to a saline group. Thompson & Rioja (2015) demonstrated in dogs premedicated with methadone (0.2 mg kg\(^{-1}\), IV) that lidocaine (2 mg kg\(^{-1}\), IV or 0.4 mg kg\(^{-1}\), topical) attenuated pressor and cough responses to tracheal intubation with anesthetic induction with propofol with doses ranging from 4-5 mg kg\(^{-1}\), IV.
1.7 MECHANICAL VENTILATION IN ANESTHETIZED DOGS

Induction of general anesthesia promotes a reduction in lung volume and atelectasis formation associated with a deterioration of both gas exchange and respiratory mechanics (Severgini et al. 2013). Pulmonary atelectasis is a condition in which there is an absence of gas exchange in portions of the lungs because of failure of the alveoli to open or impairment of gas absorption from the alveoli. After induction of anesthesia, the diaphragm relaxes and moves cranially; therefore, it is less effective in maintaining pressure difference in the 2 body cavities (Staffieri et al. 2007).

1.7.1 Indications for Mechanical Ventilation

The fundamental physiological objectives for the use of mechanical ventilation in acutely ill patients are:

a) To support pulmonary gas exchange by improving alveolar ventilation (arterial PCO₂, pH) and maintaining a normal level of arterial blood oxygenation (PaO₂, SaO₂, CaO₂);

b) To increase lung volume, prevent atelectasis, and increase and maintain functional residual capacity (FRC);

c) To decrease the work of breathing, especially in long anesthetic procedures (Slutsky 1993); and

d) To promote a smooth transition from injectable induction to maintenance with inhalant anesthesia.

During surgery with general anesthesia most of our patients require mechanical ventilation due to depressant effect on the respiratory system of anesthetic drugs. Ventilation may induce
lung injury through various mechanisms. Large tidal volumes and high airway pressures may cause overdistention of the alveoli, which may result in barotrauma and volutrauma (Beitler et al. 2016). Factors such as reduced functional residual capacity, cranially displaced diaphragm, a high inspiratory oxygen concentration and no positive end expiratory pressure (PEEP) may lead to atelectrauma. Atelectasis occurs in nearly all anesthetized patients and might lead to life threatening postoperative pulmonary complications such as hypoxemia and pneumonia. The effects would be more significant in some situations like obese patients, pregnancy, one lung ventilation and laparoscopic surgery (Davis & Musk 2014; Jiang et al. 2016).

Modern anesthetic workstations allow selection of either volume-controlled ventilation (VCV) or pressure-controlled ventilation (PCV), when conventional positive pressure ventilation is applied. While both modes are time cycled, termination of the inspiratory phase is determined when either a set tidal volume is delivered (VCV) or a set peak inspiratory pressure (PIP) is achieved (PCV). During VCV, therefore, PIP may vary from breath to breath while during PCV the tidal volume is likely to vary. The variations are functions of lung and thoracic wall compliance (Davis & Musk 2014).

Both VCV and PCV offer some advantages and disadvantages, In VCV mode it is relatively easy to adjust ventilator settings based on tidal volume which can be estimated from the animal’s body weight. Once tidal volume is set, the ventilator will deliver the volume regardless of the PIP generated, unless a maximum allowed PIP has also been set. High inspiratory pressures may reduce venous return and therefore cardiac output, which is fundamental to maintain between normal limits during anesthesia. Ventilation with PCV can be less user friendly as the delivery of tidal volume varies from breath to breath, again as a function of respiratory compliance and resistance. A recognized benefit of PCV mode is a more homogeneous distribution of volume
throughout different areas of the lung, thus improving gas exchange and potentially improving ventilation perfusion ratio and reduction of atelectasis lessening risk of hypoxemia (Davies & Musk 2014).

In critically ill patients a systematic review and meta-analysis in human medicine showed that the use of PCV led to improved intraoperative oxygenation and lower airway pressure (peak and plateau) and was more efficient in eliminating carbon dioxide. Under normal circumstances the selection between PCV and VCV may be of little significance and can be chosen by clinician preference (Jiang et al. 2016).

1.7.2 Veterinary Ventilators

There are different types of ventilators currently in use in veterinary medicine. They differ according: a) power source (compressed gas, electricity or both); b) drive mechanism (double circuit [bellows], single circuit [piston]); c) cycling mechanism (fluidic or solid timing device); d) bellows classification (ascending or descending during expiration). The most commonly used ventilators in anesthesia are powered by compressed gas and electricity and the drive mechanism is double circuit (patient gas and driving gas). In terms of bellows classification, most modern ventilators include ascending bellows because they ascend during the expiration phase; therefore, if there is a leak or disconnection, they would descend during this phase and warn the operator.

1.7.2.1 Clinical settings

The primary goal of mechanical ventilation during anesthesia is to achieve normocapnia (35-45 mmHg), and in order to achieve this anesthetists have to set ventilation parameters:
a) Tidal volume (TV): the recommendation for TV in small animal anesthesia is 15 mL kg$^{-1}$ during IPPV. This TV is associated with less physiological dead space and higher fraction of alveolar ventilation than 10 or 12 mL kg$^{-1}$, whereas a TV of 15 mL kg$^{-1}$ was not associated with alveolar overdistention and cardiovascular parameters were kept within the normal physiological range (Bumbacher et al. 2017);

b) I:E ratio: the inspiratory time compared with time for expiration. Inspiratory time should be shorter, ratio should be 1:2;

c) Peak inspiratory pressure (PIP): TV and I:E ratio affect PIP. In small animal anesthesia the value should be between 15 and 20 cm H$_2$O in normal and compliant lungs;

d) Respiratory rate: in dogs RR should be between 8 and 14 breaths per minute (Tranquilli et al. 2007).

1.7.3 Cardiovascular Effects

While mechanical ventilation is important and necessary in more critical patients, it is not without negative cardiovascular consequences. These effects can be summarized as a decrease in venous return due to compression on the vena cava, decreased preload, stroke volume and cardiac output, which are more significant the more critically ill the patient is (Pinsky et al. 1983; van den Berg et al. 2002; Michard 2005).

Mechanical ventilation induces cyclic changes in vena cava, pulmonary artery and aortic blood flow. During inspiration, vena cava blood flow decreases first, followed by a decrease in pulmonary artery flow and then in aortic blood flow. The decrease in vena cava blood flow (i.e., venous return) is related to an increase in right atrial pressure and to the compression of the vena cava due to the inspiratory increase in pleural pressure during mechanical ventilation (van den
Berg et al. 2002; Michard 2005). According to the Frank-Starling mechanism, an increase in inspiratory pressure results in a decrease in right ventricular preload, which results in a decrease in right ventricular output and pulmonary artery blood flow that finally leads to a decrease in left ventricular filling and output (van den Berg et al. 2002; Michard 2005). In critically ill patients, for example during hypovolemic conditions, respiratory variations in stroke volume and arterial pressure are of greater magnitude, and the ventricles are more sensitive to changes in preload when they operate on the steep portion of the Frank-Starling curve, hence a given change in preload will induce a significant change in stroke volume (Michard 2005). However, in dogs with acute ventricular failure, an increase in intrathoracic pressure can improve left ventricular function due to an increase in left ventricle diastolic compliance, an improvement in myocardial contractility, and a reduction in left ventricular afterload (Pinsky et al. 1983).

Considering the cardiovascular changes associated with mechanical ventilation itself, allowing for short-term spontaneous ventilation while assessing the cardiovascular effects of anesthetic induction drugs is probably more appropriate initially, especially in the critical patient with cardiovascular compromise. As mechanical ventilation is initiated in the patient, cardiovascular changes are related to the induction technique, pre-operative stabilization, and inhalant anesthetic maintenance, as well as ventilator settings. Monitoring is key in this timeframe, especially if patient positioning is changed. If necessary, cardiovascular support with intravenous fluids and sympathomimetics can preserve or improve cardiovascular function.
1.8 CARDIAC OUTPUT

1.8.1 Definition and Relevance

Cardiac output (CO) is the volume of blood pumped by the heart per minute and is a product of the heart rate and stroke volume. The stroke volume of the ventricle is determined by the interactions between its preload, contractility and afterload (Hall & Guyton 2011). Cardiac output measurement is crucial for guidance of therapeutic decisions in critically ill and high risk surgical patients (Joosten et al. 2017). The measurement of CO can be extremely useful when assessing circulatory function and a simple and reliable method of measuring CO is frequently required both clinically and for research purposes (Critchley & Critchley 1999). Clinical assessment of CO and systemic vascular resistance is not reliable and cannot be used as a replacement for objective CO measurement (Kutter et al. 2016). Knowledge of CO values is potentially valuable in clinical settings, and the ability to measure and adjust these values in real time during anesthesia and in the ICU environment could improve patient outcomes (Morgaz et al. 2014). Kutter et al. (2016) using pulmonary thermodilution found that the median CO in dogs was 2.27 L/min (range 0.98-3.4).

Although there are no veterinary evidence-based recommendations for the measurement of CO alone for improving outcome in ill patients, the relationship between CO and tissue perfusion has led many authors to recommend the measurement of CO in patients such as those with septic shock, gastric dilation, or systemic inflammatory response syndrome (Morgaz et al. 2014). Cardiac output measurement to optimize tissue perfusion is of great interest in the field of goal-directed therapy as it may improve patient outcomes, reduce complications and, reduce length of hospitalization (Morgaz et al. 2014).
For veterinarians, CO and oxygen delivery have been difficult to monitor in clinical settings and are commonly estimated using of other variables. These may include a combination of heart rate and rhythm, pulse rate and quality, capillary refill time, rectal temperature, serum lactate concentration, arterial blood pressure, urine output, and acid-base status. The combination of these indirect indices has been associated with inaccurate estimates of CO in humans and animals (Duffy et al. 2008).

Clinicians rely heavily on pressure measurements as an index of perfusion despite available data indicating that there is virtually no correlation between changes in pressure and changes in blood flow (Duffy et al. 2008). Changes in mean arterial pressure do not reflect corresponding changes in CI (Duffy et al. 2008).

There is a continuing search for new methods of CO monitoring that are more precise and less invasive than its predecessor (Critchley & Critchley 1999). Monitors that measure CO can be used both to diagnose states of low, normal or high CO, and to assess the response to therapeutic interventions by continuous or serial measurements. The use of such monitors is common in critical care and is recommended in certain perioperative situations (Crossingham et al. 2016). The “gold standard” is normally considered to be the thermodilution technique using a pulmonary artery catheter, which is a common reference standard to which newer methods have been compared (Crossingham et al. 2016).

1.8.2 Measurement Techniques

1.8.2.1 Pulse Contour Method

Two classes of arterial waveform analyzer are currently in existence – calibrated devices, which periodically recalibrate based on a second measurent technique (e.g. transpulmonary thermodilution and lithium dilution), and uncalibrated devices (Thiele et al. 2015).
Frank’s Windkessel model of blood flow formed the basis of most early attempts at measuring cardiac output from the arterial pulse contour. Modern pulse contour devices are an extension of this technique. The model assumes that the volume of blood entering a vessel of infinite length must equal the volume of blood leaving a vessel over a period of cardiac contraction and that during systole, the vessel will expand, whereas during diastole, it will contract. The aorta acts as a capacitor and systemic arterioles act as resistor (Thiele et al. 2015). In this model stroke volume is related to the area under the systolic portion of the aortic pressure waveform over a beat to beat basis as well as in relation to aortic impedance (Morgaz et al. 2014).

Pulse contour devices provide the user with estimates of pulse pressure variation, SVV and in some cases dP/dt, and extravascular lung water (Thiele et al. 2015). The PulseCO system incorporates characteristic impedance into its model using a transfer function to estimate aortic blood pressure. The PulseCO system can be used as an uncalibrated device or it can be used in combination with a lithium dilution curve (referred to as LiDCO) (Thiele et al. 2015). Because the arterial waveform is influenced by factors such as aortic impedance, systemic vascular resistance, and damping, PulseCO is calibrated by lithium dilution CO (LiDCO) or other reference techniques (e.g. pulmonary artery thermodilution) (Kutter et al. 2014).

1.8.2.2 Indicator Methods

Until the last decade, pulmonary artery thermodilution was the standard clinical method for measuring CO in people. This method uses a cold solution as an indicator, which can be detected by a thermistor placed in the pulmonary artery by means of a pulmonary catheter; the degree of change in temperature is inversely proportional to blood flow. However, morbidity associated with this technique is high due to its invasiveness and has prompted the development
of new, less invasive CO monitors. In veterinary medicine over the past years several studies have been conducted using different methods with other indicators such as lithium (Morgaz et al. 2014).

The lithium dilution cardiac output monitor (LiDCO\textsuperscript{R}) uses a lithium-sensitive electrode situated in a flow-through cell, and attached to an arterial catheter. The electrode consists of polyurethane with a central lumen electrode through which blood is drawn from the artery to come in contact with a selectively permeable membrane to lithium. The voltage that results across the membrane is related to the plasma lithium concentration, and is digitalized and analyzed to provide a cardiac output value. A correction is applied for plasma sodium concentration because in absence of lithium, the baseline voltage is determined by the sodium concentration (Jonas et al. 2002; Duffy et al. 2008).

Cardiac output calculated from the lithium dose and the area under the concentration-time curve, prior to recirculation, uses the following equation:

\[
\text{CO} = \frac{\text{lithium dose} \times 60}{(\text{area} \times [1-\text{PCV}])}
\]

where the area is the integral of the primary curve, and PCV is calculated as hemoglobin concentration divided by 34. A correction for PCV is necessary because lithium is distributed into plasma. The voltage response of the lithium ion-sensitive electrode represents the percentage change of ion concentration, and because lithium is not typically present in plasma, extremely low doses can be used (Duffy et al. 2008).

The PulseCO monitor is a variation of the LiDCO monitor, which can calculate continuous CO (after LiDCO calibration) by use of an analysis of the arterial blood pressure trace using pulse contour technology. The arterial blood pressure trace undergoes a 3-step transformation that incorporates pulse power analysis.
In the first step, the arterial waveform is transformed into a volume-time waveform on the basis of the curvilinear relationship between pressure and volume (i.e. compliance) as follows:

$$\text{Change in } V / \text{change in } P = k \times 250 \times e^{(-k \times P)}$$

Where $V$ is volume, $P$ is blood pressure, $k$ us the scaling or calibration factor, 250 is the arterial tree saturation (full expansion) volume in milliliters for the calibration factor of $k = 1$, and $e$ is the natural logarithm. This can be used to determine CO when the relationships are constant. The relation between the capacity of the arterial tree and intravascular pressure can be expressed as the compliance (pressure change per unit volume change). This could be used to determine cardiac output if this relation were constant. However, arterial compliance changes as arterial pressure changes. The vessel wall will stiffen as pressure and volume increase and become less compliant; this can be plotted as a curvilinear relationship (approximately exponential). A table can be generated, allowing the pressure waveform to be used as the basis for calculating volume changes and, hence cardiac output for each pressure cycle (Jonas et al. 2002; Duffy et al. 2008).

In the second step, an estimate of SV is calculated. The value of the derived arterial blood volume is subtracted from the volume trace. This generates a sine-like waveform, which yields an estimates of change around the mean value. By squaring the values of the sine-like curve, a double waveform is generated. The square root of the mean of this double waveform, known as the root mean square, yields an estimate of nominal stroke volume (Duffy et al. 2008).

In the final step, heartbeat duration is calculated by moving 1 version of the volume waveform successively, step by step, relative to another until maximum reinforcement is achieved. This time period represents the duration of the cardiac cycle. The final value is scaled on the basis of calibration to a value derived by dilution of the lithium indicator, which provides the actual SV. The PulseCO algorithm uses the duration of the cardiac cycle (i.e. the interval between systolic
pressure waves) to calculate heart rate and multiply this by the derived nominal SV to calculate CO (Duffy et al. 2008).

An advantage of PulseCO is that it can use a central artery or peripheral artery such as the dorsal metatarsal artery for measurement of CO, whereas other pulse contour techniques, such as PiCCO require a femoral artery catheter to be more accurate (Morgaz et al. 2014).

Limitations of this technique include possible effects of other drugs; for example, a large bias for LiDCO and cardiac output measurement with bolus thermodilution was demonstrated in horses receiving xylazine, ketamine, and midazolam infusions, and in subsequent studies in vitro showed an influence of different drugs on LiDCO sensor accuracy (Ambrisko et al. 2012; Ambrisko et al. 2013). Furthermore, Hopster et al. (2015) found that xylazine caused concentration pendant error in LiDCO measurements (overestimation) in anesthetized horses, and that voltage differences between the saline-exposed and blood-exposed sensor may be used to predict the presence of such an error. Additional drawbacks associated with repeated LiDCO determinations include excessive blood loss and accumulation of the indicator (lithium) in the body (Beaulieu et al. 2005).

Recently a study assessing accumulation of lithium after repeated determinations/calibrations using LiDCO did not support major risk of accumulation. Morgaz et al. (2014) calibrated the LiDCOPlus 18 times in each of 14 research dogs, which could increase the risk for toxicity or even interfere with the accuracy of the monitor, as a progressive increase in the blood lithium concentration increases the overestimation of CO by LiDCO. They did not observe signs of toxicity in their dogs after recovery from anesthesia. The highest levels of lithium measured in the study subjects (~0.2142 mmol/L) were still < 0.4 mmol/L, which is considered the maximum level that does not decrease the accuracy of the monitor.
1.8.3 Validation in Dogs

1.8.3.1 Lithium Dilution Method

Lithium dilution is one of the first monitors used in veterinary medicine to measure CO and is considered to be a good monitor with good agreement with pulmonary artery thermodilution, considered the gold standard method (Mason et al. 2001; Beaulieu et al. 2005), and in some instances has been more reliable than thermodilution (Kurita et al. 1997). This monitor has a high signal to noise-ratio because lithium is not a normal constituent of the body, therefore determination of CO by this method is safe because the lithium-selective electrode is activated by doses much lower than toxic doses. (Mason et al. 2001; Morgaz et al. 2014).

1.8.3.2 Pulse Contour Method

In general, agreement between CO methods based on pressure waveform analysis and clinical standards, such as thermodilution have been poor, especially when there are large changes in systemic vascular resistance. Because the PulseCo system is dependent on pressure waveform, concerns for its accuracy center on the validity of its algorithm with waveform variation associated with changes in vascular tone (Duffy et al. 2008). In a study comparing continuous arterial pressure waveform analysis with the lithium dilution technique to monitor cardiac output in conscious dogs with systemic inflammatory response syndrome, the authors concluded that there was an inadequate agreement between LiDCO and PulseCO measurements in conscious, critically ill dogs despite no significant changes in CO values (Duffy et al. 2008). Hence, frequent recalibration is recommended in order to increase accuracy (Morgaz et al. 2014).
1.9 RATIONALE, HYPOTHESIS and OBJECTIVES

The reason for this research is to assess the commonly used veterinary anesthetic injectable induction drug propofol with or without midazolam, and to determine if the potential dose reduction obtained is beneficial in terms of cardiovascular and respiratory effects in critical canine patients undergoing surgery.

To the authors’ knowledge, advanced cardiopulmonary measurements of propofol co-induction with or without midazolam in fentanyl pre-medicated canine cases of ASA III-IV status are not available. This clinical research study will provide insight into terms of administration of propofol with or without midazolam after pre-medication with fentanyl in hemodynamically compromised patients undergoing exploratory laparotomies. This information is vital to answer the question of whether or not the potential dose reduction, if any, with midazolam co-induction with propofol actually improves the cardiopulmonary stability of these compromised patients during and after induction, as well as maintenance with isoflurane in mechanically ventilated patients until early phases of surgical preparation (draping).

This study will also provide insights about the use of illness severity scores in clinical research in veterinary medicine, which may link to or assess the ASA status of the patient, injectable dose reduction as well as give more specific information of the potential for anesthetic hypotension or complications (days in ICU). Ideally the severity scoring will demonstrate homogeneity in our clinical case population. We hope that our results will increase knowledge about how commonly used induction drugs in veterinary anesthesia impact our sick compromised patients, in terms of hemodynamic stability.
1.9.1 Research Objectives

a. To determine the anesthetic quality and dose reduction of propofol when midazolam is administered as a co-induction drug in ASA III-IV clinical canine patients pre-medicated with fentanyl requiring abdominal surgery.

b. To determine the cardiovascular and respiratory effects of propofol with or without midazolam co-induction for anesthesia in ASA III-IV clinical canine patients pre-medicated with fentanyl at induction, during initiation of mechanical ventilation and during surgical preparation for abdominal surgery while maintained with isoflurane.

c. To determine if the severity score SPI2 correlates with ASA status, injectable dose requirements, and hypotension, as well as identify if it is a useful tool to ensure that patients randomized into both research groups of ASA III-IV canine patients requiring abdominal surgery are homogeneous.

1.9.2 Hypothesis

We hypothesize that co-induction of midazolam with propofol will not only reduce the anesthetic injectable dose, but also this reduction will be beneficial with respect to cardiopulmonary effects of the primary induction drug in critically ill canine patients.

In addition, we hypothesize that SPI2 will correlate with ASA classification as well as give an indication of the level of cardiopulmonary depression produced with induction and maintenance of general anesthesia.
2.0 REFERENCES


Hopkins A, Giuffrida M, Larenza MP. (2014) Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. Vet Anaesth Analg 41, 64-72.


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


CHAPTER II

A COMPARISON OF CARDIOPULMONARY FUNCTION AND TOTAL DOSAGES REQUIRED FOR ANESTHETIC INDUCTION WITH PROPOFOL VERSUS PROPOFOL-MIDAZOLAM IN CRITICAL CANINE PATIENTS
2.1 ABSTRACT

Objective: This study determined the induction dose and cardiopulmonary effects of propofol alone or with midazolam in dogs requiring emergency abdominal surgery.

Study design: Prospective, randomized, blinded, clinical trial.

Animals: Nineteen client-owned dogs.

Methods: Dogs were scored for ASA status and survival prediction index (SPI2) before surgery, then sedated with fentanyl (2 µg kg⁻¹, IV) for instrumentation and after additional fentanyl (3 µg kg⁻¹, IV) (T1), heart rate (HR; bpm), direct arterial blood pressures (BP; mmHg), cardiac index (CIL; mL kg⁻¹ min⁻¹), systemic vascular resistance index (SVRIL; mmHg mL⁻¹ min⁻¹ kg⁻¹), respiratory rate (fR; brpm), arterial blood gases and electrolytes, and temperature (temp; °C) were recorded and quality of sedation was scored, followed by induction with propofol (1 mg kg⁻¹, IV) and saline (0.06 mL kg⁻¹) (P; n = 9) or propofol and midazolam (0.3 mg kg⁻¹, IV) (M; n = 10), and subsequent propofol (0.25 mg kg⁻¹; q6 seconds) for intubation. Induction/intubation quality was scored. Thereafter, anesthesia was maintained with isoflurane (1.2% end-tidal; FE’Iso) and the above measurements, in addition to FE’Iso and end-tidal CO₂ (PE’CO₂; mmHg) were recorded within 5 minutes from induction and intubation (T2), in lateral recumbency and spontaneous ventilation within 10 minutes from induction (T3) and in dorsal recumbency and mechanical ventilation within 20 minutes from induction (T4). A general linear mixed model was used with
post-hoc analysis for multiple comparisons between groups. A Spearman correlation was used to compare SPI2 to ASA scores in all dogs ($p < 0.05$).

**Results:** There was no difference in age or weight ($P [9.1 \pm 0.4 \text{ years}; 28.8 \pm 1.3 \text{ kg}]; M [6.2 \pm 0.4 \text{ years}; 25.1 \pm 1.3 \text{ kg}]) or HR, BP, RR, CIL, SVRIL, FE′Iso, fR, PE′CO$_2$, SPI2 and ASA scores between groups or within groups at any time interval. In the M group, the induction dose was lower ($1.1 \pm 0.5$ versus $1.9 \pm 0.5 \text{ mg kg}^{-1}$) than $P (p = 0.002)$ and the induction/intubation score was significantly better ($p = 0.0012$). There were no significantly differences between groups for SPI2; the median (95% CI) was 0.82 (0.76, 0.88) in the P group, and 0.87 (0.81, 0.93) in the M group. The ASA status was also not significantly different between groups, the median (95% CI) in the P group was 3.0 (2.8, 3.2), and 3.1 (2.9, 3.3) in the M group. There was no correlation between SPI2 and ASA scores.

**Conclusion and clinical relevance:** Midazolam co-induction reduced the propofol induction dose in critically ill dogs without an improvement in cardiopulmonary parameters, when compared to a higher dose of propofol alone. Therefore, both induction techniques are similar, except for smoother inductions when midazolam is included. The SPI2 and ASA scores were not correlated for assessing critically ill dogs.

*Keywords* co-induction, propofol, midazolam, critical patient, dog
2.2 INTRODUCTION

Propofol is a nonopioid, nonbarbiturate sedative/hypnotic drug with rapid onset and short duration of action, commonly used as an induction drug in veterinary medicine. However, it is associated with dose-dependent respiratory depression and hypotension (Covey-Crump & Murison 2008).

Co-induction refers to the administration of a sedative, anesthetic or analgesic drug along with the main anesthetic induction drug, in order to the reduce induction dose and potentially ameliorate some of the cardiopulmonary depression associated with the induction drug (Liao 2016; Minghella et al. 2016). To achieve a beneficial effect from co-induction, the drug selected should not only have a hypnotic dose sparing effect but must have minimal cardiovascular depressant effects of its own (Minghella et al. 2016).

In veterinary anesthesia, co-induction drugs are often used during the induction period principally to reduce the dose of the primary induction drug and ensure a smooth overall endotracheal intubation process. Co-induction with the benzodiazepines, diazepam or midazolam, are the most extensively studied in combination with propofol induction in dogs. Midazolam shows the most consistent dose-reduction results especially when given after the initial bolus of propofol, however the benefit of a reduced dose on cardiopulmonary function has not been clearly defined (Covey-Crump & Murison, 2008; Robinson & Borer-Weir 2013; Sanchez et al. 2013; Martinez-Taboada & Leece 2014; Hopkins et al. 2014; Liao 2016).

Only a few investigations have assessed cardiopulmonary variables during the induction phase. One study compared the effects of propofol with or without midazolam co-induction on indirect blood pressure in healthy dogs (ASA classification I) and demonstrated lower systolic blood pressures when midazolam co-induction was administered followed by propofol over 15
seconds (Hopkins et al. 2014).

Liao (2016) did not demonstrate a difference in direct arterial blood pressure, cardiac output, and derived hemodynamic variables between healthy research dogs (ASA status I) receiving propofol with midazolam co-induction or propofol alone, despite a dose reduction of 1.5 mg kg\(^{-1}\) \textit{versus} 2.1 mg kg\(^{-1}\), respectively, in the propofol group. Healthy dogs may not be significantly affected by induction doses of propofol, since the decrease in cardiopulmonary function after induction with potent anesthetics mainly originates from sympatholysis, rather than direct injectable anesthetic depression, and autonomic function can be maintained in healthy dogs (Goodchild & Serrao 1989; Liao 2016). It is possible that the true benefit of a decreased dose of propofol with midazolam co-induction, and resultant preservation of cardiopulmonary function, may only be evident in clinical patients that are already compromised (ASA \(\geq\) III) and where autonomic function is unbalanced. However, to the authors’ knowledge, assessing direct arterial blood pressure and cardiac output measurements during co-induction in critical clinical patients has not been investigated in a controlled research environment to answer this question.

Critically ill patients, affected by life-threatening conditions represent a heterogeneous group due to multiple organ dysfunction. An illness severity scoring system that includes such alterations in biochemical values and cardiorespiratory parameters could help place a numeric value on the degree of illness for inclusion into a clinical study (King et al. 2001). The survival prediction index (SPI2) is a validated mathematical system that uses a logistic regression equation, developed on critically ill dogs admitted to an intensive care unit and uses seven different parameters: mean arterial pressure, respiratory rate, creatinine, packed cell volume, albumin, age, medical versus surgical status (King et al. 2001). Similarly, ASA classification status is a scoring system that predicts operative risk and outcome of patients to undergo anesthesia, and has been
compared to other scoring systems, such as the Acute Physiology and Chronic Health Evaluation index (APACHE II), used in human medicine to evaluate preoperatively the risk of postoperative morbidity and death after major general surgical operations (Goffi et al. 1999). A comparison between SPI2 and ASA has not been completed in veterinary patients.

The objectives of this research were to 1) quantify the dose reduction of propofol with midazolam in critical canine patients (ASA ≥ III), 2) to compare cardiopulmonary function when propofol is co-administered with either saline or midazolam during anesthetic induction under standard clinical conditions in canine patients requiring of an emergency exploratory laparotomy, and 3) to compare SPI2 and ASA scores in these cases to determine if there is a difference in ASA status compared to SPI2.

We hypothesize that there will be a benefit to cardiopulmonary function during anesthetic induction with propofol using midazolam as a co-induction drug versus propofol alone in critically ill dogs, due to a reduction in propofol dose. We also hypothesize that risk prediction scores such as ASA and illness severity scores such as SPI2 provide similar information in these type of dogs.
2.3 MATERIALS AND METHODS

2.3.1 Animals

All procedures were approved by the Animal Care Committee, University of Guelph, and followed Canadian Council on Animal Care Guidelines. Client-owned dogs admitted to the Companion Animal Hospital of the Ontario Veterinary College and fulfilling the following study inclusion criteria were enrolled in the study: owner consent, body weight \( \geq 10 \text{ kg} \), requirement for emergency general anesthesia for abdominal exploration, and pre-operative clinical signs compatible with an ASA status III or IV. A complete blood count and biochemistry panel, thoracic and abdominal focused assessment with sonography for triage (TFAST/AFAST), packed cell volume (PCV), total protein (TP), and venous blood gas was performed prior to general anesthesia. Dogs were stabilized in the intensive care unit prior to anesthetic induction and surgical exploration, which included aseptic percutaneous placement of a cephalic intravenous (IV) catheter, 20 or 22-gauge (Insyte-W; Becton Dickinson Infusion Therapy Systems, UT, USA), IV crystalloid fluid administration (Plasmalyte-A Baxter Corporation. Mississauga, ON, Canada), and analgesic drug administration.

All dogs were assigned an ASA score before premedication, and data for SPI2, including mean arterial pressure, respiratory rate, creatinine, PCV, albumin, age, medical versus surgical status were collected and applied to the logistic equation below (King et al. 2001) to compare it with ASA status of the dog and induction dose of propofol.

\[
\text{Logit } P = 0.3273 + (0.0108 \cdot \text{MAP}) - (0.0102 \cdot \text{respiratory rate}) - (0.2183 \cdot \text{creatinine}) + (0.0164 \cdot \text{PCV}) + (0.3553 \cdot \text{albumin}) - (0.1184 \cdot \text{age}) - (0.8069 \cdot \text{medical vs surgical status})
\]

Where medical vs surgical status was a dichotomous variable (medical = 1, surgical = 0).
2.3.2 Study Design

This study was a prospective, blinded, randomized clinical trial. Randomization was performed using a computer software program (GraphPad, California, USA). Once enrolled, an anesthesia technician or a veterinarian not involved in data collection, confirmed the anesthetic treatment allocation of the dog from a randomization list and prepared anesthetic drugs for each dog to receive one of two anesthetic treatments: group M, induction with propofol (Propofol 1%, Fresenius KABI, Toronto, Ontario, Canada) with midazolam (Midazolam 0.5%, Pharmaceutical Partners of Canada Inc, Richmond Hill, Ontario, Canada) or group P, induction with propofol and saline (0.9% sodium chloride; Hospira, Saint-Laurent, Quebec, Canada). An anesthesia technician was dedicated to monitoring depth and cardiopulmonary parameters throughout anesthesia and surgery, while the blinded investigator focused on recording induction dose volume, quality of induction, and cardiopulmonary data at selected time points of induction and surgical preparation.

2.3.3 Instrumentation and Measurements

Once stabilized for their presenting condition, dogs were maintained in the ICU until anesthesia and surgery commenced. Once stable and prior to general anesthesia, dogs were categorized accordingly in regards to ASA Score by Anesthesia faculty or senior resident. A pre-anesthetic rectal temperature (Temp; °C), pulse and heart rate (HR, beats minute⁻¹) with LEAD II electrocardiography (EKG), respiratory rate (/R, breaths minute⁻¹), non-invasive arterial blood pressures (mmHg) for mean (MAP), systolic (SAP) and diastolic (DAP), hemoglobin oxygen saturation (SPO2) (CC5; Cardiocap/5, GE, Datex Ohmeda, Mississauga, Canada) were obtained prior to sedation and arterial catheterization, with the dogs in lateral recumbency (T0 = on arrival in anesthesia) (Appendix 2.1). Sedation was achieved with an initial IV dose of fentanyl (F1, 2 μg
kg$^{-1}$) (Fentanyl Citrate Injection USP; Sandoz Canada Inc., Canada), followed by clipping of the skin over the dorsal pedal artery and subcutaneous infiltration of 0.3 mL lidocaine (Lidocaine 2%, Alveda Pharmaceuticals, Canada) at the site for catheterization with a 20 or 22-gauge catheter. The arterial catheter was connected by non-compliant extension tubing (Arterial Pressure Tubing, ICU Medical Inc, California, USA) to a pressure transducer (Transducer set; Becton Dickinson Critical Care System Pte, Ltd, Singapore) and the multi-channel monitor for determination of direct arterial blood pressures, SAP, MAP and DAP, and pulse contour cardiac output (CO) measurement (PulseCO hemodynamic monitor, LiDCO Ltd, UK). The level of the right atrium was assumed to be at the level of the manubrium (in lateral recumbency) and used as the zero reference for all blood pressure determinations (level of transducer was adjusted when patients were placed in dorsal recumbency). The clinical equipment used for blood pressure measurement was assessed for accuracy at 100 mmHg against a mercury manometer (Mercurial Sphygmomanometer, Japan) weekly.

Once a direct arterial catheter was placed, a second IV dose of fentanyl, (F2, 3 μg kg$^{-1}$) was administered, and 2 minutes later, the degree of sedation was scored (Appendix 2.2; Sedation score [SedQ]), and cardiopulmonary measurements, including Temp, HR, EKG, fR, direct arterial blood pressures, arterial blood gases and electrolytes, SPO$_2$ and CO, were measured prior to induction (T1), within 5 minutes post-induction on spontaneous ventilation (T2), once the animal was placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction (T3), and during surgical preparation 20 minutes after induction (T4). Measurements of PE`CO$_2$ and FE`Iso were included at T2, T3 and T4 postinduction. Time from induction to the beginning of surgery was recorded.
Cardiac output using lithium dilution CO (LiDCO; LiDCO plus Hemodynamic Monitor, LiDCO Ltd, UK) was determined with the following steps. Arterial blood was sampled from the dorsal pedal arterial catheter less than 5 minutes before every LiDCO measurement and analyzed immediately for arterial partial pressures of oxygen (PaO$_2$) and carbon dioxide (PaCO$_2$), pH, hemoglobin (Hb), lactate and electrolyte concentrations (ABL 750; Radiometer, Denmark).

The Cardiocap/5 multi-parameter monitor was connected to the LiDCO plus hemodynamic monitor to allow for PulseCO determinations using a 1-volt analog signal for 100 mmHg pressure. With each LiDCO determination the PulseCO monitor was calibrated with the LiDCO to allow for continuous measurements. Steps for preparing the lithium sensors, and for checking for suitable sensor voltage and stable baseline signals were performed as described in the operation manual (LiDCO Plus Hemodynamic Monitor User's Manual 1.0; LiDCO Ltd., UK). For LiDCO determinations, lithium chloride (Lithium Chloride Injection; LiDCO Ltd., UK) was injected (6 µmol kg$^{-1}$) rapidly into the cephalic vein catheter 6 seconds after starting the injection phase on the LiDCO computer. Arterial blood was drawn at a standard rate of 4 mL minute$^{-1}$ rate through the sensor (Flow through Cell Electrode Assembly, CM10; LiDCO Ltd., UK) for determination of lithium concentration (approximately 30 seconds). Cardiac index (CIL), stroke volume index (SVIL) and systemic vascular resistance index (SVRIL) were calculated from the CO measured by LiDCO and cardiac index from the PulseCO was used to calculate systemic vascular resistance index (SVRIP). Where applicable, the formulas below were used 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.

2.3.4 Anesthetic Induction

In both groups, an initial dose of propofol (1 mg kg\(^{-1}\), IV) was administered as a bolus, flushed with 2 mL of saline IV and then followed immediately by midazolam (0.3 mg kg\(^{-1}\), IV; M group) or an equal volume of saline (0.06 mL kg\(^{-1}\), IV; P group). Additional smaller doses of propofol (0.25 mg kg\(^{-1}\)) were administered every 6 seconds until successful endotracheal intubation could be attempted in the absence of a lateral palpebral reflex, absence of jaw tone and no reaction to laryngoscope. Induction/intubation scores based on numbers of additional boluses, response to the laryngoscope placement, speed of relaxation and presence of excitement were also assessed and recorded after intubation (Appendix 2.3; Induction/intubation score [IndQ]). The time from beginning of sedation (F1) to induction was recorded.

After endotracheal intubation the dogs were connected to a small animal anesthesia machine (Boyle Apparatus, London, England) with rebreathing circuit (Universal F-Circuit; Dispomed, Joliette, Quebec, Canada) using an oxygen flow of 1.5-2.5 L minute\(^{-1}\), allowed to breathe spontaneously and maintained on isoflurane (AErrane; Baxter Corporation, Mississauga, Ontario) in oxygen (FiO\(_2\) 100%), using a precision vaporizer (Fortec, Orchard park, New York, USA), to maintain an appropriate anesthetic depth at a monitored end-tidal isoflurane concentration (FE\(^{\text{Iso}}\)) of 1.2-1.3%. Respiratory rate was manually counted over 30 seconds. If the dog did not spontaneously ventilate for more than 1 minute, a manual breath was administered. After 10 minutes, dogs were placed in dorsal recumbency and mechanical ventilation (IPPV) (Hallowell EMC, Pittsfield, Massachusetts, USA) was instituted as follows: tidal volume 10-15 mL kg\(^{-1}\), fR 10-12 breaths min\(^{-1}\) and adjusted to keep the dog at an end-tidal CO\(_2\) (PE\(^{\text{CO}}\)_2) of 35-
45 mmHg, and a peak inspiratory pressure of 10-20 cm H₂O.

Hypotension was defined as MAP < 60 mmHg for more than five minutes with an appropriate anesthetic depth. As long as volume status was deemed adequate, hypotension was treated with an infusion of dopamine (2–7 µg kg⁻¹ minute⁻¹) at the anesthetist’s discretion.

2.3.5 Statistical analysis

Statistical analyses were performed with standard computer software (SAS version 9.4 SAS Institute Inc., Raleigh, North Carolina, USA). Normality of data was tested using Shapiro-Wilk and Kolmogorov-Smirnov. 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 test for mean differences in cardiopulmonary data measured over time. The fixed effects of group and time as well as group/time interaction and the random effect of dog where included in the models. The error structure, among correlation structures, was chosen based upon the lowest Akaike Information Criteria, to account for repeated measures. Appropriate adjustments (Tukey or Dunnet test) for multiple comparisons were used. Single time parameters (total induction dose of propofol, sedation and induction scores) were analyzed for mean differences between the two groups with a student t-test, or a Wilcoxon Mann Whitney test if not normally distributed. The chi square test was used to test for differences in sex, and need for dopamine between treatments. Significance was set at $p < 0.05$.

The results are presented with adjusted mean if data are normally distributed, or ordinal and adjusted median if not normally distributed with 95% confidence intervals (CI). 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 difference between groups for SPI2, admission values for mean arterial blood pressure, lactate, packed cell volume (PCV), and total protein (TP) were analyzed for mean differences between the two groups with a Student’s t-test. A Spearman correlation was used to test for an association of SPI2 and ASA status.

The number of dogs in the study was determined by estimating the mean (SD) induction dose of propofol in the P group at 2 (0.4) mg kg$^{-1}$ and at least a 30% reduction with midazolam co-induction (M). For a type-I error ($\alpha$) of 0.05 and a desired power of 0.90, a sample size of 9 dogs per group was required.
2.4 RESULTS

A total of 19 dogs were enrolled in the study. There were no significant differences in demographics between the groups for weight or age (Table 2.1 and Table 2.2). The ASA status was also not significantly different between groups, the median (95% CI) in the P group was 3.0 (2.8, 3.2), and 3.1 (2.9, 3.3) in the M group.

All patients were eventually discharged from the hospital.

2.4.1 Induction dose requirements, Sedation and Intubation/Induction scores

Dogs in the M group had a significantly lower propofol induction dose requirement than in the P group, associated with similar sedation scores between groups, but a significantly better (lower score) intubation/induction score in the M group (Table 2.2). No signs of excitement were observed in any of the dogs in either group, however, the number of additional propofol doses required for induction of anesthesia was significantly higher in the P group than in the M group.

There were no significant differences between the groups for time from sedation to induction and time from induction to beginning of surgery (Table 2.2).

2.4.2 Cardiopulmonary parameters

There were no significant baseline differences between groups or within groups in HR, CIL, MAP, SAP, DAP, SVRIL, SVRIP, RR, FE\(^\text{I}_\text{so}\), PE\(^\text{CO}_2\), Temp, and blood gases and electrolytes, Hb, PCV, and TP, for time and treatment interactions (Figures 2.1-2.10; Table 2.3-2.5).

There was no difference in the need for dopamine to support blood pressure between treatment groups at the different time intervals.
2.4.3 SPI2 and ASA scores

There were no significant differences between groups for SPI2 (Table 2.5). The ASA score was also not significantly different between groups. The SPI2 and ASA scores were not correlated (Spearman correlation of -0.17784 and a \( p \) value of 0.47).
2.5 DISCUSSION

This research shows that in critically ill dogs premedicated with fentanyl, a significant reduction (42%) in the dose of propofol is obtained with co-induction with midazolam. It also improved the quality of induction/intubation, when compared to the group in which midazolam was not included. Despite these positive outcomes, the inclusion of midazolam did not result in better cardiopulmonary function than propofol with saline.

Several studies have demonstrated reductions in the dose of induction drugs, including propofol and alfaxalone, when co-induction with benzodiazepines, including midazolam and diazepam, is performed (Covey-Crump & Murison 2008; Hopkins et al. 2013; Sanchez et al. 2013; Robinson & Borer-Weir 2013; Minghella et al. 2016; Liao et al. 2017; Zapata et al. 2018). The interaction between propofol and midazolam to achieve intubation has been described as synergistic (Short & Chui 1991; McClune et al. 1992).

The dose reduction obtained in the present study is within the same range of those studies; however, there are differences between the type of dogs used in the different studies, as some have included healthy research dogs (ASA I) (Liao et al. 2017) and client-owned healthy dogs undergoing elective procedures (ASA I and II) (Covey-Crump & Murison 2008; Hopkins et al. 2013; Sanchez et al. 2013; Robinson & Borer-Weir 2013; Minghella et al. 2016; Zapata et al. 2018). There are also differences in the type of premedication used, as some dogs only received fentanyl (Liao et al. 2017), methadone and acepromazine (Robinson & Borer-Weir 2013), or morphine and acepromazine (Covey-Crump & Murison 2008; Hopkins et al. 2013; Sanchez et al. 2013; Minghella et al. 2016; Zapata et al. 2018). Therefore, generalizations about the degree of reduction in the induction dose should be cautious because they are influenced by the degree of sedation obtained by premedication and possibly the health status of the animal. In addition, the
order and speed with which the benzodiazepine is administered, as well as the dose, influences the
degree of reduction in the dose of the induction drug. In this study, both groups achieved a similar
degree of sedation, which was equivalent to calm dogs and minimal sedation, probably because
the sedative effects of fentanyl are mild (Gomes et al. 2011). Dogs were induced approximately
20 minutes after fentanyl, and based on pharmacokinetic data, it is expected that the degree of
sedation was still at the same level, since plasma concentrations are maintained at levels of at least
1 ng mL⁻¹ for approximately 40 minutes in dogs administered 10 µg kg⁻¹, IV (Sano et al. 2006),
and has been shown to maintain the same degree of sedation in dogs administered acepromazine
at 0.05 mg kg⁻¹, IV followed by fentanyl at 5 µg kg⁻¹, IV, for at least 55 minutes (Gomes et al.
2011).

Midazolam administered at 0.25 mg kg⁻¹, IV over 15-60 seconds immediately before or up
to two minutes before propofol, did not cause a dose reduction and resulted in excitement in 95%
of dogs in one study (Covey-Crump & Murison 2008), up to a 47% reduction and excitement in
45% of dogs in another study (Sanchez et al. 2013), and an 18% reduction and excitement in 55%
of dogs in yet another study (Hopkins et al. 2013), despite premedication with acepromazine and
morphine in all of those studies. Similar results were obtained when propofol was substituted with
alfaxalone (Zapata et al. 2018). The shorter the delay between midazolam and subsequent propofol
administration, the lower the incidence of excitement (Covey-Crump & Murison 2008; Hopkins
et al. 2013; Sanchez et al. 2013). Conversely, when midazolam is administered after propofol or
alfaxalone, the more consistent is the resultant dose reduction of induction drug and excitement is
less likely to occur (Robinson & Borer-Weir 2013; Sanchez et al. 2013; Liao et al. 2017; Minghella

This study showed that critically ill dogs had a smoother induction when midazolam was
used as a co-induction drug after propofol administration. Liao et al. (2017) also showed smoother inductions in research dogs, using the same anesthetic protocol of fentanyl premedication, before propofol followed by midazolam co-induction, than in dogs not receiving midazolam co-induction. Similarly, when alfaxalone was substituted for propofol, the same findings were obtained (Liao et al. 2017). The reduction in propofol dose in this study (42%) is higher than that observed by Liao et al. (2017) of 25% for propofol and 37% for alfaxalone, which can perhaps be attributed to the lower health status of the dogs (ASA III and IV) and the reduced requirement for induction drug in those circumstances, when compared to the healthy (ASA I) dogs studied by Liao et al. (2017), despite their use of a higher dose of fentanyl (7 µg kg⁻¹, IV). A better or lower induction quality score is associated with a reduction in the number of additional boluses of propofol to allow for endotracheal intubation. Considering this, it fits that the number of additional doses was significantly reduced from a mean of 3.4 in P to 0.3 in M. Only 2 dogs required 1 additional dose of propofol in M. This dose reduction is similar to other studies (Minghella et al 2016; Liao et al. 2017).

The end-point of allowing intubation was similar in both groups, therefore, the induction dose of propofol necessary for this purpose was deemed as equipotent in both groups. Liao et al. (2017) using a similar anesthetic protocol to this study, except for a higher IV fentanyl dose of 7 µg kg⁻¹ versus the dose used in this study (5 µg kg⁻¹, IV) required a mean propofol dose of 2.1 mg kg⁻¹ when midazolam was not included in healthy dogs, which is slightly higher (17%) than the mean dose of 1.9 mg kg⁻¹ used in critically ill patients in this study. Interestingly, the difference in the mean propofol dose with midazolam co-induction was similar in both studies (18%) (1.5 mg kg⁻¹ and 1.1 mg kg⁻¹), except that the critically ill dogs in this study required a lower dose than the healthy dogs in Liao et al. (2017).
There are several advantages to a smooth induction process allowing for endotracheal intubation, especially in sick patients. A longer duration of the anesthetic induction period without an airway may be detrimental in certain cases, for example brachycephalic patients and emergency cases where there is an increase in risk of regurgitation (Fayyaz et al. 2009). In the current study, most dogs had a presenting complaint of vomiting from their primary gastrointestinal illness, but none had respiratory difficulty. The main aim of a smooth co-induction with midazolam in our case population was to allow for an induction dose reduction to minimize decreases in cardiopulmonary function in patients that already have a compromised cardiovascular system despite pre-operative stabilization. However, we did not find statistically significant differences in cardiopulmonary function between the groups P or M. In fact, the M group was found to have the lowest SAP at T3, despite lower FE′Iso compared to P, although there were no overall treatment differences ($p = 0.06$). Perhaps the decrease in SAP, despite the propofol dose reduction, is related to a decrease in sympathetic stimulation and catecholamine release from a smoother induction process, despite the lower requirements of FE′Iso. This could be beneficial to avoid increases in overall oxygen demand, heart rate, and contractility, which could further compromise myocardial and tissue oxygenation in compromised patients (Clutton 2007). The real benefit of this dose reduction of propofol in healthy animals may merely be cost. It may seem clinically inconvenient spending extra time with two injections, but promoting a smooth endotracheal intubation is advantageous irrespective of patient’s condition (Liao et al. 2017).

The actions of benzodiazepines are due to potentiation of the neural inhibition that is mediated by the gamma-aminobutyric acid (GABAA) receptor. Practically all effects of this group of drugs result from the allosteric modulation of the ionotropic GABAA receptor (Olkkola et al. 2008). *In vitro* research shows that benzodiazepines potentiate both GABA and a variety of
GABA\textsubscript{A} receptor allosteric agonists by inhibiting transitions from the open state to the longest-duration closed states (Li et al. 2013). Liao, 2016 was able to demonstrate a reduction in the TIVA requirements with midazolam co-induction. This is similar to the higher level of isoflurane required in propofol alone in this group to maintain an acceptable anesthetic plane for positioning the dogs in dorsal recumbency and preparing the dogs for a laparotomy, although cardiopulmonary differences were not evident. Midazolam exhibits dose-dependent isoflurane and enflurane MAC reduction in dogs with a maximum effect to approximately 30\% and 60-70 \% respectively (Hall et al. 1988; Seddighi et al. 2011) and likely contributed to the reduction in inhalant concentrations in M group.

Midazolam reduces blood pressure in sedative and induction doses, both in human volunteers and critically ill patients (ASA III) (Lebowitz et al. 1982; Lebowitz et al. 1983; Sunzel et al. 1988). These changes are associated with a decrease in systemic vascular resistance, vasodilatation, a decrease in myocardial contractility, depression of baroreflex function and a decrease in sympathetic tone (Reves et al. 1985; Marty et al. 1986). In dogs, clinical doses of midazolam range between 0.1 to 0.5 mg kg\(^{-1}\), administered by IV or IM routes (Plumb 2011). The cardiovascular effects of midazolam also include decreases in blood pressure, vascular resistance, and myocardial contractility, at doses between 0.25, 1.0 and 10 mg kg\(^{-1}\). The magnitude of these changes is usually between 10 to 20\%, and considered minimal (Jones et al. 1979). Furthermore, because there is an increased in HR by 10 to 20 \% and no change in stroke volume, CO can increase by 10 to 12 \% following midazolam administration (Jones et al. 1979).

Propofol also decreases MAP due to a drop in systemic vascular resistance, cardiac contractility, and preload (Robinson et al. 1997; Pagel et al. 1998). Liao (2016) found that the co-induction with midazolam and propofol resulted in similar cardiopulmonary effects, including
direct MAP, CI, fR, prevalence of apnea, PE’CO₂ and blood gas values, to propofol alone in healthy dogs. In the present study, with critical dogs the same findings were obtained, indicating that the interaction of propofol and midazolam may result in additive effects that compare to those of propofol alone. There was no difference in the need for dopamine to support blood pressure in either group despite these results.

Several studies involving healthy dogs also showed that indirect SAP measurements were lower, but clinically acceptable, and HR was similar when midazolam co-induction with propofol was compared to propofol alone, in dogs undergoing elective surgeries (Hopkins et al. 2013). Similarly, no differences in indirect MAP, HR, fR and PE’CO₂ were detected between dogs undergoing elective surgeries and administered lidocaine and propofol, midazolam and propofol, or propofol alone (Minghella et al. 2016). These findings are similar to those in elderly humans, where remifentanil premedication and co-induction of midazolam with propofol resulted in a decrease in indirect arterial blood pressure (You et al. 2019).

Cardiac index was similar throughout anesthesia with respect to T1, despite changes in blood pressure and vascular resistance. It is likely that the increase in HR is responsible for this and a likely explanation is the stimulatory effect of endotracheal intubation on HR (Xue et al. 2006).

The other main effects on the cardiopulmonary parameters following the induction with P or M at T1, T2, T3, and T4 are the effects of fentanyl’s sedation, maintenance with isoflurane, placing the animal in dorsal recumbency and the initiation of mechanical ventilation (T3). While changes noted cannot be solely placed on P or M treatments, this does mimic the clinical situation of private and referral practices anesthetizing these cases for exploratory laparotomies. Fentanyl sedation reduced HR from initial values when dogs arrived in anesthesia as to be expected. It is
common to administer fentanyl as a bolus for sedation, MAC reduction, and pain control pre-operatively in compromised patients that are nauseous to provide a rapid onset and short duration of action (Ilkiw, 1999). When used alone, fentanyl is associated with moderate bradycardia that results from increased parasympathetic tone; however, other cardiorespiratory variables remain within reference limits (Grimm et al. 2005). Keating et al. (2013) reported that cardiopulmonary variables significantly changed after administration of fentanyl bolus of (5 µg kg\(^{-1}\), IV), with the exception of SAP and SVRI, which did not differ significantly from baseline values at any point. These authors observed a significant decrease in HR, CI, and oxygen delivery occurred within 5 minutes of fentanyl administration (Keating et al. 2013).

Prior to mechanical ventilation, f\(R\) decreased similarly in both groups after induction despite the dose reduction in M. This equated to an increase in PE′CO\(_2\) which as expected was offset at T3 and T4 by mechanical ventilation. No differences in PE′CO\(_2\), PaO\(_2\) or PaCO\(_2\) were noted within groups at T2, T3, or T4, hence the impact of ventilation on cardiovascular parameters was similar between groups. Placement of the dogs in dorsal recumbency and mechanical ventilation added to the decrease in arterial blood pressures, and SVRI, with increasing F\(E′\)Iso as expected (Michard 2005).

Both the ASA and SPI2 were assessed in this study. For both scores, the individual scores were similar in both the P and M groups. The ASA classification system assigns a score to the patient that needs to undergo anesthesia, based on preoperative health, which may indicate anesthesia risk and need for surgery. This scoring system has established itself as the most widely used patient risk assessment scheme in anesthesia; it represents a simple estimation of physiological status without the need for clinical resources and can be applied to every patient before operation (Wolters et al. 1996). In this study, dogs were classified as ASA status ≥ III, in
which morbidity and mortality associated with general anesthesia is significantly higher than in healthy dogs (Dyson et al. 1998; Brodbelt et al. 2008). Several studies have shown a significant higher risk (4.73 times) of anesthesia-related death in dogs, during anesthesia until up to 24 hours after the end of anesthesia, with ASA status ≥ III compared with ASA < III. (Portier & Kazue Ida 2018). In this study, all the patients were discharged from the Hospital.

The SPI2 has been validated in critical dogs. All parameters necessary to calculate this index were recorded in each patient and used for the calculation of risk (King et al. 2001). The predicted probability value obtained using SPI2 is within the range of 0 to 1, with 0 indicating the more severe disease with high risk of fatality and 1 a disease with a lower risk of fatality (King et al. 2001). In this study, the ASA and SPI2 scores were compared to detect if one of them could provide a better risk outcome for the dogs used, and they did not be correlate, which indicates that they may denote different outcomes for risk predictive value. The ASA score is easier to perform, although is more subjective and leads to high interobserver and maybe intraobserver variability; therefore experience and repeatability are important to avoid bias. The ASA status was not significantly different between groups. The SPI2 was also not different between treatment groups, despite the clinical differences in regards to type of required surgery. The values obtained for SPI2 of > 0.80 in both groups indicate that survival rate was high, despite their ASA classification. It is important, however, that the SPI2 allowed to establish that for this investigation, despite all possible confounding factors associated with the individual illnesses of the dogs, the two groups were homogenous for their comparisons.

This study hypothesized that in critically ill dogs, the benefits of a reduction in the propofol dose when using midazolam co-induction would include improved cardiopulmonary function. However, this was not the case, and cardiopulmonary function was similar in dogs receiving a
higher dose of propofol in the absence of midazolam co-induction to dogs receiving a lower dose of propofol with midazolam co-induction.

In conclusion, this study demonstrates that co-induction with midazolam improves endotracheal intubation and the induction phase. Despite a reduction in the induction dose of propofol, midazolam co-induction did not improve cardiopulmonary function in critically ill dogs, when compared to a higher dose of propofol alone. In addition, ASA and SPI2 scores were not correlated in this population of critically ill dogs.
2.6 REFERENCES


Hopkins A, Giuffrida M, Larenza MP. (2014) Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. Vet Anaesth Analg 41, 64-72.

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


### TABLE 2.1 Demographic distribution of patients enrolled in the study.

<table>
<thead>
<tr>
<th>Dog number</th>
<th>ASA status</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Sex/breed</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>6</td>
<td>22.2</td>
<td>MC/Wheaten terrier</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>2</td>
<td>IV</td>
<td>11.5</td>
<td>11.8</td>
<td>MC/Shetland Sheepdog</td>
<td>Hepatic mass</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>5</td>
<td>28.3</td>
<td>F/Australian Shepherd</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>13</td>
<td>36.3</td>
<td>MC/Labrador Retriever</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>5</td>
<td>IV</td>
<td>10</td>
<td>9</td>
<td>MC/Bichon Frisse</td>
<td>Gallbladder mucocele</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>2</td>
<td>47.5</td>
<td>FS/Mixed breed</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>7</td>
<td>III</td>
<td>13</td>
<td>23</td>
<td>MC/Nova Scotia Duck Tolling</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
<td>2.5</td>
<td>20.5</td>
<td>MC/Mixed breed</td>
<td>Foreign body/Splenectomy</td>
</tr>
<tr>
<td>9</td>
<td>IV</td>
<td>6</td>
<td>11.4</td>
<td>FS/Cocker Spaniel</td>
<td>Gallbladder mucocele</td>
</tr>
<tr>
<td>10</td>
<td>III</td>
<td>16</td>
<td>16.7</td>
<td>FS/Mixed breed</td>
<td>Gallbladder mucocele</td>
</tr>
<tr>
<td>11</td>
<td>III</td>
<td>2.5</td>
<td>10.8</td>
<td>MC/Mixed breed</td>
<td>Intussusception</td>
</tr>
<tr>
<td>12</td>
<td>IV</td>
<td>7</td>
<td>45.8</td>
<td>MC/Saint Bernard</td>
<td>Foreign body</td>
</tr>
<tr>
<td>13</td>
<td>III</td>
<td>5.5</td>
<td>20.4</td>
<td>M/Australian Cattle</td>
<td>Foreign body</td>
</tr>
<tr>
<td>14</td>
<td>IV</td>
<td>2</td>
<td>33.2</td>
<td>MC/Mixed breed</td>
<td>Nephrectomy</td>
</tr>
<tr>
<td>15</td>
<td>III</td>
<td>2</td>
<td>33.7</td>
<td>MC/Mixed breed</td>
<td>Foreign body</td>
</tr>
<tr>
<td>16</td>
<td>III</td>
<td>9.5</td>
<td>45.7</td>
<td>F/Mixed breed</td>
<td>Foreign body</td>
</tr>
<tr>
<td>17</td>
<td>III</td>
<td>5</td>
<td>21.6</td>
<td>MC/Springer Spaniel</td>
<td>Foreign body</td>
</tr>
<tr>
<td>18</td>
<td>IV</td>
<td>8.5</td>
<td>38.6</td>
<td>M/Golden Retriever</td>
<td>Foreign body/Splenectomy</td>
</tr>
<tr>
<td>19</td>
<td>III</td>
<td>8</td>
<td>33.3</td>
<td>FS/Golden Retriever</td>
<td>Foreign body</td>
</tr>
</tbody>
</table>

F- female; FS- female spayed; M- male; MC- male castrated
TABLE 2.2 Comparison of the two treatment groups, propofol and saline (P) and propofol and midazolam (M), after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation.

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>M</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(n = 9)</strong></td>
<td>(n = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>28.8 (12.5)</td>
<td>25.1 (12.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.1 (3.8)</td>
<td>6.2 (3.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Time from sedation to induction (min)</td>
<td>21 (19)</td>
<td>24 (16)</td>
<td>0.40</td>
</tr>
<tr>
<td>Time from induction to beginning of surgery (min)</td>
<td>108 (43)</td>
<td>87 (24)</td>
<td>0.24</td>
</tr>
<tr>
<td>ASA score</td>
<td>3.0 (0.2)</td>
<td>3.1 (0.2)</td>
<td>0.36</td>
</tr>
<tr>
<td>Dose of propofol (mg kg(^{-1}))</td>
<td>1.9 (0.5)*</td>
<td>1.1 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of top ups of propofol(^a)</td>
<td>3.4 (0.0,8.0)*</td>
<td>0.3 (0.0,2.0)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Sedation score(^a)</td>
<td>1.0 (0.6,1.4)</td>
<td>1.1 (0.8,1.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Intubation/Induction score(^a)</td>
<td>2.3 (1.0)*</td>
<td>0.2 (0.44)</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD. \(^a\) Value expressed as mean (95% Confidence Intervals). *

Significantly different from PM.
TABLE 2.3 Cardiovascular parameters after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction.

<table>
<thead>
<tr>
<th>AFTER SEDATION</th>
<th>INDUCTION/MAINTENANCE</th>
<th>p VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>80 (67,95)</td>
<td>89 (74,106)</td>
</tr>
<tr>
<td>M</td>
<td>78 (65,92)</td>
<td>89 (75,106)</td>
</tr>
<tr>
<td>Cardiac index (mL min(^{-1}) kg(^{-1}))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>115 (90,147)</td>
<td>130 (104,164)</td>
</tr>
<tr>
<td>M</td>
<td>97 (73,129)</td>
<td>111 (88,141)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>M</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>Mean arterial pressure</strong> (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>107</td>
<td>100</td>
</tr>
<tr>
<td>(95,121)</td>
<td>(87,115)</td>
<td>(87,115)</td>
</tr>
<tr>
<td><strong>Systolic arterial pressure</strong> (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>155</td>
<td>168</td>
</tr>
<tr>
<td>(137,173)</td>
<td>(146,190)</td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic arterial pressure</strong> (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>87</td>
<td>78</td>
</tr>
<tr>
<td>(77,98)</td>
<td>(67,90)</td>
<td>(77,98)</td>
</tr>
</tbody>
</table>
### Systemic vascular resistance

(PulseCO)  
(mmHg mL⁻¹ min⁻¹ kg⁻¹)

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>M</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(788,1166)</td>
<td>(953,1369)</td>
</tr>
<tr>
<td></td>
<td>(576,911)</td>
<td>(661,1007)</td>
</tr>
<tr>
<td></td>
<td>(548,908)</td>
<td>(593,954)</td>
</tr>
<tr>
<td></td>
<td>(537,896)</td>
<td>(430,842)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>977</td>
<td>1161</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>743</td>
<td>834</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>728</td>
<td>774</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>716</td>
<td>636</td>
</tr>
</tbody>
</table>

0.3152

### Systemic vascular resistance

(LiDCO)  
(mmHg mL⁻¹ min⁻¹ kg⁻¹)

<table>
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(729,1091)</td>
<td>(920,1355)</td>
</tr>
<tr>
<td></td>
<td>(534,859)</td>
<td>(642,983)</td>
</tr>
<tr>
<td></td>
<td>(560,922)</td>
<td>(637,999)</td>
</tr>
<tr>
<td></td>
<td>(548,910)</td>
<td>(503,936)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>910</td>
<td>1138</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>696</td>
<td>812</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>7418</td>
<td>818</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>729</td>
<td>720</td>
</tr>
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</table>

0.6337

### End-tidal isoflurane

(%)  

<table>
<thead>
<tr>
<th></th>
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<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0.52,0.90)</td>
<td>(0.59,1.00)</td>
</tr>
<tr>
<td></td>
<td>(1.09,1.52)</td>
<td>(0.76,1.19)</td>
</tr>
<tr>
<td></td>
<td>(1.04,1.48)</td>
<td>(0.95,1.47)</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>ND</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>ND</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>1.30</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>1.26</td>
<td>1.21</td>
</tr>
</tbody>
</table>

0.2135
Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups.
TABLE 2.4  Blood gas parameters after IV administration of fentanyl in 2 boluses of 2 µg kg^{-1} and 3 µg kg^{-1} separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg^{-1}) followed immediately by saline (P, 0.06 mL kg^{-1}) or midazolam (M; 0.3 mg kg^{-1}) to allow a smooth endotracheal intubation. T0 = prior to sedation and arterial catheterization with the dogs in lateral recumbency; T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction.

<table>
<thead>
<tr>
<th></th>
<th>AFTER SEDATION</th>
<th>INDUCTION/MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td><strong>Na⁺ (mmol L⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>150 (147,154)</td>
<td>152 (148,155)</td>
</tr>
<tr>
<td>M</td>
<td>148 (142,154)</td>
<td>145 (141,149)</td>
</tr>
<tr>
<td><strong>K⁺ (mmol L⁻¹)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>3.8 (3.5,4.2)</td>
<td>3.7 (3.2,4.1)</td>
</tr>
<tr>
<td>M</td>
<td>3.6 (3.3,3.9)</td>
<td>3.4 (3.0,3.9)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>M</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Cl(^{-}) (mmol L(^{-1}))</td>
<td>114 (109,118)</td>
<td>117 (113,120)</td>
</tr>
<tr>
<td>Hb (g dL(^{-1}))</td>
<td>13.6 (10.6,16.6)</td>
<td>12.6 (10.1,15.2)</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 (7.35,7.42)</td>
<td>7.36 (7.32,7.39)</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>M</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>PaCO₂</strong> (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>38 (31,44)</td>
<td>37 (30,43)</td>
</tr>
<tr>
<td>M</td>
<td>40 (35,46)</td>
<td>42 (35,50)</td>
</tr>
<tr>
<td><strong>PaO₂</strong> (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>69 (55,83)</td>
<td>72 (59,85)</td>
</tr>
<tr>
<td>M</td>
<td>253 (144,362)</td>
<td>249 (115,384)</td>
</tr>
<tr>
<td><strong>HCO₃⁻</strong> (mmol L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>21.3 (18.2,24.5)</td>
<td>22.2 (19.2,25.1)</td>
</tr>
<tr>
<td>M</td>
<td>23.2 (19.7,26.7)</td>
<td>23.7 (21.7,25.7)</td>
</tr>
<tr>
<td><strong>ABE</strong> (mmol L⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>−4.0 (−6.1,−1.9)</td>
<td>−3.2 (−4.5,−1.9)</td>
</tr>
<tr>
<td>M</td>
<td>−2.3 (−5.6,0.9)</td>
<td>−1.9 (−3.5,−0.3)</td>
</tr>
</tbody>
</table>
Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups.

<table>
<thead>
<tr>
<th>Lactate (mmol L(^{-1}))</th>
<th>P</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>(0.4,1.3)</td>
<td>(0.3,1.3)</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>(0.3,0.8)</td>
<td>(0.3,0.8)</td>
</tr>
</tbody>
</table>
**Table 2.5** Survival prediction index (SPI2), mean arterial pressure, lactate, packed cell volume and total protein of the two treatment groups, propofol and saline (P) and propofol and midazolam (M), after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P ( (n = 9) )</td>
<td>M ( (n = 10) )</td>
</tr>
<tr>
<td>SPI2</td>
<td>0.82 (0.76,0.88)</td>
<td>0.87 (0.81,0.93)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>120.1 (107.0,133.2)</td>
<td>111.8 (99.4,124.2)</td>
</tr>
<tr>
<td>Lactate (mmol L(^{-1}))</td>
<td>1.7 (1.1,2.4)</td>
<td>1.4 (0.8,2.0)</td>
</tr>
<tr>
<td>Packed cell volume (%)</td>
<td>42.0 (34.4,49.6)</td>
<td>44.7 (37.9,51.5)</td>
</tr>
<tr>
<td>Total protein (g dL(^{-1}))</td>
<td>7.2 (6.3,8.0)</td>
<td>6.7 (5.9,7.5)</td>
</tr>
</tbody>
</table>

Data expressed as mean (95% Confidence Intervals). No significant differences were detected between groups.
**Figure 2.1** Heart rate (HR) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg$^{-1}$ and 3 µg kg$^{-1}$ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg$^{-1}$) followed immediately by saline (P, 0.06 mL kg$^{-1}$) or midazolam (M; 0.3 mg kg$^{-1}$) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.2 Cardiac index measured by LiDCO (CIL) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg⁻¹ and 3 µg kg⁻¹ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg⁻¹) followed immediately by saline (P, 0.06 mL kg⁻¹) or midazolam (M; 0.3 mg kg⁻¹) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.3 Mean arterial blood pressure (MAP) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg⁻¹ and 3 µg kg⁻¹ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg⁻¹) followed immediately by saline (P, 0.06 mL kg⁻¹) or midazolam (M; 0.3 mg kg⁻¹) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.4 Systolic arterial blood pressure (SAP) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg⁻¹ and 3 µg kg⁻¹ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg⁻¹) followed immediately by saline (P, 0.06 mL kg⁻¹) or midazolam (M; 0.3 mg kg⁻¹) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time interval.
Figure 2.5 Diastolic arterial blood pressure (DAP) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg⁻¹ and 3 µg kg⁻¹ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg⁻¹) followed immediately by saline (P, 0.06 mL kg⁻¹) or midazolam (M; 0.3 mg kg⁻¹) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
**Figure 2.6** Systemic vascular resistance index measured by PulseCO (SVRIP) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P; 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.7 Systemic vascular resistance index measured by LiDCO (SVRIL) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg⁻¹ and 3 µg kg⁻¹ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg⁻¹) followed immediately by saline (P; 0.06 mL kg⁻¹) or midazolam (M; 0.3 mg kg⁻¹) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.8  Respiratory rate ($f_R$) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg$^{-1}$ and 3 µg kg$^{-1}$ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg$^{-1}$) followed immediately by saline (P, 0.06 mL kg$^{-1}$) or midazolam (M; 0.3 mg kg$^{-1}$) to allow a smooth endotracheal intubation. T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.9 End-tidal CO$_2$ (PE’CO$_2$) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg$^{-1}$ and 3 µg kg$^{-1}$ separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg$^{-1}$) followed immediately by saline (P, 0.06 mL kg$^{-1}$) or midazolam (M; 0.3 mg kg$^{-1}$) to allow a smooth endotracheal intubation. T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
Figure 2.10 End-tidal isoflurane concentration (FE\(^{\prime}\)Iso) in dogs after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation. T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction. Data expressed as mean (95% Confidence Intervals). No significant differences were detected within or between groups for the same time intervals.
**Appendix 2.1** Study timeline in dogs after IV administration of fentanyl in 2 boluses of 2 μg kg\(^{-1}\) (F1) and 3 μg kg\(^{-1}\) (F2) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (P, initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (S, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow a smooth endotracheal intubation. Measurement times are as follows: T0 = Transfer of patients to anesthesia from ICU before sedation with F1 (2 μg kg\(^{-1}\), IV); T1 = Prior to induction; T2 = Within 5 minutes post-induction on spontaneous ventilation and maintenance with isoflurane; T3 = Placed in dorsal recumbency and mechanically ventilated within 10 minutes from induction; T4 = During surgical preparation 20 minutes after induction.
Appendix 2.2 Simple descriptive quality score for sedation (SedQ) after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, prior to anesthetic induction in dogs.

<table>
<thead>
<tr>
<th>Sedation Quality Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>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.</td>
</tr>
<tr>
<td>1</td>
<td>Calm - minimal sedation, quiet but still alert and aware of surroundings, mild resistance to restraint in lateral recumbency, moderate response to noise or touch.</td>
</tr>
<tr>
<td>2</td>
<td>Mild to moderate sedation - quiet, relaxed, minimal restraint required in lateral recumbency, mild response to noise or touch.</td>
</tr>
<tr>
<td>3</td>
<td>Profound sedation - quiet, very relaxed, no restraint necessary in lateral recumbency, no response to noise or touch.</td>
</tr>
</tbody>
</table>

From Liao 2016.
**Appendix 2.3** Simple descriptive quality scale for induction and intubation (IndQ) after IV administration of fentanyl in 2 boluses of 2 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) separated by 5 min, followed by IV induction of anesthesia with propofol to effect (initial dose of 1 mg kg\(^{-1}\)) followed immediately by saline (P, 0.06 mL kg\(^{-1}\)) or midazolam (M; 0.3 mg kg\(^{-1}\)) to allow endotracheal intubation in dogs.

<table>
<thead>
<tr>
<th>Induction and Intubation Quality Score</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER III

GENERAL DISCUSSION AND FINAL CONCLUSION
3.1 GENERAL DISCUSSION

This research aimed at determining if midazolam co-induction would decrease the induction dose of propofol in critically ill (ASA III, IV) dogs, as it has been demonstrated in healthy dogs. In this study, critically ill dogs had a significant reduction (42%) in the dose of propofol, after premedication with fentanyl and co-induction with midazolam, that was also associated with a higher quality of induction/intubation, when compared to the group in which midazolam was not included. Despite these positive outcomes, the dose reduction obtained in the propofol midazolam group did not result in a benefit in terms of cardiopulmonary function compared with the propofol group.

The dose reduction in the induction dose of propofol obtained with midazolam co-induction in the present study is within the same range of studies completed with healthy (ASA I and II) research and client-owned dogs. However, there are differences between the study protocols of some of those studies and our study, since other premedication drugs were used, including acepromazine with methadone or morphine (Covey-Crump & Murison 2008; Hopkins et al. 2013; Sanchez et al. 2013; Robinson & Borer-Weir 2013; Minghella et al. 2016). One study used a similar protocol to ours in healthy research dogs, with a slightly higher dose of fentanyl (7 µg kg\(^{-1}\) versus 5 µg kg\(^{-1}\)) (Liao 2016). One hypothesis of this study was that due to the compromised health status of the dogs enrolled, the reduction in the dose of propofol obtained from the use of midazolam co-induction would benefit the patients in terms of a smoother induction but more importantly in terms of improved cardiopulmonary function immediately after induction and during maintenance of anesthesia. The latter has not been shown to be the case in healthy dogs (Hopkins et al. 2013; Minghella et al. 2016; Liao 2016) and also was disproven in this
study. It appears then that the interaction of midazolam and propofol results in similar cardiopulmonary effects to those of propofol alone.

The surgical risk of dogs in this study was assessed using the ASA and SPI2 scores, important tools used in different scenarios for predictive risk of morbidity/mortality. The ASA is used in anesthesia and the SPI2 is used in critical care units. The ASA score is easier to perform, because it does not necessarily require of blood parameters and physiological measurements used by the SPI2 score, anesthetists are more familiar with it, but it can be more subjective if the anesthetist lacks experience. In this study, both scores did not yield similar interpretations of predictive risk.

This project had several limitations. The power and the clinical nature of the study, could have affected the interpretation of the results. Dogs were presented with different conditions in their health status, and although classified as ASA III or IV, the degree of stabilization of the animals and severity of the specific condition could not be predicted to be similar for all of them. The sample size was based on an assumed dose of propofol required for induction, based on research in healthy dogs and then adjusted to the health status of the dogs used in this study. A mean (SD) induction dose of 2 (0.4) mg kg\(^{-1}\) was considered maximum and appropriate and that at least a 30% reduction could be attained with midazolam co-induction. For a type-I error (\(\alpha\)) of 0.05 and a desired power of 0.90, a sample size of 9 dogs per group was required. We used 9 dogs in the propofol group and 10 dogs in the propofol-midazolam group.
3.2 FINAL CONCLUSIONS

The following results were demonstrated in this investigation:

1. Midazolam co-induction reduces the induction dose of propofol by 42% in critically ill dogs (ASA III, IV), after premedication with fentanyl.
2. Midazolam co-induction combined with propofol results in a higher quality of induction than propofol alone, through synergistic effects.
3. Midazolam co-induction with propofol and induction with propofol alone in critically ill dogs (ASA III, IV), after premedication with fentanyl, result in similar cardiopulmonary effects through additive effects.
4. Predictive risk scores such as ASA status and SPI2 did not yield similar results.
4.3 REFERENCES


Hopkins A, Giuffrida M, Larenza MP (2014) Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. Vet Anaesth Analg 41, 64-72.


