INCIDENCE OF BRADYCARDIA, HYPOTENSION, AND BRADYCARDIA WITH HYPOTENSION AND THEIR RISK FACTORS IN DOGS UNDERGOING GENERAL ANESTHESIA

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For the most supportive and loving family in the whole world.

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ABSTRACT

Author: Lin, Hung-Chun (Avril), MS
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Title: Incidence of Bradycardia, Hypotension, and Bradycardia with Hypotension and Their Risk Factors in Dogs Undergoing General Anesthesia.
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Background: Bradycardia and hypotension are complications commonly occurring during general anesthesia in small animals. Intraoperative hypotension has been found to be associated with adverse postoperative consequences.

Objectives: The objectives of his study were first, to determine the incidence of bradycardia, hypotension, and bradycardia with hypotension in dogs undergoing general anesthesia, and second, to identify the risk factors associated with these three complications. The third objective was to evaluate the relationship between these three intraoperative complications and the recovery quality in these dogs.

Methods and Materials: A retrospective cohort study was performed using anesthetic records from 250 dogs undergoing general anesthesia between May 23, 2018 and October 1, 2018 at the Purdue University Veterinary Teaching Hospital. Intraoperative bradycardia was defined as heart rate < 60 beats/min for at least two consecutive readings at 5 minutes apart. Hypotension was defined as mean arterial pressure (MAP) < 60 mmHg or a systolic arterial pressure (SAP) < 80 mmHg for at least two consecutive readings. A univariate analysis followed by multiple logistic regression was performed to build the model for bradycardia, hypotension, and bradycardia with hypotension. The relationships between the three complications and the recovery quality were analyzed using the Pearson's chi-square test.

Results: The study found that out of the 250 dogs, 114 (45.6%) developed bradycardia, 113 (45.2%) developed hypotension, and 32 (12.8%) dogs developed bradycardia with hypotension. The use of dexmedetomidine-based tranquilizers/sedatives, longer duration of anesthesia, and subjection to orthopedic and neurologic surgical procedures were all identified as risk factors for the dogs to develop bradycardia. The use of acepromazine-based tranquilizers/sedatives, young and old age dogs, and dogs subjected to neurologic surgery were associated with the development of intraoperative hypotension. When the length of the anesthesia

increased, the chance for developing bradycardia with hypotension increased. There was no significant association between these intraoperative complications and the recovery quality.

Conclusions: We found a high incidence of bradycardia or hypotension while a much lower incidence of bradycardia with hypotension in the anesthetized dogs. The risk factors for bradycardia were the use of dexmedetomidine-based tranquilizers/sedatives, the longer duration of anesthesia, and the performance of orthopedic surgery and neurosurgery. The risk factors for hypotension included the use of acepromazine-based tranquilizers/sedatives, the older or younger age of dogs, and the performance of neurosurgery. The risk factor for bradycardia with hypotension was the longer duration of anesthesia. While these adverse events developed intraoperatively, we could not identify a direct influence of these complications on the recovery quality.

CHAPTER 1. INTRODUCTION

Intraoperative bradycardia and hypotension are common complications in anesthetized dogs. Previous studies have shown that the incidence of bradycardia in anesthetized dogs was 36.3% (Redondo et al., 2007), and the incidences of hypotension were 22% to 49% (Costa, Raisis, Hosgood, & Musk, 2015; Gordon & Wagner, 2006; Redondo et al., 2007). The development of intraoperative hypotension has been linked to postoperative neurological deficit in dogs (Rossmeisl, White, Pancotto, Bays, & Henao-Guerrero, 2013; Fenn et al., 2017), acute kidney injury in humans (Geist, 2011; Walsh et al., 2013; Sun, Wijeysundera, Tait, & Beattie, 2015), and mortality in both dogs and humans (Beck et al., 2006; Walsh et al., 2013; Monk et al., 2015; Itami et al., 2017).

In humans, ASA III-IV, older age, baseline arterial blood pressure < 70 mmHg, the use of angiotensin blockade, and type of surgery were identified as the risk factors for intraoperative hypotension (Reich et al., 2005; Cheung et al., 2015; Jor et al., 2018). However, very few studies have explored the risk factors associated with intraoperative bradycardia and/or hypotension (Costa, Raisis, Musk, & Hosgood, 2013; Costa et al., 2015) in dogs.

Intraoperative hypotension has attracted more attention because it may be linked to the high incidence of postoperative delirium in human patients (Edlund, Lundström, Bucht, Gustafson, & Brännström, 2001; Griebling, 2011; Patti, Saitta, Cusumano, Termine, Di Vita, 2011; Tognoni et al., 2011) Similar to postoperative delirium in humans, postoperative dysphoria in dogs, which is characterized by whining, paddling, and reduced awareness of surroundings, was reported to have 23.9% to 33% occurrence rates following orthopedic surgery (Becker et al., 2008; Becker et al., 2013). Although the mechanisms of both postoperative delirium and dysphoria are not yet well understood, it is very likely that the development of these symptoms is multifactorial (Ansaloni et al., 2010; Hirsch, DePalma, Tsai, Sands, & Leung, 2015).

A review of the current literature shows that very few reported risk factors for bradycardia, hypotension, and bradycardia with hypotension have been identified in dogs. Furthermore, the reported incidence rates for these three intraoperative complications varied significantly. The main objectives of the current study were first, to investigate the incidence of bradycardia, hypotension, and bradycardia with hypotension in anesthetized dogs, and second, to identify a set of risk factors for each of these three complications. The pool of candidate risk factors for these three

complications included patients' signalment, anesthetic protocols, types of procedure, duration of anesthesia, controlled ventilation, and hypothermia. Multivariable regression was used to select a set of significant predictors among candidate risk factors for each of the three intraoperative complications while taking into account the interrelationships among each other. The third objective was to examine whether these three complications were associated with the recovery quality of the dogs. For this objective, we hypothesized that patients having one of the three intraoperative complications were more likely to have dysphoria.

CHAPTER 2. LITERATURE REVIEW

Monitoring blood pressure during anesthesia is essential because organ perfusion depends on the blood pressure to deliver oxygenated blood and nutrition to meet the tissue metabolic demand. (Sivertsson, 1979; Thooft et al., 2011; Lighthall & Singh, 2014). Heart rate plays an important role in determining blood pressure. If heart rate decreases, the blood pressure is likely to be affected. A low heart rate, however, does not necessarily cause a low blood pressure since compensatory reaction such as increased myocardial contractility can modulate blood pressure without significant changes (Sivertsson, 1979; Copland, Haskins, & Patz, 1992).

On the other hand, if hypotension occurs, it warrants aggressive interventions because if the hypotension is left untreated, it likely leads to serious consequences. The literature review covers the various consequences associated with intraoperative hypotension both in humans and dogs. It also reviews the frequency of hypotension and bradycardia in small animal anesthesia as well as the potential causes and the risk factors associated with such intraoperative adverse events.

2.1 Effects of Intraoperative Hypotension on Postoperative Outcome

2.1.1 Neurological deficit

Under normal physiologic circumstances, autoregulation of the blood flow in the spinal cord remains constant regardless of the fluctuation in the systemic blood pressure (Martirosyan et al., 2011; Olby, 1999; Park, White, & Tieber, 2012). However, when acute spinal cord injury occurs, the hemodynamic stability of the spinal blood flow is disrupted by the extruded intervertebral disc materials or by the dislocated vertebrae. Following this primary damage, inflammation, hemorrhage, and production of free radical species occur, which results in secondary injury to the spinal cord (Olby, 2010; Park et al., 2012). Once the spinal cord autoregulation is lost, the spinal cord perfusion becomes mean arterial blood pressure (MAP) dependent. Consequently, the occurrence of systemic hypotension can further exacerbate ischemic injury of the spinal cord. A study conducted by Rossmeisl et al. (2013) investigated the perioperative adverse events that occurred in dogs undergoing ventral slot decompression for cervical intervertebral disease. The study shows that 12% (60/508) of the hypotensive dogs, which were identified as direct MAP ≤

60 mmHg or indirect systolic arterial blood pressure (SAP) ≤ 80 mmHg for more than 2 consecutive readings, were 23 times (OR 23.08, CI 10.81-49.25, $P < 0.0001$) more likely to develop perioperative adverse events than the normotensive dogs. The adverse events included persistent postoperative pain, intraoperative hemorrhage, and postoperative neurologic deterioration. In a retrospective study, 48 out of 84 (58%) dogs experienced hypotension, defined as MAP < 60 mmHg or SAP < 90mmHg, and 58 out of 84 (69%) dogs experienced bradycardia, defined as heart rate < 60 beats/min while undergoing hemilaminectomy for thoracolumbar intervertebral disk extrusion. The study revealed that the duration of bradycardia and hypotension was associated with a poor chance of regaining ambulatory function 6 weeks after surgery (Fenn et al., 2017). Based on this evidence in dogs, it is therefore important to manage intraoperative blood pressure. It has been suggested by human guidelines that the MAP should be maintained at 85-90 mmHg after acute cervical spine and spinal cord injuries (Walters et al., 2013).

2.1.2 Acute kidney injury

The definition of acute kidney injury (AKI) is an abrupt reduction in renal function, which is evaluated by the changes of serum creatinine concentration (50% relative or 0.3 mg/dl absolute increase in creatinine) before and after procedure and which usually occurs within 48 hours (Mugford, Li & Humm, 2013). The mechanism behind the development of postoperative AKI may be attributed to the ischemia-reperfusion injury resulting from the hypotension. With the impairment of oxygen delivery, the microvascular and tubular cells in the kidney are injured. This hypoxic response triggers inflammation and subsequently produces reactive oxygen species during the reperfusion phase, leading to diminished renal function (Malek & Nematbakhsh, 2015). Hypotension is considered a risk factor of AKI in dogs and cats (Mugford et al., 2013), and so maintaining a MAP above 70 mmHg is recommended for small animal patients with chronic kidney disease (Clark-Price & Grauer, 2015). In a case report, a 5-year-old castrated male Doberman pincher with unremarkable preanesthetic physical examination, complete blood count, serum chemistry profile, and echocardiographic examination underwent general anesthesia for dental prophylaxis. During the general anesthesia, the dog experienced hypotension with a systemic arterial pressure of 60 mmHg. In spite of fluid therapy to reverse hypotension, after the procedure, the serum creatinine increased from baseline 0.9 to 5.2 mg/dl. Azotemia and vomiting were also noted. AKI secondary to ischemia was therefore diagnosed (Geist, 2011). In human

anesthesia, a large cohort study was conducted in 27,381 patients without chronic kidney disease to determine the threshold and the duration of hypotension that was associated with postoperative AKI. The risk of developing AKI increased with a MAP of less than 60 mmHg regardless of the hypotensive duration. Patients with a MAP of less than 55 mmHg even with a short duration (1-5 minutes) were 1.18 times more likely to develop AKI compared with those who did not experience such hypotension. Furthermore, the odds of AKI increasing from 1.18 to 1.19, 1.32, and 1.51 when the duration spent with a MAP of less than 55 mmHg increased from 1-5 to 6-10,11-10, and >20 minutes, respectively (Walsh et al., 2013). Sun et al. (2015) evaluated the association between the length of intraoperative hypotension (three thresholds, MAP 55, 60, and 65 mmHg) and the postoperative AKI in 5,127 human patients, including those diagnosed with preoperative renal disease and with stricter AKI criteria. Patients exposed to 11-20 minutes of hypotension with a MAP of less than 60 mmHg had almost a 2-fold increase in AKI, while patients exposed to the same amount of time with a MAP of less than 55 mmHg had a 2.34-fold increase in AKI. Similarly, with the duration of hypotension increasing from 11 to 20 min, to >20 min, the odds ratio for patients to develop AKI increased from 2.34 (95% CI, 1.35-4.05) to 3.53 (95% CI, 1.51-8.25) when these patients exposed to an intraoperative MAP of less than 55 mmHg. These findings are consistent with the findings in Walsh's study, indicating a strong association between the development of AKI with the duration and magnitude of intraoperative hypotension in anesthetized human patients.

2.1.3 Mortality

The first large observational cohort study in small animal anesthesia looking at intraoperative hypotension as a potential risk factor of mortality was undertaken between 2010 and 2011 in several referral hospitals. A total of 4,342 dogs were enrolled in the study with hypotension defined as MAP < 60 mmHg. The results showed that hypotensive dogs were significantly related to higher mortality rates (OR, 3.45; 95% CI, 1.63-7.27; p<0.001) compared with normotensive dogs (Itami et al., 2017). The link between hypotension and death rate was also examined in critical canine patients. It has been shown that hypotension (SAP < 80 mmHg or MAP < 60 mmHg) at any time during the hospitalization period was one of the most significant factors associated with death in the 166 dogs undergoing surgery for gastric dilatation-volvulus (Beck et al., 2006). In humans, the effect of intraoperative hypotension on patient survival has been an important area of research.

In order to determine the threshold of intraoperative hypotension related to mortality within 30 days after surgery, records acquired from 6 hospitals and 3 methods were used to define hypotension, including the absolute blood pressure threshold, the threshold relative to baseline blood pressure, and the threshold calculated by the population mean and 2 standard deviation. No matter which method was adopted, intraoperative hypotension was found to be associated with 30-day mortality (Monk et al., 2015). Also, as the length of MAP < 55 mmHg time increased, the odds ratio of 30-day mortality increased as well (Walsh et al., 2013). A prospective observational study evaluating 1-year mortality after non-cardiac surgery found that with every minute of increase in spending at SAP < 80 mmHg, the risk of death at 1 year after surgery increased by 3.6% (95% CI, 0.6-6.6%) (Monk, Saini, Weldon, & Sigl, 2005). In the examination of the intraoperative hypotension associated with adverse outcomes, the hypotension threshold and the duration are of equal importance. With a MAP < 60 mmHg, 30 min of hypotension was associated with 1-year mortality; however, with a MAP < 50 mmHg, 5 min of hypotension was associated with 1-year mortality in elderly patients (Bijker et al., 2009). Although no causality effect can be concluded from this study due to the study design, all the studies seem to strongly support that a low blood pressure as a possible risk factor for postoperative mortality.

2.1.4 Delirium

In human patients, delirium is an acute circumstance of brain dysfunction with consciousness and cognition abnormality. According to the diagnostic criteria for delirium published in 2000 by the American Psychiatric Association, clinical signs of disturbance of consciousness include a decline in awareness of the environment and reduced capacity to focus. An impaired cognition can be detected by memory dysfunction, disorientation and reduced ability to speak. Other features, such as psychomotor abnormality and emotional disturbances which covers euphoria, dysphoria, and depression may also be noted but are not necessary for the diagnosis of delirium (Lipowski, 1987; Lipowski, 1990). Due to the high incidence, up to 53.3% in hip fracture patients (Bruce, Ritchie, Blizard, Lai, & Raven, 2007), and due to the severe subsequent outcomes, such as prolonged hospitalization and increased mortality (Monk et al., 2008; Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009), delirium has been found to be one of the most significant postoperative complications in human patients. Yet the pathophysiology is not well understood, and multiple factors have been identified for delirium, including older age,

female, longer duration of surgery, emergency surgery, and comorbidities (e.g. anemia, diabetes, cardiovascular diseases, anxiety disorders, and impaired preoperative cognition) (Ansaloni et al., 2010; Hirsch et al., 2015; Aldecoa et al., 2017). Although it remains a question as to whether intraoperative hypotension plays a role in the development of postoperative delirium, more and more studies found that blood pressure drops were associated with the development of postoperative delirium (Edlund et al., 2001; Gustafson et al, 1988; Patti et al., 2011; Tognoni et al., 2011). A recent prospective cohort study recruited 594 patients aged 65 years or older and receiving non-cardiac surgery to evaluate the relationship between intraoperative hypotension and postoperative delirium. Intraoperative hypotension was defined as either a reduction of 20% to 40% from baseline SAP or MAP, or a MAP lower than 50 mmHg. Although the frequency of postoperative delirium did not differ between patients with and without hypotension, patients exposed to a wider fluctuation in blood pressure were more likely to develop delirium after surgery (Hirsch et al., 2015).

In veterinary medicine, a rough recovery from anesthesia might result from delirium, dysphoria, or pain. However, it is difficult to differentiate these three from each other partially due to the definition of dysphoria, which is a general term for unpleasant feelings that sometimes occur with agitation (Starcevic, 2007) and also due to the similar clinical signs which include vocalization, restlessness, and reduced awareness of surroundings shared by both dysphoria and pain (Hofmeister, Herrington, & Mazzaferro, 2006). The prevalence of dysphoria, defined as receiving naloxone, acepromazine, or dexmedetomidine within 30 minutes of extubation was reported as ranging from 23.9% to 33% during recovery in dogs undergoing orthopedic surgery (Becker et al., 2008; Becker et al., 2013). It was found that the administration of opioid was associated with dysphoria (Zacny, Lichtor, Zaragoza, & Wit, 1992). Although this is similar to the development of delirium in human patients, the underlying mechanism of dysphoria is unclear. In this study, the author concluded that it is very likely that there were multiple risk factors for the development of dysphoria other than just the use of opioids.

2.2 Incidences of Bradycardia and Hypotension in Dogs

Intraoperative bradycardia and hypotension are two relatively common complications during general anesthesia in small animals. However, it can be challenging to compare such complication rates among different studies due to differences in the study definition of anesthetic

complications, study populations, monitoring methods, and study designs. A systemic literature search performed by Bijker et al. (2007) found that 140 definitions of intraoperative hypotension were used in 130 human anesthesia articles. Although a relatively consistent definition for hypotension was used, similar challenges as mentioned above are likely to be found in veterinary medicine articles.

In the following literature, hypotension was defined as MAP < 60 mmHg or SAP < 80 mmHg unless otherwise stated. In a retrospective study between 1998 and 2004 in two veterinary teaching hospitals, 453 out of 1247 (36.3%) dogs were bradycardic (HR < 50 beats/min), 362 out of 959 dogs (37.9%) were hypotensive, and 28 out of 959 (2.9%) dogs were bradycardic with hypotensive during general anesthesia (Redondo et al., 2007). A study investigating the frequency of anesthesia-related hypotension in healthy dogs and cats undergoing elective surgery in a private practice reported that hypotension, defined as SAP < 90 mmHg was recorded in 22% (13/59) of dogs (Gordon & Wagner, 2006). Itami et al. (2017) published a multicenter prospective study of anesthetic-related deaths and their risk factors between 2010 and 2011, and hypotension (MAP < 60 mmHg) was recorded in 25% (1,089/4,310) of the study dogs. The first study exploring risk factors for intraoperative hypotension in veterinary medicine was conducted between 2007 and 2011 in 188 healthy dogs undergoing elective desexing (Costa et al., 2013). In the study, 46% (87/188) of dogs were recorded as hypotensive. The same research team performed another study in 71 healthy dogs to identify predictors for hypotension, and they found that hypotension (MAP < 60 mmHg) was identified in 49% (35/71) of dogs under general anesthesia with their blood pressure measured by a direct arterial method (Costa et al., 2015). Morbidity was also reported in dogs with or without cardiac disease who received dental procedures. In both cardiac and non-cardiac disease groups, about 49% of dogs were hypotensive and 35% of dogs were bradycardic (HR < 60 beats/min) in cardiac disease group while 36% of dogs were affected by bradycardia in the non-cardiac disease group (Carter et al., 2017). Collectively, the frequency of hypotension ranged between 22% to 49%, while the frequency of bradycardia ranged between 35% to 36.3% among the veterinary studies reviewed.

2.3 Potential Causes of Bradycardia in Dogs

Heart rate is one of the important components of cardiac output. When severe reduction in heart rate occurs, it may diminish cardiac output and subsequent arterial blood pressure (Watterson,

Morris, Westhorpe, and Williamson, 2005). The potential causes of bradycardia can be divided into three categories: patient-related, anesthesia-related, and surgery-related causes.

Patient-related causes

Patient-related causes are associated with a patient's characteristics, comorbidities, and medication use. Regarding dogs' characteristics, brachycephalic breeds, for instance, have been known to have higher vagal tone than non-brachycephalic breeds and so they may be more prone to having sinus bradycardia (Doxey and Boswood, 2004). The Dachshund is another breed that was reported to have a lower mean heart rate (75 ± 21 beats/min) than the heart rate (84 ± 21 beats/min) in other breeds of dog of comparable size under general anesthesia, yet the etiology of this finding is still unclear (Harrison, Clark, & Corletto, 2012). The common comorbidities that may cause bradycardia include sick sinus syndrome (Kavanagh, 2002), hypothyroidism (Mooney, 2011), brain diseases accompanied with increased intracranial pressure (Agrawal, Timothy, Cincu, Agarwal, & Waghmare, 2008; Meyer & Winter, 1970), and any causes of severe hyperkalemia (Tag and Day, 2008). Less commonly, bradycardia may be induced by hypoglycemia, although the pathophysiology has not been clarified (Little, 2005; Idowu & Heading, 2018). Medication that is used mainly for treatment of cardiac diseases, such as beta-adrenergic blockers and calcium channel blockers, is also associated with bradycardia. Beta-adrenergic blockers reduce heart rate via reducing automaticity in the sinoatrial (SA) node and prolonging the conduction time in the atrioventricular (AV) node (Frishman and Saunder, 2011; Murrell, 2015). Calcium channel blockers reduce heart rate via inhibiting the inflow of calcium into the SA and AV cells, thus slowing the pacemaker activity and conduction through the AV node (Cooke and Snyder, 1998).

Anesthesia-related causes

Anesthesia-related causes include drug administration and intraoperative complications. Anesthetic drugs play an important role in contributing to the occurrence of bradycardia. Opioids and alpha-2 adrenergic receptor agonists are commonly used as premedication as well as intraoperative pain management in dogs. Bradycardia is induced by opioids and alpha2 receptor agonists through enhanced vagal tone (KuKanich & Wiese, 2015) and through a combination of baroreceptor reflex in response to high systemic blood pressure and a reduction in sympathetic activity in the central nervous system, respectively (Morais & Muir, 1995; Murrell & Hellebrekers, 2005). Epidural anesthesia may block the sympathetic nerves that modulate cardiac function when the local anesthetics spread to the spinal cord of T1 to T4, possibly causing bradycardia and other

hemodynamic instability (Steagall, Simon, Teixeira Neto, & Luna, 2017). In addition, local anesthetic toxicity has a dose-dependent effect on depressing the heart and can result in a decrease in heart rate, contractility, and blood pressure (Neal et al., 2010). With regard to intraoperative complications, hypothermia is a common complication that has a high incidence of 53.2% to 83.6% in dogs under general anesthesia (Redondo et al., 2007; Redondo et al., 2012). Depending on the severity of hypothermia, bradycardia may occur via reduced responsiveness to catecholamine and reduced baroreceptor function (Armstrong, Roberts, & Aronsohn, 2005; Clark-Price, 2015). Systemic hypertension with an incidence of 3.6% in dogs undergoing anesthesia (Redondo et al., 2007) may activate the baroreceptors located in the carotid sinus and aortic arch, and lead to a compensatory decrease in heart rate to return the arterial pressure to normal level (Warltier, Campagna, & Carter, 2003). Other intraoperative complications including severe hypovolemia, hypoxia, and hypercapnia can also cause bradycardia (Muir, 2015; Warltier et al., 2003; Kinsella & Tuckey, 2001). In contrast to the response of increasing heart rate and blood pressure during moderate hypovolemia, a profound hypovolemia may induce a paradoxical activation of the Bezold-Jarish reflex and thus results in hypotension and bradycardia (Warltier et al., 2003; Kinsella & Tuckey, 2001). Under normal condition, awake animals usually respond to hypoxemia or hypercapnia by showing tachycardia. However, this compensatory reaction may be greatly diminished under deep anesthesia, and bradycardia can emerge when an increase in ventilation is prevented (Marshall, 1998).

Surgery-related causes

Surgical manipulation in abdominal, ophthalmic, facial, and cervical areas, as well as irritation of the larynx or trachea by the endotracheal tube have been reported to trigger vagally-mediated bradycardia (Chowdhury et al., 2015; Doyle and Mark, 1990; Muir, 2015; Reiter & Castejon-Gonzalez, 2018). Several terms are given to describe reflex bradycardia originating from a particular area including abdominocardiac reflex, craniocardiac reflex, oculocardiac reflex, and vagovagal reflex (Muir, 2015). Although the afferent pathway of these reflex arcs may be different, the efferent pathway is formed by the vagus nerve that innervates the SA and AV nodes (Brodal, 2010; Chowdhury et al., 2015; Doyle and Mark, 1990).

2.4 Potential Causes of Hypotension in Dogs

Although there are various causes of hypotension, they usually affect arterial blood pressure through certain regulatory mechanisms. Thus, understanding the physiological mechanisms of blood pressure regulation and the main cardiovascular factors that determine blood pressure is the key to understanding the development of hypotension.

2.4.1 Blood Pressure Regulation

The management of blood pressure is mainly through three important mechanisms: the autonomic nervous system, the hormonal mechanism, and the local control system. The autonomic nervous system, which consists of afferent input, central integration, and efferent output provides a rapid regulation of cardiovascular function (Brodal, 2010; McCorry, 2007). Once the baroreceptors located in the aortic arch and carotid sinus and chemoreceptors located in the aortic bodies and carotid bodies sense changes in blood pressure, volume, oxygen and carbon dioxide tension, respectively, the inputs are transmitted through afferent fibers and integrated into the medulla oblongata. The vasomotor center in the medulla oblongata controls the rate of sympathetic and parasympathetic output and hence modulates the heart rate and vascular tone by efferent fibers that innervate the heart and arterioles (Brodal, 2010; Shepherd & Vanhoutte, 1979). When hypotension is present, increased discharge of neurotransmitter norepinephrine from the activated sympathetic system in combination with reduced parasympathetic activity lead to vasoconstriction and an increase in cardiac contractility and heart rate in an attempt to increase the blood pressure. Conversely, a rise in blood pressure stretches the baroreceptors, resulting in inhibition of the sympathetic activity and activation of the parasympathetic activity (Simmons & Wohl, 2009; Muir, 2015).

The humoral mechanism also facilitates the regulation of blood pressure with a more sustained effect. Circulating hormones including epinephrine and norepinephrine, renin, and vasopressin are produced by the adrenal medulla, kidney, and hypothalamus, respectively (Simmons & Wohl, 2009). The Renin-angiotensin system (RAS) is activated when hypotension, vascular volume or sodium depletion, or increased sympathetic nerve firing occurs (Colson, Ryckwaert, & Coriat, 1999; Mirenda & Grissom, 1991). The end product of the activation of RAS, angiotensin II, helps to restore blood pressure and vascular volume via enhancing water

reabsorption and producing arteriolar constriction. The release of arginine vasopressin is triggered by changes in plasma osmolality and blood volume (Feher, 2017). In addition to returning plasma osmolality and blood volume to normal through adjustment in water conservation, vasopressin also exerts vasoconstriction in mesenteric vessels. Epinephrine and norepinephrine released from the adrenal medulla, which is part of the sympathetic nervous system can increase heart rate and cardiac contractility as well as induce vasoconstriction in splanchnic and cutaneous arterioles (Shepherd & Vanhoutte, 1979). Overall, the humoral mechanism provides a relatively long-term blood pressure modulation which compensates for the short-term effect brought about by the autonomic nervous system.

The capability of blood vessels to modulate blood flow in correspondence with the metabolic demand for oxygen in spite of the fluctuation in perfusion pressure is termed autoregulation (Lipowsky, 2005; Olsson, 1981). Aside from the neurogenic vassal tone, local vasodilatory and vasoconstrictory mediators assist in maintaining local blood flow as well. For instance, prostaglandins released from endothelium cells in response to decreased oxygen tension cause vascular smooth muscle relaxation (Messina, Sun, Koller, Wolin, & Kaley, 1992; Simmons & Wohl, 2009). Other substances that also produce the vasodilatory effect include nitric oxide (NO), bradykinin, prostacyclin, and histamine (Simmons & Wohl, 2009). Thromboxane A2, generated by platelets is not only an agonist for platelet aggregation but also a potent vasoconstrictor (Gryglewski, Dembínska-Kieć, & Korbut, 1978). Endothelins produced by vascular endothelium cells possess positive inotropic (contraction) and chronotropic (heart rate) properties (Watts, 2010). Collectively, the autonomic nervous system produces an immediate and generalized modulation in response to fluctuation in hemodynamic changes. Humoral mechanism and autoregulation assist in regulating the blood pressure in the long run and redistributing the blood flow to meet the metabolic need for oxygen, respectively.

2.4.2 Determinants of Blood Pressure

The elements determining blood pressure can be described in the important formula as mean arterial pressure being the function of cardiac output times systemic vascular resistance. Further, cardiac output is the product of stroke volume (the volume of blood ejected by the ventricle per contraction) and heart rate. Stroke volume is directly dependent on cardiac contractility (the intrinsic capability of the heart to produce force), preload (the stretch of

myocardial wall prior to contraction), and is reversely related to afterload (the force impeding ventricular ejection) (Cooper, 2014; Muir, 2015). Therefore, impairment in any of these elements may lead to the development of hypotension, and some causes of hypotension may involve more than one determinant of arterial blood pressure. Following is a categorical approach to recognizing the pathophysiology involved in the potential causes of hypotension.

Reduction in venous return

Venous return plays an essential role in preload and thereby factors decreasing venous return include absolute and relative hypovolemia resulting in decreased preload. Absolute hypovolemia refers to the loss of fluid from the vascular compartment such as hemorrhage, severe dehydration resulting from vomiting, diarrhea, or polyuria, and third space (interstitial) fluid shift (Cooper, 2014; Noel-Morgan & Muir, 2018; Taghavi & Askari, 2018). In contrast, relative hypovolemia means that the fluid that remains in the vascular compartment is normal or increased. However, the effective circulating blood volume decreases due to an increase in the capacity of the vascular space (Noel-Morgan & Muir, 2018). Vasodilation, especially venodilation, is the primary cause of relative hypovolemia since the venous system accounts for up to 70% of the total blood volume as well as the high compliance of splanchnic veins compared with arteries (Gelman, 2008). The occurrence of vasodilation could result from anesthetic drugs, metabolic or respiratory acidosis, sepsis, brain or spinal cord injury, and hypothermia (Cooper, 2014; Noel-Morgan & Muir, 2018). Almost all anesthetic drugs that are commonly used can produce the vasodilatory effect except ketamine, which was observed to decrease the vascular capacity in dogs with normovolemia or hypovolemia (Sohn et al., 1998) and alpha-2 agonist (Murrell & Hellebrekers, 2005). One of the hallmarks of sepsis is the dysregulation of the vasomotor tone. This can mainly be attributed to the over production of nitric oxide. As mentioned previously, NO is a powerful vasodilator and the generation of excessive NO resulting from the systemic inflammation in the face of infection becomes a contributor to vasodilatory shock (De Kock, Van Daele, & Poelaert, 2010; Fernandes & Assreuy, 2008). Since the distribution of alpha- 1 and 2 adrenergic receptors in the vasculature, and the particular abundance in the splanchnic vascular bed, the disruption of sympathetic outflow as a consequence of brain or spinal cord injury or epidural anesthesia can lead to systemic vasodilation (Cooper, 2014; Partida, Mironets, Hou, & Tom, 2016; Steagall, 2017; Valverde, 2008). It is important to remember that vasodilation not only diminishes venous return but also decreases systemic vascular resistance, which is another critical determinant of blood pressure.

Aside from the two types of hypovolemia, physical obstruction in large vessels may also impede venous return to the ventricles. Gastric dilatation-volvulus (GDV), for instance, decreases venous return through compressing the intraabdominal veins and the subsequent blood pooling in the splanchnic vascular bed (Sharp, 2014). Inappropriate positive pressure ventilation, tension pneumothorax, mesenteric volvulus, and pulmonary embolus can all impair venous return via similar mechanisms, thus falling under this category (Cooper, 2014; Kelley, 2005).

Reduction in cardiac function

Cardiac dysfunction can be further divided into systolic dysfunction, diastolic dysfunction, and impaired systolic efficiency. Dilated cardiomyopathy (DCM) is the second common cardiac disorder in dogs. It is characterized by reduced cardiac contractility and results in decreased stroke volume and cardiac output (Perkowski & Oyama, 2015). Medication, including beta-blockers, calcium channel blockers, and almost all the drugs used for anesthesia, such as inhalants, injectable hypnotic agents, opioids, alpha-2 agonists, acepromazine, and local anesthetics, have a negative inotropic effect (Noel-Morgan & Muir, 2018). Hypertrophic cardiomyopathy (HCM), in contrast to DCM, is rarely seen in dogs and is associated with diastolic dysfunction (Perkowski & Oyama, 2015; Ware, 2014a). The thickening of the left ventricular wall increases the stiffness of the left ventricle, which leads to difficulty of the ventricle in relaxing during diastole. As a result, the ventricular chamber volume (stroke volume) decreases, with subsequent diminished cardiac output (Ware, 2014a). Pericardial effusion implies an abnormal fluid accumulation in the pericardial space (Dunning, Monnet, Orton, & Salman, 1998; Shaw & Rush, 2007). When the accumulated fluid generates enough pressure on the heart to compromise the diastolic filling, this situation is termed cardiac tamponade, which again decreases the preload, stroke volume, and potential cardiac output (Shaw & Rush, 2007). Besides, any causes of excess tachycardia can decrease time for ventricular filling and thus have the same consequence of reduction in stroke volume as other cardiac disorders with diastolic dysfunction (Ware, 2014b). Severe mitral valve regurgitation is associated with impaired systolic efficiency since a large portion of ventricular volume flows backward into the atrium instead of flowing forward into the systemic circulation (Cooper, 2014). Subaortic stenosis and hypertrophic obstructive cardiomyopathy can keep the blood flow from entering into the aorta due to a narrowed outflow tract, resulting in a restricted stroke volume (O'Grady, Holmberg, Miller, & Cockshutt, 1989; Steinbacher & Dörfelt, 2013).

Last, as heart rate together with stroke volume determine cardiac output, severe bradycardia can cause hypotension (Ware, 2014b).

2.5 Risk Factors for Intraoperative Hypotension or Bradycardia Identified in Human Anesthesia

Given that intraoperative hypotension has been identified as a contributing factor to serious adverse events in many studies such as of postoperative acute kidney injury, myocardial injury, and death (Bijker et al., 2009; Monk et al., 2015; Sun et al., 2015; Walsh et al., 2013; Wesselink, Kappen, Torn, Slooter & van Klei, 2018), it is of great interest to build a model that predicts the occurrence of hypotension in human anesthesia. The HEART score represents five variables including preoperative Heart rate (< 60 beats/min) or Hypotension (SAP < 110 and DAP < 60 mmHg), Elderly age (> 65 years), preoperative use of Angiotensin blockade, Revised Cardiac Risk Index (which is a tool used to predict perioperative cardiac complications), and type of surgery (major surgery) was established to predict the higher frequency of intraoperative bradycardia or hypotension in 193 patients receiving elective surgery (Cheung et al., 2015).

Other risk factors identified to predict the occurrence of hypotension after induction but before the initiation of the surgery included age (>50 years), ASA status (III-IV), baseline MAP (< 70 mmHg), increased fentanyl dosage, use of propofol for induction (Reich et al., 2005), emergency surgery, lower preoperative systolic blood pressure (Südfeld et al., 2017), and presence of diabetes (Jor et al., 2018). The risk factors for the occurrence of intraoperative bradycardia (HR < 60 beats/min) included male gender, no atropine given as premedecation, performance of laparoscopic cholecsystectomy, and administration of vecuronium for intubation in 499 patients who underwent selective surgery (Yorozu, Iijima, Matsumoto, Yeo, & Takagi, 2007).

2.6 Risk Factors for Intraoperative Hypotension Identified in Dogs

To our knowledge, so far there have been two studies exploring the risk factors for intraoperative hypotension. The first study revealed that normotensive dogs were significantly older (mean age of 12 months) than hypotensive dogs (mean age of 6 months) and the use of acepromazine with methadone was associated with higher frequency of hypotension compared with the use of acepromazine with morphine in 188 healthy dogs which are undergoing anesthesia for elective neutering (Costa et al., 2013). The second study evaluated the relationship between

patients' signalment and hydration status, which was assessed by urine specific gravity (USG), packed cell volume (PCV), and total solids (TS) and intraoperative hypotension in healthy dogs receiving elective neutering and standardized anesthetic protocol. Their results showed that the higher USG was associated with hypotension (MAP < 60 mmHg). Therefore, they concluded that subclinical dehydration may result in low blood pressure during anesthesia (Costa et al., 2015). Currently, no study has identified the risk factors for intraoperative bradycardia.

CHAPTER 3. MATERIALS AND METHODS

3.1 Study Design

This was a retrospective cohort study carried out from a review of the electronic records of those dogs undergoing general anesthesia between May 23, 2018 and October 1, 2018 at the Purdue University Veterinary Teaching Hospital anesthesia section. Of all records reviewed, the following cases were excluded: 1) cases with incomplete or missing data on cardiorespiratory values or the recovery quality was not noted; 2) patients diagnosed with neurological diseases, especially with potential of increased intracranial pressure, thyroid disorders, adrenal gland disorders, cardiac diseases, or diseases with hemodynamic instability (e.g., gastric dilation and volvulus); 3) patients which were taking antihypertensive agents; and 4) surgical procedures that were directly involved in disturbance of cardiac rhythms (e.g., pacemaker placement).

3.2 Data Collection

Data extracted from the anesthetic records were patient identification, dog breed, sex, age in years, body weight, body condition score (BCS, with 1 being emaciated and 9 being extremely obese) (Laflamme, 1997), American Society of Anesthesiologists (ASA) classification for patient's health status (Table 1), co-existing diseases, disease diagnosed, types of procedures, and whether the procedure was emergency or not. In addition to, the total duration of inhalant anesthesia (which was defined as the beginning to the end of an inhalant anesthesia), spontaneous or control ventilation, baseline (prior to anesthetic induction) heart rate, respiratory rate, and body temperature was also recorded. The information obtained from the records is summarized in Table 2.

For data analysis, Dachshund and brachycephalic breeds (Koch, Arnold, Hubler, & Montavon, 2003; Packer, Hendricks, & Burn, 2012; Rowena, Anke, Michael & Charlotte, 2015) including Boston Terrier, Boxer, Pug, Bulldog, American Bulldog, English Bulldogs, French Bulldogs, Shih Tzu, Chihuahua, Shar-Pei, Lhasa Apso, Mastiff, American Staffordshire Terrier, Miniature Pinscher, and Yorkshire Terrier were separated from other breeds of dogs. Life stage was assigned by age and body size (Table 3) according to the previous published literature (Greer,

Canterberry & Murphy, 2007; Hosgood & Scholl, 1998). ASA status was subdivided into ASA status 1-2 and ASA status 3-5 two groups.

The types of procedures that the dogs received were classified into seven categories: neurosurgery (hemilaminectomy and imaging in combination with hemilaminectomy), abdominal surgery (abdominal exploratory, gastrotomy, gastropexy, abdominal exploratory, splenectomy, ovariohysterectomy, enterectomy, caesarean section, urethrostomy revision, and cystotomy), orthopedic surgery (fracture repair, tibial plateau leveling osteotomy, total hip replacement, total knee replacement, arthroscopy, pin removal, limb amputation, mandibulectomy and medial patella luxation correction), thoracic surgery (lung lobectomy, median sternotomy and thoracotomy and lung biopsy), ophthalmologic surgery (phacoemulsification, canthoplasty, third eyelid resection, parotid duct transposition, ectopic cilia removal, enucleation, intravitreal injection and Gundersen flap), minor surgery (mass removal, dental cleaning and extraction, wound debridement, castration, episioplasty and deep ear clean), and non-surgical procedure (diagnostic imaging procedures and radiation therapy). If a dog received two or more of different procedures, then the case was classified according to the type of the major procedure.

3.3 Anesthetic Regimen

For data analysis, drugs used for anesthesia were categorized as tranquilizers/sedatives, opioids, induction agents, intraoperative analgesics, and inhalants. Tranquilizers/sedatives included their use as a premedication as well as dexmedetomidine continuous rate infusion and/or bolus during procedure. Tranquilizers/sedatives were grouped into three categories: ‘dexmedetomidine-based,’ ‘acepromazine-based,’ and ‘other tranquilizers/sedatives’ The ‘dexmedetomidine-based’ group included dexmedetomidine alone and in association with acepromazine, midazolam or tiletamine-zolazepam. The ‘acepromazine-based’ group included acepromazine alone, and acepromazine in combination with midazolam. The ‘other tranquilizers/sedatives’ group included midazolam alone, alfaxalone along with midazolam, and no tranquilizers or sedatives at all. Opioids were classified based on the opioid receptors and were grouped into either ‘full mu-opioids’ or ‘non-full mu-opioids.’ Intravenous inductions agents were grouped into either ‘propofol’ or ‘other induction agents,’ which included alfaxalone, ketamine with midazolam, and etomidate with midazolam. Intraoperative analgesia was grouped into three categories: ‘opioid continuous rate infusion (CRI),’ ‘opioid intermittent bolus,’ and ‘none.’

Epidural injection was classified into three groups: epidural analgesia if morphine alone was given, epidural anesthesia if morphine and bupivacaine were given, and no epidural injection. The dogs were either maintained with isoflurane or sevoflurane.

3.4 Physiological Variables

The highest and lowest values in the heart rate, diastolic, mean, systolic arterial blood pressures, and the body temperature under general anesthesia were recorded. In addition, cases that had one of the three investigated anesthetic complications, bradycardia (heart rate [HR] < 60 beats/min), hypotension (mean arterial blood pressure [MAP] < 60 mmHg or systolic arterial blood pressure [SAP] < 80 mmHg), or bradycardia with hypotension (of the same mentioned criteria), which occurred at two consecutive times (recorded at 5-minute intervals) were identified for analysis. Hypothermia was defined as present when there was a body temperature [BT] < 37°C (98.6 °F). The cases with presence or absence of hypothermia were recorded.

When bradycardia, hypotension, or bradycardia with hypotension were identified in a case, the corresponding information including the duration of the complication and the time when the complication occurred during the procedure were also identified. The time when the bradycardia, hypotension, or bradycardia with hypotension occurred were further subdivided into early intraoperative phase (EIP) from the time the dog was maintained with the inhalant to the time the intended procedure began. The late intraoperative phase (LIP) was from the time the intended procedure started to the end of the inhalant anesthesia.

3.5 Recovery Quality

The quality of the recovery was categorized as ‘good,’ dysphoria,’ ‘pain,’ or ‘dysphoria and pain’ according to the note on the record as well as whether the dog received tranquilizers or sedatives, opioids, or a combination of both drugs within 30 minutes after extubation. These drugs’ information was used to differentiate dysphoria and pain situation during the early recovery period. For example, if a dog’s recovery was recorded as dysphoric, then it would fall into either the ‘dysphoria’ or ‘dysphoria and pain’ group depending on whether it received an opioid after extubation or not. If the record indicated that the dysphoric dog received an opioid after extubation, then it would belong to ‘dysphoria and pain’ group. Likewise, if the record indicated that the dog experienced pain (‘pain’ group) but also received a tranquilizer or sedative following extubation,

then this dog would belong to the 'dysphoria and pain' category. However, if the note indicated the characteristics, such as vocalization, which shared by both dysphoria and pain during the early recovery period, the categorization would be based on the drugs information. Dogs received opioids, tranquilizers or sedatives, or the combination of both would belong to 'pain,' 'dysphoria,' and 'pain and dysphoria,' respectively. A good recovery quality means that the record indicated the dog recovering smoothly or uneventfully without receiving a tranquilizer, sedative or an opioid after extubation.

3.6 Statistical Analysis

Statistical analysis was carried out using Stata Statistical Software (StataCorp. 2017. Version 15, College Station, TX: StataCorp LLC). Interval scale variables were tested for normality using the Shapiro-Wilk test. The mean (SD) was presented for the normally distributed variables, whereas the median (range) was for non-normally distributed variables and ordinal scale variables. Nominal scale variables were expressed as frequency and percentage. Incidence proportion and the corresponding 95% confidence interval (CI) were reported for bradycardia, hypotension, and bradycardia with hypotension in the study population. To identify the potential risk factors of bradycardia, hypotension, and bradycardia with hypotension, a two-step approach was taken. First, univariate analysis was performed to determine the association between individual risk factors and each of the three intraoperative complications. Specifically, Pearson's chi-square tests (or Fisher's exact tests, if any of the expected cell counts were < 5) and Student's t tests (or Kolmogorov-Smirnov tests, if Shapiro-Wilk test was significant or ordinal scale variables) were used to analyze the categorical and continuous variables, respectively. Second, variables with $P \leq 0.20$ in the univariate analysis were further investigated in the multiple logistic regression. The use of a liberal P was to reduce the chance of excluding any important risk factors in the multivariable analysis. A forward stepwise procedure with an entry criterion of $P < 0.05$ and existing criterion of $P > 0.1$ was used to select the significant predictors. Final model fit was evaluated by the Hosmer-Lemeshow goodness-of-fit test. Regression models were established for the three study outcomes separately.

Last, the association between the incidence of bradycardia, hypotension, and bradycardia with hypotension and recovery quality was assessed by Pearson's chi-square or Fisher's exact tests. The statistical significance was set at $P < 0.05$ unless otherwise stated.

Table 1 ASA physical status classification system

ASA physical status	Patient description
I	Normal healthy patient
II	Patient with mild systemic disease (e.g., obesity, mild dehydration and simple fracture)
III	Patient with severe systemic disease (e.g., compensated renal insufficiency, controlled diabetes mellitus and cesarean section)
IV	Patient with severe systemic disease that is a constant threat to life (e.g., gastric dilation and volvulus)
V	Moribund patient who is not expected to survive without intervention (e.g., massive trauma, intracranial bleed with mass effect, multiple organ/system dysfunction)

Table 2 Information obtained from the medical records of dogs undergoing general anesthesia

Patient signalment	Breeds, sex, age, BCS and weight
Preoperative evaluation	ASA status
	Disease diagnosed
	Co-existing diseases
	Baseline heart rate, respiratory rate, and body temperature
Procedure	Emergency or not
	Types of procedures
Anesthetic regimen	Tranquilizers/sedatives
	Opioids
	Induction agents
	Intraoperative analgesics
	Inhalants
	Epidural injection
Monitoring	Lowest and highest value in heart rate, diastolic, mean and systolic arterial blood pressure, and body temperature
	Spontaneous or control ventilation
	Total duration of inhalant anesthetic time
Intraoperative complications	Bradycardia (HR < 60 beats/min)
	Hypotension (MAP < 60 mmHg or SAP < 80 mmHg)
	Bradycardia with hypotension
	Hypothermia (BT < 37°C [98.6 °F])
	Duration and time of bradycardia, hypotension and bradycardia with hypotension
Recovery	Recovery quality
	Tranquilizers/sedatives or opioids given within 30 minutes after extubation

Table 3 Life Stage based on body size in the enrolled dogs

Weight (kg)/age (year)	Young	Middle-aged	Old
Small (≤10kg)	<7	7-12	>12
Median (>10 and ≤ 20kg)	<6	6-10	>10
Large (>20 and ≤ 45kg)	<5	5-9	>9
Giant (> 45kg)	<3	3-7	>7

CHAPTER 4. RESULTS

4.1 Patient Demographics

The medical records of a total of 832 dogs were reviewed at the PUVTH anesthesia section between May 23, 2018 and October 1, 2018, and 250 of these dogs, 138 (55.2%) females and 112 (44.8%) males, met the inclusion criteria and so were included in the study. The median (range) age of dogs was 5.1 (range 0.4-14.4) years, and the median weight (range) of dogs was 22.8 (range 1.4-113.0) kg. Among the study dogs, 142 dogs had ideal BCS (4-5/9), while 2 dogs were thin (BCS 3) and 105 dogs were overweight (BCS 6-9), and 1 dog did not have information about BCS. There was a total of 71 different breeds of dogs in this study, with the most common being Mixed (56, 22.4%), Labrador Retriever (15, 6.0%), German Shepherd (14, 5.6%), Dachshund (14, 5.6%), Golden Retriever (12, 4.8%), Great Dane (9, 3.6%), American Pit Bull Terrier (7, 2.8%), Goldendoodle (6, 2.4%), and Siberian Husky (5, 2.0%). Among the study dogs, 39 (15.6%) dogs were brachycephalic breeds (Koch, et al. 2003; Packer et al. 2012; Rowena et al. 2015), including Chihuahua (5), French Bulldog (4), Mastiff (4), Yorkshire Terrier (4), Boston Terrier (3), Boxer (3), American Bulldog (2), English Bulldog (2), Pug (3), Shar Pei (1), Lhasa Apso (3), Shih Tzu (3), American Staffordshire Terrie (1), and Miniature Pinscher (1).

Twenty-two dogs (8.8%) were classified as ASA I, 179 (71.6%) as ASA II, 45 (18%) as ASA III, and 4 (1.6%) as ASA IV. Fifteen (6.0%) procedures were considered as emergency while 235 (94.0%) were non-emergency. The types of procedures consisted of 27 (10.8%) neurosurgeries, 50 (20.0%) abdominal surgeries, 70 (28.0%) orthopedic surgeries, 3 (1.2%) thoracic surgeries, 13 (5.2%) ophthalmologic surgeries, 51 (20.4%) minor surgeries, and 36 (14.4%) non-surgical procedures (Fig 1). The median (range) duration of anesthesia time was 3.1 (0.25-6.7) hours. The median (range) baselines HR, RR, and BT were 112 (48-192) beats/min, 30 (12-120) times/min, and 101.7 (96.8-104.7) °F, respectively. Body temperature was not recorded in two dogs during the procedure. The distribution of the signalment of the study dogs is summarized in Table 4.

Table 4 Descriptive statistics of the signalment of study dogs (N=250)

Characteristics	
Age (yr), median (range)	5.1 (0.4-14.4)
Female, n (%)	138 (55.2)
Male, n (%)	112 (44.8)
Weight (kg), median (range)	22.8 (1.4-113.0)
BCS, n (%)	
1-2	0 (0.0)
3	2 (1.3)
4-5	142 (57.0)
6-9	105 (42.1)
Breeds (Top 10 breeds), n (%)	
Mixed breed dogs	56 (22.4)
Labrador Retrievers	15 (6.0)
German Shepherd	14 (5.6)
Dachshund	14 (5.6)
Golden Retriever	12 (4.8)
Great Dane	9 (3.6)
American Pit Bull Terrier	7 (2.8)
Goldendoodle	6 (2.4)
Siberian Husky	5 (2.0)
Brachycephalic breeds	39 (15.6)
ASA status, n (%)	
I	22 (8.8)
II	179 (71.6)
III	45 (18)
IV	4 (1.6)
V	0 (0.0)
Emergency, n (%)	15 (6)
Duration of anesthesia (hr), median (range)	3.1 (0.25-6.7)

Table 4 Continued

Baseline HR (beats/min), median (range)	112 (48-192)
Baseline RR (times/min), median (range)	30 (12-120)
Body temperature (°F), median (range)	101.7 (96.8-104.7)

4.2 Anesthetic Regimen

With regards to tranquilizers or sedatives, acepromazine was either used alone in 102 (40.8%) dogs or in combination with dexmedetomidine in 66 (26.4%) dogs, with midazolam in 6 (2.4%) dogs, with dexmedetomidine and midazolam in 3 (1.2%) dogs, and with dexmedetomidine and tiletamine-zolazepam in 2 (0.8%) dogs. Dexmedetomidine was either used alone in 40 (16.0%) dogs and in combination with midazolam in 1(0.4%) dog. Midazolam was used alone in 5 (2%) dogs, and in combination with alfaxalone in 1 (0.4%) dog. Twenty-four (9.6%) dogs did not receive any tranquilizers or sedatives. Several opioids were used as a premedication in this study including hydromorphone in 147 (58.8%) dogs, butorphanol in 38 (15.2%) dogs, methadone in 34 (13.6%) dogs, fentanyl in 21 (8.4%) dogs, buprenorphine in 3 (1.2%) dogs, and remifentanil in 1 (0.4%) dog. Six (2.4%) dogs did not receive any opioids as a premedication. Anesthesia was induced with propofol alone in 118 (47.2%) dogs and propofol in combination with midazolam in 104 (41.6%) dogs. Other anesthetic induction agents included ketamine and midazolam/diazepam in 13 (5.2%) dogs, alfaxalone alone in 8 (3.2%) dogs, alfaxalone in combination with midazolam in 2 (0.8%) dogs, tilelamine-zolazepam with butorphanol and dexmedetomidine combination in 1 (0.4%) dog, etomidate in combination with midazolam in 1 (0.4%) dog, and propofol in combination with ketamine and diazepam in 1 (0.4%) dog. Only 1 (0.4%) dog was induced with a face mask using isoflurane and 1 (0.4%) dog did not have information about induction agent dog. For maintenance of anesthesia, isoflurane was used in 234 (93.6%) dogs while sevoflurane was used in 16 (6.4%) dogs.

In terms of continuous rate infusion for intraoperative pain management, 56 (22.4%) dogs had fentanyl CRI (F-CRI) alone, 16 (6.4%) dogs had F-CRI with lidocaine, 14 (5.6%) dogs had F-CRI with dexmedetomidine, 4 (1.6%) dogs had F-CRI with lidocaine and ketamine, 1(0.4%) dog had F-CRI with ketamine, and 1 (0.4%) dog had F-CRI with lidocaine, ketamine and dexmedetomidine. Seven (2.8%) dogs had dexmedetomidine CRI alone. Three (1.2%) dogs had lidocaine CRI (L-CRI) alone, 1 (0.4%) dog had L-CRI with morphine and ketamine, 1 (0.4%) dog

had L-CRI with remifentanil, and 146 (58.4%) dogs did not receive any CRI infusion. Intermittent boluses of hydromorphone alone were used in 47 (18.8%) dogs. Hydromorphone boluses were used in combination with fentanyl in 4 (1.6%) dogs, and with dexmedetomidine in 1 (0.4%) dog. Intermittent boluses of fentanyl alone were used in 32 (12.8%) dogs and in combination with methadone in 1 (0.4%) dog. Butorphanol boluses were used alone in 10 (0.4%) dogs. Methadone boluses was used alone in 8 (3.2%) dogs, and in combination with ketamine in 1 (0.4%) dog. Boluses of Buprenorphine and remifentanil were both used in 1 (0.4%) dog, respectively. One-hundred and forty-four (57.6%) dogs did not receive intermittent boluses of opioids.

Regarding routes of opioid administration, 94 (37.6%) dogs received opioids CRI, 63 (25.2%) dogs received intermittent boluses only, while 93 (37.2%) dogs did not receive any opioids intraoperatively. Collectively, 213 (85.2%) dogs received opioid full mu-receptor agonist, while 37 (14.8%) dogs received other receptor agonists. The epidural analgesia was performed in 30 (12.0%) dogs, epidural analgesia and anesthesia was performed in 18 (7.2%) dogs. The details of the anesthetic protocol of the drugs are summarized in Table 5.

Table 5 Anesthetic protocols of the study dogs (N=250)

Variables	Category	Number (%)
Tranquilizers/sedatives	Acepromazine-based	108 (43.2)
	Dexmedetomidine-based	112 (44.8)
	Other tranquilizers/sedatives	30 (12)
Opioids	Full mu-opioids	213 (85.2)
	Non-full mu-opioids	37 (14.8)
Induction agents	Propofol	222 (88.8)
	Non-propofol	28 (11.2)
Inhalants	Isoflurane	234 (93.6)
	Sevoflurane	16 (6.4)
Intraoperative analgesics	Opioid CRI	94 (37.6)
	Opioid intermittent bolus alone	63 (25.2)
	None	93 (37.2)
Epidural injection	Epidural analgesia	30 (12.0)
	Epidural analgesia and anesthesia	18 (7.2)

Table 5 Continued

No epidural	202 (80.8)

4.3 Incidence of Intraoperative Complications

A total of 114 (45.6%, 95% CI 39.3%-52.0%) out of the 250 dogs experienced bradycardia, 113 (45.2%, 95% CI 38.9%-51.6%) dogs experienced hypotension, and 32 (12.8%, 95% CI 8.9%-17.6%) dogs experienced both bradycardia and hypotension. The median (range) durations of bradycardia, hypotension, and bradycardia with hypotension were 55 (5–250) minutes, 25 (5–115) minutes, and 10 (5–95) minutes, respectively. In 222 of 250 dogs, blood pressure was measured indirectly. In 220 of these dogs, blood pressured was monitored by the oscillometric method, while 2 of these dogs were monitored by oscillometric method in combination with Doppler ultrasonography. Direct arterial blood pressure monitoring was used in 3 dogs. The oscillometric method in combination with invasive blood pressure monitoring were used in 24 dogs, while in 1 dog, blood pressure was monitored by both the invasive method and Doppler ultrasonography.

Among all the complications, 19 (16.7%) episodes of bradycardia occurred in the early intraoperative phase (EIP), 28 (24.6%) episodes occurred in the late intraoperative phase (LIP), and 67 (58.7%) episodes occurred in both the EIP and the LIP. For hypotension, 48 (42.5%) episodes occurred in the EIP and in both the EIP and LIP, while 17 (15.0%) episodes of hypotension occurred in the LIP. Thirteen (40.6%) episodes of bradycardia with hypotension occurred in the EIP or LIP. The rest of the 6 episodes (18.8%) of bradycardia with hypotension occurred in both the EIP and LIP (Fig 2).

4.4 Risk Factors of Intraoperative Complications

Using the univariate analyses, the following variables were identified to be included in the multivariable analysis for assessing the risk factors of bradycardia: age (p=0.075), body weight (p=0.018), duration of anesthesia (p=0.0001), tranquilizer/sedative (p<0.001), full mu-opioid (p=0.036), inhalant (p=0.036), intraoperative analgesic (p=0.197), epidural injection (p=0.029), controlled ventilation (p=0.002), abdominal surgery (p=0.005), orthopedic surgery (p<0.001), ophthalmologic surgery (p=0.007), and neurosurgery (p<0.001). The following factors were excluded from the multivariable analysis for assessing the risk factors of bradycardia: breed

(p=0.250), ASA status (p=0.453), emergency (p=0.653), induction agent (p=0.62), thoracic surgery (p=1.000), non-surgical procedure (p=0.382), and hypothermia (p=0.472).

Similarly, the following variables were identified to be included in the multivariable analysis for assessing the risk factors of hypotension: breed (p=0.007), age (p=0.093), ASA status (p=0.061), body weight (p=0.002), duration of anesthesia (p=0.124), emergency (p=0.085), tranquilizer/sedative (p<0.001), induction agent (p=0.141), intraoperative analgesic (p=0.044), minor surgery (p=0.111), neurosurgery (p=0.001), and hypothermia (p=0.039). The following variables were excluded from hypotension: inhalant (p=0.904), full mu-opioid (p=0.537), epidural injection (p=0.256), abdominal surgery (p=0.253), orthopedic surgery (p=0.856), thoracic surgery (p=1.000), ophthalmologic surgery (p=0.520), non-surgical procedure (p=0.792), and controlled ventilation (p=0.697).

Variables included in the multivariable analysis for bradycardia with hypotension were duration of anesthesia (p=0.0004), emergency (p=0.109), neurosurgery (p=0.001), orthopedic surgery (p=0.2), abdominal surgery (p=0.035), minor surgery (p=0.156), hypothermia (p=0.173), and controlled ventilation (p=0.081). Variables excluded from multivariable analysis for bradycardia with hypotension were breed (p=0.5), age (p=0.256), body weight (p=0.548), ASA status (p=0.410), tranquilizer/sedative (p=0.8), induction agent (p=0.55), inhalant (p=0.702), intraoperative analgesic (p=0.258), full mu-opioid (p=0.695), epidural injection (p=0.823), thoracic surgery (p=0.338), ophthalmologic surgery (p=0.384), and non-surgical procedure (p=0.790). Table 6 summarizes the results of the univariate analyses of individual variable against each of the three anesthesia complications.

Factors identified as significant predictors for bradycardia in the multivariable analysis were tranquilizers/sedatives, duration of anesthesia, orthopedic surgery, and neurosurgery (Table 7). In the model, dogs receiving dexmedetomidine-based tranquilizers/sedatives were approximately 6 times more likely to experience bradycardia compared with dogs receiving acepromazine-based tranquilizers/sedatives. For every hour increase in the duration of anesthesia, the odds of bradycardia increased by 1.37 times. Dogs undergoing orthopedic surgery were 2.31 times more likely to have bradycardia compared with dogs undergoing non-orthopedic surgery, while dogs undergoing neurosurgery were 10.34 times more likely to develop hypotension compared with dogs undergoing non-neurosurgery.

Factors significantly associated with hypotension were tranquilizers/sedatives, age, and neurosurgery (Table 8). Based on the results in the model, dogs receiving dexmedetomidine-based tranquilizers/sedatives were 74% less likely to have hypotension compared with those receiving acepromazine-based tranquilizers/sedatives. The odds of hypotension in geriatric dogs, and in young-aged dogs increased approximately 2-fold and 1.22-fold compared with middle-aged dogs. Dogs receiving neurosurgery were 2.47 times more likely to be hypotensive compared with dogs receiving non-neurosurgery.

The only variable identified as significantly predicting bradycardia with hypotension was the duration of the anesthesia (OR, 1.73; 95% CI, 1.31-2.29; $P<0.001$). For every hour increase in the duration of anesthesia, the odds of developing bradycardia with hypotension increased by 1.73 times. The fit of models for the three complications was assessed by the Hosmer-Lemeshow goodness-of-fit statistic with $p=0.68$, $p=0.81$, and $p=0.46$ for the logistic regression model of bradycardia, hypotension, and bradycardia with hypotension, respectively. This suggests that these models did not departure significantly from the data distribution.

Table 6 Univariate analysis of the risk factors for intraoperative bradycardia, hypotension and bradycardia with hypotension. Statistical significant results ($P \leq 0.20$) are in bold. Data are presented as number (%) for categorical variables; median (range) for continuous variables.

Variable	Category	Bradycardia		P value	Hypotension		P value	Bradycardia with Hypotension		P value
		Present	Absent		Present	Absent		Present	Absent	
Breed				0.250			**0.007**			0.500
	Brachycephalic breeds	15(38.5)	24(61.5)		22(56.4)	17(43.6)		4(10.3)	35(89.7)	
	Dachshund	9(64.3)	5(35.7)		11(78.6)	3(21.4)		3(21.4)	11(78.6)	
	Others	90(45.7)	107(54.3)		80(40.6)	117(59.4)		25(12.7)	172(87.3)	
Age				**0.075**			**0.093**			0.256
	Young	70(51.5)	66(48.5)		70(51.5)	66(48.5)		22(16.2)	114(83.8)	
	Middle-aged	33(41.8)	46(58.2)		30(38.0)	49(62.0)		7(8.9)	72(91.1)	
	Old	11(31.4)	24(68.6)		13(37.1)	22(62.9)		3(8.6)	32(91.4)	
Body weight (kg)		26.9 (5-75.3)	17.0 (1.4-113)	**0.018**	15.2 (1.4-113)	27.0 (2.6-75.3)	**0.002**	19.8 (5.1-63.5)	22.8 (1.4-113)	0.548
ASA status				0.453			**0.061**			0.410
	1-2	94(46.8)	107(53.2)		85(42.3)	116(57.7)		24(11.9)	177(88.1)	
	3-4	20(40.8)	29(59.2)		28(57.1)	21(42.9)		8(16.3)	41(83.7)	
Emergency				0.653			**0.085**			**0.109**
	Yes	6(40.0)	9(60.0)		10(66.7)	5(33.3)		4(26.7)	11(73.3)	
	No	108(46.0)	127(54.0)		103(43.8)	132(56.2)		28(11.9)	207(88.1)	

Table 6. Continued

Duration of anesthesia (hr)		3.7 (0.8-6.6)	2.6 (0.3-6.7)	**0.0001**	3.3 (0.5-6.7)	3.0 (0.25-6.4)	**0.124**	4.4 (0.9-6.6)	3.0 (0.25-6.7)	**0.0004**
Tranquilizers/ sedatives				**<0.001**			**<0.001**			0.800
	Acepromazine -based	32(29.6)	76(70.4)		65(60.2)	43(39.8)		12(11.1)	96(88.9)	
	Dexmedetomidine -based	72(64.3)	40(35.7)		32(28.6)	80(71.4)		16(14.3)	96(85.7)	
	Others	10(33.3)	20(66.7)		16(53.3)	14(46.7)		4(13.3)	26(86.7)	
Induction agent				0.620			**0.141**			0.550
	Propofol	100(45.1)	122(54.9)		104(46.8)	118(53.2)		30(13.5)	192(86.5)	
	Non-propofol	14(50)	14(50)		9(32.1)	19(67.9)		2(7.1)	26(92.9)	
Inhalant				**0.036**			0.904			0.702
	Isoflurane	111(47.4)	123(52.6)		106(45.3)	128(54.7)		31(13.3)	203(86.7)	
	Sevoflurane	3(18.8)	13(81.2)		7(43.7)	9(56.3)		1(6.3)	15(93.7)	
Intra-op analgesics				**0.197**			**0.044**			0.258
	Opioid CRI	48(51.1)	46(48.9)		52(55.3)	42(44.7)		16(17.0)	78(83.0)	
	Opioid bolus	23(36.5)	40(63.5)		25(39.7)	38(60.3)		5(7.9)	58(92.1)	
	None	43(46.2)	50(53.8)		36(38.7)	57(61.3)		11(11.8)	82(88.2)	

Table 6. Continued

Full mu-opioids				**0.036**			0.537		0.695
	Yes	103(48.4)	110(51.6)		98(46.0)	115(54.0)		28(13.1)	185(86.9)	
	No	11(29.7)	26(70.3)		15(40.5)	22(59.5)		4(10.8)	33(89.2)	
Epidural injection				**0.016**			0.256		0.821
	Epidural analgesia	21(70.0)	9(30.0)		11(35.5)	19(64.5)		4(13.3)	26(86.7)	
	Epidural anesthesia and analgesia	7(38.9)	11(61.1)		11(61.1)	7(38.9)		3(16.7)	15(83.3)	
	No epidural injection	86(42.6)	116(57.4)		91(45.1)	111(54.9)		25(12.4)	177(87.6)	
Neurosurgery				**<0.001**			**0.001**		**0.001**
	Yes	22(81.5)	5(18.5)		20(74.1)	7(25.9)		9(33.3)	18(66.7)	
	No	92(41.3)	131(58.7)		93(41.7)	130(58.3)		23(10.3)	200(89.7)	
Abdominal surgery				**0.005**			0.253		**0.035**
	Yes	14(28.0)	36(72.0)		19(38.0)	31(62.0)		2(4.0)	48(96.0)	
	No	100(50.0)	100(50.0)		94(47.0)	106(53.0)		30(15.0)	170(85.0)	
Orthopedic surgery				**<0.001**			0.856		**0.200**
	Yes	46(65.7)	24(34.3)		31(44.3)	39(55.7)		12(17.1)	58(82.9)	
	No	68(37.8)	112(62.2)		82(45.6)	98(54.4)		20(11.1)	160(88.9)	

Table 6. Continued

Thoracic surgery				1.000			1.000		0.338
	Yes	1(33.3)	2(66.7)		1(33.3)	2(66.7)		1(33.3)	2(66.7)	
	No	113(45.7)	134(54.3)		112(45.3)	135(54.7)		31(12.5)	216(87.5)	
Ophthalmologic surgery				**0.004**			0.520		0.384
	Yes	1(7.7)	12(92.3)		7(53.8)	6(46.2)		0(0.0)	13(100.0)	
	No	113(47.7)	124(52.3)		106(44.7)	131(55.3)		32(13.5)	205(86.5)	
Minor surgery				**0.022**			**0.111**		**0.156**
	Yes	16(31.4)	35(68.6)		18(35.3)	33(64.7)		3(5.9)	48(94.1)	
	No	98(49.3)	101(50.7)		95(47.7)	104(52.3)		29(14.6)	170(85.4)	
Non-surgical procedure				0.382			0.792		0.790
	Yes	14(38.9)	22(61.1)		17(47.2)	19(52.8)		5(13.9)	31(86.1)	
	No	100(46.7)	114(53.3)		96(44.9)	118(55.1)		27(12.6)	187(87.4)	
Controlled ventilation				**0.002**			0.697		**0.081**
	Yes	74(54.4)	62(45.6)		63(46.3)	73(53.7)		22(16.2)	114(83.8)	
	No	40(35.1)	74(64.9)		50(43.9)	64(56.1)		10(8.8)	104(91.2)	
Hypothermia (°F)				0.472			**0.039**		**0.173**
	Yes	76(43.7)	98(56.3)		86(49.4)	88(50.6)		25(14.4)	149(85.6)	
	No	36(48.7)	38(51.3)		26(35.1)	48(64.9)		6(8.1)	68(91.9)	

4.5 Association between Intraoperative Complications and Recovery Quality

Of the 250 dogs' recovery quality, 23 (9.2%) of them were identified as 'pain,' 28 (11.2%) dogs were identified as 'dysphoria,' 38 (15.2%) dogs were identified as 'pain and dysphoria,' and the rest of the 161 (64.4%) dogs were identified as 'good'. There was no significant association between the incidence of the three complications and the recovery quality (p=0.643). Among the dogs that underwent non-invasive procedures, no dog (0.0%) was identified as 'pain', 6 (16.7%) dogs were identified as 'dysphoria', 1 (2.8%) dog was identified as 'pain and dysphoria', and the rest of the 29 (80.5%) were identified as 'good'. In contrast, among the dogs undergoing invasive procedures, 23 (10.7%) dogs were identified as 'Pain', 22 (10.3%) dogs were identified as 'dysphoria', 37 (17.3%) dogs were identified as 'pain and dysphoria', and the rest of the 132 (61.7%) were identified as 'good'. To minimize the possibility of mis-identification of the dogs that were in 'pain' as 'dysphoria' or vice versa, the association between the three complications and the recovery quality was further examined in the noninvasive procedure group, and there was no significant association between the intraoperative complications and the recovery quality (p=0.550).

Table 7 Significant risk factors of bradycardia identified in the multiple logistic regression model.

Variable	OR (95% CI)	P value
Tranquilizers/sedatives		
Acepromazine-based	1.00	Referent
Dexmedetomidine-based	6.05(3.14-11.68)	<0.001
Other tranquilizers/sedatives	0.96(0.33-2.79)	0.939
Anesthesia time (every 1 hr)	1.37(1.06-1.77)	0.018
Neurosurgery (vs non-neurosurgery)	10.34(3.06-34.90)	<0.001
Orthopedic surgery (vs non-orthopedic surgery)	2.31(1.08-4.92)	0.030

OR, odds ratio; CI, confidence of interval

Table 8 Significant risk factors of hypotension identified in the multiple logistic regression model.

Variable	OR (95% CI)	P value
Tranquilizers/sedatives		
Acepromazine-based	1.00	Referent
Dexmedetomidine-based	0.26(0.14-0.47)	<0.001
Other tranquilizers/sedatives	0.71(0.30-1.65)	0.422
Age		
Young	2.03(1.09-3.76)	0.025
Middle	1.00	Referent
Old	1.22(0.54-3.07)	0.562
Neurosurgery (vs non-neurosurgery)	2.47(0.95-6.44)	0.065

OR, odds ratio; CI, confidence of interval

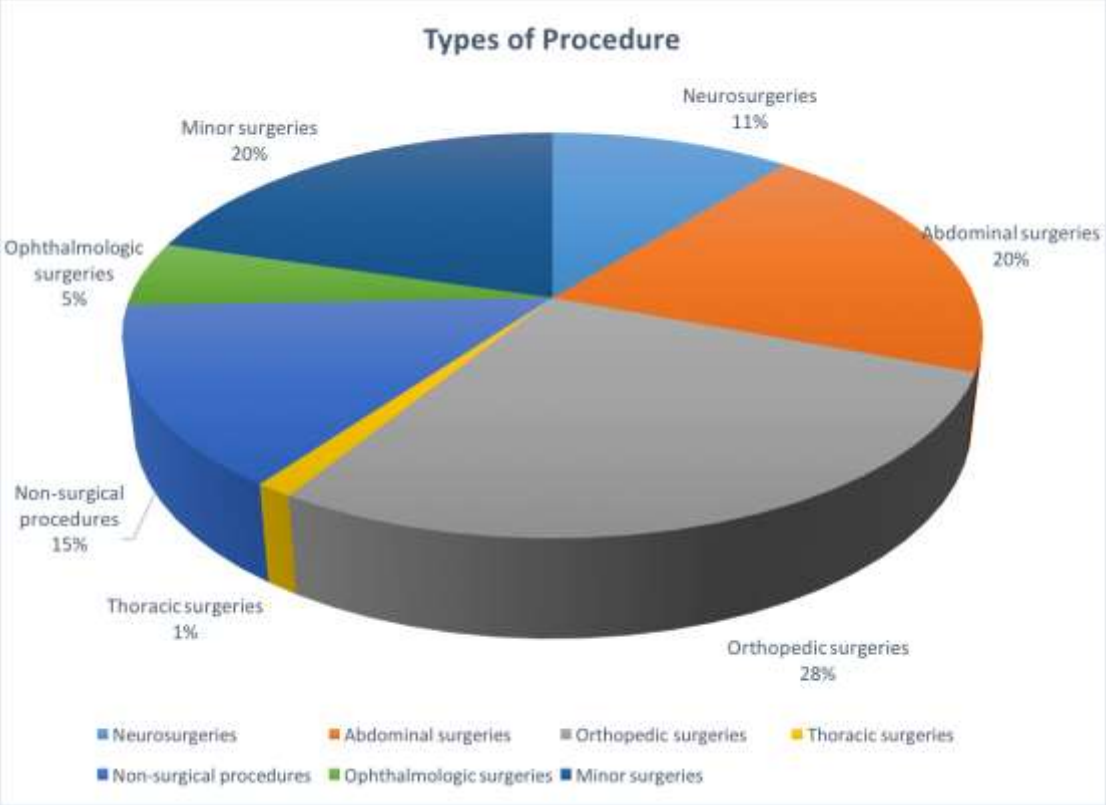

Figure 1 Distribution of types of procedure performed in 250 anesthetized dogs.

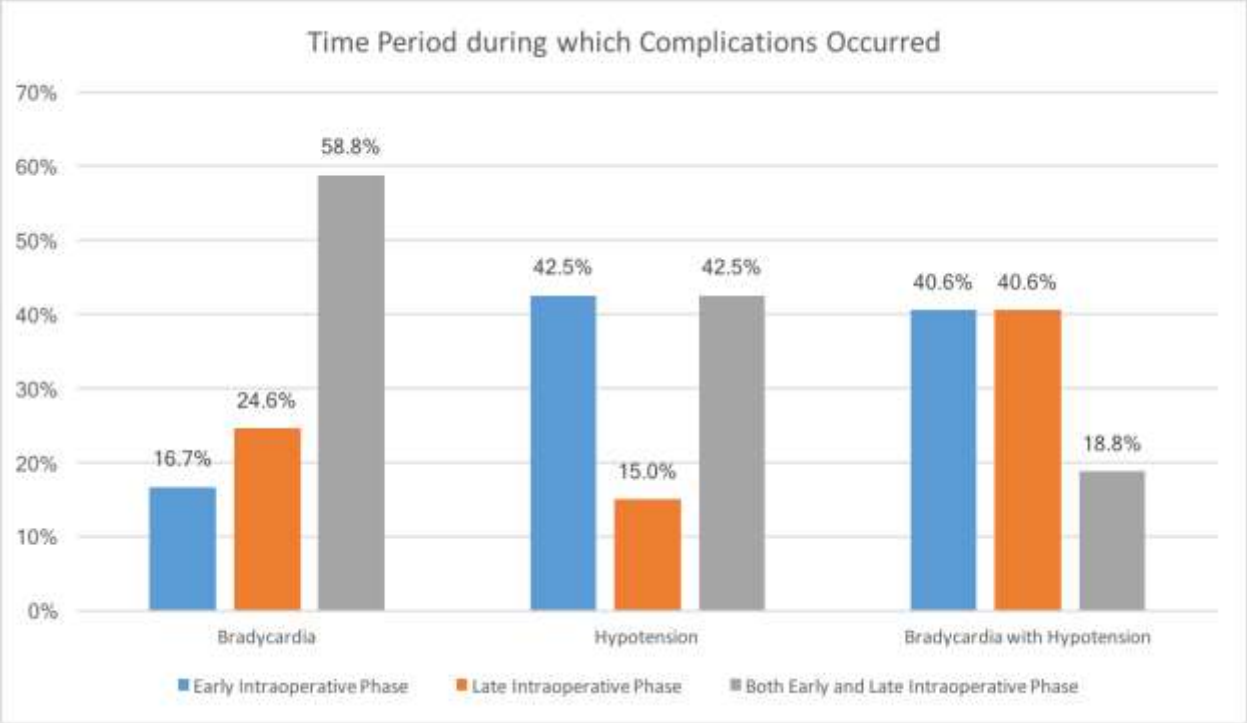

Figure 2 The intraoperative time window when each of the complication occurred in the 250 anesthetized dogs. The early intraoperative phase (blue column) was defined as the time from the beginning of inhalant anesthesia to the commencement of the procedure. The late intraoperative phase (the orange column) was defined as the beginning of the procedure to the end of inhalant anesthesia. The grey column represents the entire intraoperative time window.

CHAPTER 5. DISCUSSION

Intraoperative hypotension has been linked to adverse outcomes, such as neurological deficit, acute kidney injury, delirium, and death (Rossmeisl et al., 2013; Walsh et al., 2013; Edlund et al., 2001; Monk et al., 2015). Consequently, prevention of its occurrence has become an important area of interest in both human and veterinary medicine. Previously, Costa et al. (2013 and 2015) intended to explore the association between easily identifiable animal factors and perioperative MAP; however, only healthy dogs undergoing elective neutering were enrolled in the studies, which may have limited the extrapolation of the results. Our study not only investigated the incidence of intraoperative bradycardia, hypotension, and a combination of both in anesthetized dogs but also determined the risk factors for these three intraoperative complications in dogs with various health statuses, and which were receiving different types of procedures and anesthetic protocols. The purpose of identifying a set of risk factors for the three common complications from the pool of candidate factors, including dogs' signalment, anesthetic protocol, duration of anesthesia, controlled ventilation, intraoperative hypothermia, and different types of procedure, was to allow clinicians to target high risk dogs beforehand and if the risk factors were modifiable, the anesthetic protocol and intraoperative interventions could be adjusted accordingly.

We reviewed and analyzed 250 anesthetic records between May 23, 2018 and October 1, 2018 at the Purdue University Veterinary Teaching Hospital. The results revealed that 45.6% (95% CI 39.3%-52.0%) of these dogs had bradycardia episodes. This percentage, while not a surprise, is higher than that of a previous retrospective study (Redondo et al., 2007) which reported 36.3%. That study aimed to describe the range of cardiorespiratory variables and to determine the incidence of cardiorespiratory complications in dogs undergoing general anesthesia. In that study, a total of 453 out of 1247 dogs were found to have bradycardia (HR < 50 beats/min). Multiple anesthetic protocols were used in the study. Alpha-2 receptor agonist, acepromazine, and atropine were frequently used for premedication. Propofol and thiopental were the two main drugs used for induction. Halothane, isoflurane, sevoflurane, and desflurane were used for maintenance. Mu-receptor opioid agonists and other opioids were used for intraoperative analgesia. In addition, a variety of patient characteristics and procedures including minor surgery, trauma surgery, abdominal surgery, diagnostic techniques, thoracic surgery, and experimental anesthesia were

included. However, no further statistical analysis was performed to examine the effects of these variables on heart rate.

This discrepancy in the incidence of bradycardia could be due to the lower HR used for the bradycardia definition as well as the use of atropine in their study. In Redondo's study, 801 dogs received atropine as part of the premedication. It is well-documented that atropine induces higher heart rate via parasympathetic blockade (Alibhai, Clarke, Lee, & Thompson, 1996; Muir, 1978; Schweitzer & Mark, 1980). Thus, it is possible that the premedication of atropine prevented bradycardia and so lowered the incidence of bradycardia in their study. In contrast, the dogs in our study did not receive anticholinergics as part of the premedication.

The identified risk factors for bradycardia were 1) the use of dexmedetomidine-based tranquilizers/sedatives as part of the anesthetic protocol, 2) the performance of orthopedic or neurologic related surgical procedure, and 3) the increase in anesthesia duration. The dogs in the present study that received dexmedetomidine-based tranquilizers/sedatives were 6 times more likely to develop bradycardia when compared with the dogs that received acepromazine-based tranquilizers/sedatives. This finding was anticipated since dexmedetomidine, an alpha-2 adrenergic receptor agonist, is known to induce bradycardia in dogs (Bloor et al., 1992; Kuusela et al., 2001; Kuusela et al., 2003). However, prior or concurrent use of anticholinergics with alpha-2 receptor agonists to reverse bradycardia has not been recommended in several studies (Alibhai et al., 1996; Alvaides et al., 2008; Congdon, Marquez, Niyom, & Boscan, 2011; Sinclair, O'Grady, Kerr, & McDonell, 2003). Hypertension, tachycardia, and ventricular arrhythmias, such as premature ventricular complexes, are commonly reporded adverse events following the administration of alpha-2 agonists with anticholinergics (Alvaides et al., 2008; Congdon et al., 2011). The product of SAP and heart rate termed rate pressure product (RPP) is used as an estimate of myocardial oxygen demand in human medicine, and this value was found to be significantly higher in dogs receiving dexmedetomidine with atropine than in dogs receiving dexmedetomidine without atropine (Congdon et al., 2011). In addition, Sinclair et al. (2003) found, through echocardiographic indices, that the concurrent use of romifidine with glycopyrrolate further impaired left ventricular function and increased left ventricular wall stress, which corresponds with increased myocardial oxygen demand when compared with romifidine used alone in dogs (Vuille & Weyman, 1994). These findings suggest that the increased demand for oxygen in myocardium caused by the administration of alpha-2 agonists with anticholinergics may lead to myocardial

hypoxia and subsequent ventricular arrhythmias (Alvaides et al., 2008; Congdon et al., 2011). Furthermore, despite the increased heart rate induced by anticholinergics, the cardiac output did not improve proportionately (Congdon et al., 2011).

There are several explanations for an increase in the incidence of bradycardia in dogs undergoing orthopedic surgery. One of the reasons is the systemic use of potent full mu-receptor opioid agonist in dogs that underwent orthopedic surgery. The other reason is the use of opioids for epidural analgesia in these dogs. Potent opioids have been known to induce bradycardia through centrally mediated increase in vagal tone (KuKanich & Wiese, 2015). All the dogs in the present study that underwent orthopedic surgery received at least one of the following potent full-mu receptor opioid agonists: methadone, hydromorphone, or fentanyl. There were 29 out of 70 orthopedic surgery dogs which received preservative free morphine for epidural analgesia. Morphine is a relatively hydrophilic opioid that results in a slow uptake through systemic vascular absorption when compared with other lipophilic opioids following epidural administration (Valverde, 2008). It is likely that this epidural morphine also played a role in causing bradycardia in these dogs.

Another risk factor that was associated with bradycardia in this study was neurologic surgery. To be more specific, all the neurological surgeries collected were hemilaminectomy with or without diagnostic imaging, except one, which was spinal fracture reduction. The possible explanations for this finding are 1) vagally mediated bradycardia secondary to surgical stimulation, 2) hemodynamic instability resulting from the nature of the disease, and 3) the use of full mu-opioid. It has been reported that the manipulation of spinal dura in human patients undergoing lumbar spine surgery induced bradycardia (Dooney, 2010). This response, termed spinal cardiac reflex (SCR), is a subtype of trigeminocardiac reflex (TCR) (Chowdhury & Schaller, 2017). This means that as in every reflex bradycardia, the efferent pathway of the spinal cardiac reflex arc is composed of vagus nerve. Therefore, in SCR, the mechanical stretch of the spinal dura becomes the trigger to activate the parasympathetic nervous system and thus, bradycardia occurs. There is another case report of severe bradycardia observed in a human patient during spine surgery. The mechanism was described as suppression of the sympathetic system and hyperactivation of the vagal system initiated by the nerve root stimulation (Hoell et al., 2002). However, so far there are no case reports of SCR in veterinary medicine, so we do not know if this theory is applicable to dogs. Hemodynamic instability often presents after spinal cord injury, especially when the injury

is located at the cervical or high thoracic level (Partida et al., 2016). Neurological surgery as the risk factor for hypotension might actually be the manifestation of spinal cord injury. The sympathetic preganglionic neurons that regulate cardiac function are situated at T1 to T4 spinal cord levels, while the parasympathetic preganglionic neurons innervating the heart originate in the medulla oblongata (Partida et al., 2016; Sharif & Hou, 2017). When spinal cord injury occurs, it interrupts the sympathetic outflow and hence diminishes the compensatory mechanism in response to low hypotension by increasing the heart rate. The impaired sympathetic activity together with the intact parasympathetic control results in bradycardia (Agrawal et al., 2008; Hagen, 2015; Partida et al., 2016). Nevertheless, this mechanism should only account for a relatively small proportion of the finding since T1 to T4 is not a common site for spinal cord injury caused by intervertebral disc displacement in dogs (Smolders et al., 2013). The last possibility is related to the administration of full mu-opioid in all dogs undergoing neurosurgery.

The increase in the duration of anesthesia was also identified as a risk factor for intraoperative bradycardia. We found that for every hour increase in the length of anesthesia, the odds of bradycardia increased by 1.37 times. This finding might be attributable to hypothermia and the prolonged exposure to anesthetics, which produced cardiovascular depression. Body temperature usually begins to decrease significantly during the first hour of general anesthesia due to heat redistribution via two mechanisms. The first mechanism is the downregulation of the temperature threshold required to induce reflex vasoconstriction; the second mechanism is vasodilation resulting from the anesthetics (Armstrong et al., 2005). With the increase in the duration of anesthesia, the body temperature gradually decreases (Pottie, Dart, Perkins, & Hodgson, 2007). The impact of hypothermia on cardiovascular responses were evaluated in anesthetized dogs with or without epidural anesthesia (Yoshida, Shibata, Itoh, & Yamamoto, 2001). When body temperature dropped to 34 °C for 30 min, HR and cardiac index decreased by 17% and by 22%, respectively, in dogs maintained with isoflurane. The changes in HR and cardiac index were even more obvious during combined general and epidural anesthesia, with a 41% reduction in HR and a 47% reduction in cardiac index. Furthermore, the compensatory responses to low body temperature with increased sympathetic stimulation was blunted by the general anesthesia (Noel-Morgan & Muir, 2018). It is thus possible that the negative chronotropic effects are exaggerated with hypothermia than those observed under the normothermia condition.

In the present study, 45.2% (95% CI 38.9%–51.6%) of dogs had hypotension episodes. This percentage falls between the incidences reported in previous studies from 22% to 46% (Costa et al., 2013; Gordon & Wagner, 2006). The differences could be due to the various criteria for defining hypotension, and to different anesthetic regimens, surgical procedures, and patient characteristics. For example, the lowest rate (22%) was derived from a study that aimed to determine the frequency of intraoperative hypotension in relatively healthy dogs (ASA I-II) undergoing selective surgeries including ovariohysterectomy, onychectomy, castration, and dental procedure. This healthy study population and the relatively less complex surgery may explain the low frequency of hypotension. Interestingly, by far the highest incidence of hypotension was also derived from the healthy dogs undergoing elective neutering (Costa et al., 2013). In another study conducted by Redondo et al. (2007), 366 out of 955 (37.9%) dogs were affected by hypotension given the same definition in our study. Similar to our study population, they enrolled dogs with various health statuses, receiving various anesthetics and procedures. Although the impacts of these factors were unknown without statistical analysis, it seems that this discrepancy might result from the frequent use of alpha-2 receptor agonists in their study. Ninety-four percent of dogs were given alpha-2 receptor agonists, which may substantially increase the arterial blood pressure measured in their study. Detailed information on these studies is listed in Table 9.

The risk factors for hypotension were identified as 1) lack of use of dexmedetomidine-based tranquilizers/sedatives, 2) the younger or older age, and 3) the performance of neurologic related surgical procedure. The dogs that received dexmedetomidine-based tranquilizers/sedatives were almost 4 times less likely to develop hypotension when compared with the dogs that received acepromazine-based tranquilizers/sedatives. Dexmedtomidine is an alpha-2 adrenergic receptor agonist. The biphasic change in blood pressure induced by alpha-2 agonists has been described. Initially, the significant peripheral vasoconstriction causes an increase in blood pressure (phase 1). After the vasoconstriction subsides and the central sympatholytic effect predominates, blood pressure starts to decrease (phase 2) (Khan, Ferguson, & Jones, 1999; Murrell & Hellebrekers, 2005). Despite the reduction in blood pressure in phase 2, hypotension has not been seen in dogs given dexmedetomidine with a wide range of dosages from 0.2 μg/kg to 20 μg/kg in clinical studies (Congdon et al., 2011; Grasso, Ko, Weil, Paranjape, & Constable, 2015; Kuusela et al., 2001; Kuusela et al., 2003; Uilenreef, Murrell, McKusick, & Hellebrekers, 2008). Besides, the increased vasomotor tone induced by alpha-2 agonists can alleviate the profound vasodilation and low blood

pressure induced by isoflurane (Lemke. 2004). On the contrary, acepromazine is an alpha-1 adrenergic receptor antagonist, which not only reduces vasomotor tone and thus systemic vascular resistance but also reduces stroke volume (Grasso et al., 2015; Saponaro, Crovace, De Marzo, Centonze, & Staffieri, 2013). With the addition of isoflurane, the intensified vasodilation is responsible for the augmented hypotension (Grasso et al., 2015; Sinclair & Dyson, 2012)

Geriatric dogs were 1.22 times more likely to experience hypotension compared with middle-aged dogs. This finding is in agreement with the results found in humans. Patients of age ≥ 50 and > 65 years have been identified as a risk factor for post-induction hypotension as well as intraoperative hypotension and bradycardia, respectively (Reich et al., 2005; Cheung et al., 2015). Aging is a process composed of a series of physiological changes. For example, the cardiac output may decrease because of myocardial fibrosis, ventricular wall thickening, and less compliance of vasculature with age (Grubb, Perez Jimenez, & Pettifer, 2015). Besides, the gradual reduction in the mass of liver and functional nephrotic units may lead to a decrease in the rate of metabolism and excretion of drugs from the body; therefore, the duration of action is prolonged (Bellow et al., 2015; Hughes, 2008). Also, overdose may occur if the same dosage of drugs given to young dogs is given to geriatric dogs. This is because of the lower requirement for anesthetics resulting from the reduction in brain size, neurotransmitters, or receptors affinity for neurotransmitters in older patients (Muravchick, 1998). Besides this, geriatric individuals may have underlying diseases that are undetected. A study screening geriatric dogs before anesthesia found that nearly 30% (30/101) of them were diagnosed with new diseases. Among these dogs, almost half did not undergo intended procedures as a result of the new diagnoses (Joubert, 2007).

On the other hand, dogs that were classified in the young-aged group also had higher risk of developing hypotension compared with middle-aged and geriatric dogs. Because no study dogs were under 12 weeks of age, it is less likely that the hypotension was associated with the immature cardiac, liver, renal, or other system function that occur in the pediatric dogs (Grubb et al., 2015). This finding, however, might be explained by the fact that the majority of the study dogs that underwent neurosurgery and received acepromazine-based tranquilizers/sedatives were young dogs. Both neurosurgery and acepromazine-based tranquilizers/sedatives were found to be associated with hypotension in this study.

The performance of neurosurgery is another risk factor for hypotension. In a study evaluating the association between the anesthetic variables and neurologic outcome in dogs

undergoing decompressive surgery, 57% of these dogs had hypotension episodes. Nevertheless, the mechanism behind the high incidence of hypotension was not addressed in the study (Fenn et al., 2017). It is possible that the finding in our study is related to bleeding, surgical stimulation, the use of full mu-opioid, and the nature of spinal cord injury. Although the severity of blood loss during neurosurgery could not be evaluated, this may cause some degree of absolute hypovolemia, which decreases the venous return and the subsequent cardiac output (Cooper, 2014). The sympathetic system is located along T1 to L2 spinal levels. The nerves exiting from T1-T4 are responsible for cardiac sympathetic modulation, while the nerves exiting from T5-L2 are responsible for maintaining the vasomotor tone of the abdominal and splanchnic vasculature (Sharif & Hou, 2017; Partida et al., 2016), which serve as the largest blood volume reserve in the body (Gelman, 2008). Hence, vascular smooth muscle contraction in the abdominal and splanchnic vasculature plays a critical role in increasing venous return and subsequent cardiac output (Hainsworth, 1986). Nevertheless, depending on the location of spinal cord injury, the disruption of sympathetic descending signal transmission may diminish sympathetic reflexes in response to the reduced blood pressure, including increase in heart rate, cardiac contractility, and vascular tone (Sharif & Hou, 2017; Partida et al., 2016). Collectively, a decrease in venous return resulting from both absolute and relative hypovolemia, surgical stimulation- and/or full mu-opioid-induced bradycardia as described previously, and impaired sympathetic activity may lead to hypotension in dogs undergoing neurological procedures.

The incidence of bradycardia with hypotension was 12.8% (95% CI 8.9%-17.6%). This percentage is less than one third of the incidence of bradycardia and of hypotension, which demonstrates that bradycardia is not necessarily present with hypotension. A commonly observed example is that when alpha-2 agonists are administered, bradycardia can occur along with hypertension (Murrell & Hellebrekers, 2005). Furthermore, aside from HR, blood pressure is dependent on stroke volume, which is determined by preload, afterload, and contractility, and on systemic vascular resistance (Cooper, 2014). As a result, in the face of bradycardia, the compensatory responses can maintain blood pressure via modulating these elements. Copland et al. (1992) induced bradycardia (51 ± 5 beats/min) by giving oxymorphone to healthy dogs, while the MAP was preserved at 97 ± 4 mmHg. This was because the stroke volume increased from 1.9 ± 0.4 to 2.5 ± 0.4 ml/kg in response to the reduction in HR. Another example of bradycardia with normotension was observed in a study conducted by Ilkiw et al. (1993). In their study, dogs were

maintained with enflurane and HR reduced to 54 ± 8 beats/min following a fentanyl constant rate infusion. Nevertheless, the MAP was well-maintained at 82 ± 20 mmHg through the compensatory enhanced systemic vascular resistance.

The only risk factor related to bradycardia with hypotension was the duration of the anesthesia. With every hour increase in the length of the anesthesia, the risk of developing bradycardia with hypotension increased by 1.73 times. Clinically, a longer duration of anesthesia may indicate a prolonged exposure to anesthetic induced cardiac depression and hypothermia, as explained in the bradycardia section. This result suggests that the effect of these combinations may result in a severe reduction in heart rate that further compromises blood pressure. The number of risk factors identified for bradycardia with hypotension was fewer than those for the other two complications. This could be due to the relatively small number of outcomes of bradycardia with hypotension. If the sample size had been larger, more risk factors might have been identified for bradycardia with hypotension.

In the analysis of time when the intraoperative complications occurred, we found that unlike bradycardia and bradycardia with hypotension which had a relatively even distribution in the early intraoperative phase (EIP, from the beginning of inhalant anesthesia to the commencement of procedure) and the late intraoperative phase (LIP, from the beginning of the procedure to the end of inhalant anesthesia), a large portion of hypotension was recorded in the EIP. This is in line with the findings in human medicine. The time span after induction but before the onset of surgical stimulation is considered a period during which hypotension is relatively prevalent in human anesthesia (Reich et al., 2005), with incidences ranging from 18.1% to 36.5% (Südfeld et al., 2017; Jor et al., 2018). Possible explanations for this include the onset of intravenous anesthetics (Südfeld et al., 2017; Jor et al., 2018) as well as the lack of surgical stress response during this period (Desborough, 2000; Finnerty, Mabvuure, Ali, Kozar, & Herndon, 2013). Previous studies have found that the use of propofol as an induction agent produced the greatest fall in blood pressure compared to the magnitude caused by etomidate in humans (Benson et al, 2000; Möller Petrun, Kamenik, & Struys, 2013). This reduction in blood pressure induced by propofol was mainly attributed to the impaired cardiac output since there was little change in heart rate and systemic vascular resistance after induction (Möller Petrun et al., 2013). Surgical stress response is served to provide energy sources and to achieve cardiovascular homeostasis by inducing the release of pituitary hormones and by activating the sympathetic nervous system.

Without the stress response to surgery, dogs may be prone to becoming hypotensive as a result of diminished sympathetic stimulation (Desborough, 2000; Finnerty et al, 2013).

No significant association was found between the three complications and recovery quality ($p=0.643$). This could be due to the difficulty in distinguishing delirium, dysphoria, and pain as well as due to the nature of the retrospective design. In human medicine, early diagnosis of postoperative delirium is critical as delirium occurring during recovery may continue to be present on the ward (Sharma et al., 2005). As a result, multiple screening tools for postoperative delirium have been proposed. One of the tools is 4 A's test (4AT). It is an easily-performed and validated scoring system for screening delirium in post-anesthesia care units (Saller et al., 2019). The 4AT assesses 4 items including patients' alertness, cognition, attention, and fluctuation in alertness, cognition, and mental function. However, verbal ability, for example, describing personal information and naming months of the year backwards is used to evaluate patients' cognition and attention. Hence, this tool cannot be applied in animals. The method used for differentiating delirium, dysphoria, and pain in veterinary medicine was elaborated in a study by Becker et al. (2012). They conducted a prospective study in dogs undergoing stifle surgery to identify the risk factors for the development of dysphoria in the early recovery period. Dogs were classified as having dysphoria based on their reaction to the treatments and the length of abnormal behaviors including whining, paddling, and uncoordinated behaviors. If the abnormal behaviors subsided within 5 minutes without treatment after extubation, the dogs were then classified as having delirium. If the abnormal behaviors continued after 5 minutes but alleviated after the administration of opioids, the dogs were classified as having pain. On the other hand, if the abnormal behaviors continued after the administration of opioids and there was no reaction to wound palpation, then a tranquilizer, opioid antagonist, or a combination of these was given. Only dogs that responded to tranquilizers, opioid antagonists, or a combination of these were classified as having dysphoria. Nevertheless, in our study, the information about the dogs' reactions to treatment was not available. Furthermore, opioids and tranquilizers/sedatives were sometimes given at the same time. Consequently, cautions must be taken while interpreting the results and so a prospective study using a standardized protocol to evaluate this relationship is warranted.

The present study was the first study that utilized electronic anesthetic records after the transition from handwritten records at the PUVTH. In human medicine, after the emergence of computerized anesthetic records in the 1970s, research into the accuracy of record-keeping

practices began to reveal that there were discrepancies between handwritten and computerized anesthetic records. A phenomenon called “data smoothing” was observed in handwritten records (Block, 1991). This means that anesthesia recorders tended to avoid documenting extreme physiologic values to make the records look smooth. Previous studies compared handwritten and computerized records and demonstrated that SAP and DAP peak were significantly lower and SAP, DAP, and HR trough were significantly higher in handwritten records (Cook, McDonald, & Nunziata, 1989; Devitt, Rapanos, Kurrek, Cohen, & Shaw, 1999; Reich, 2000). Also, the frequency of low SAP, DAP, and HR were significantly lower in the handwritten records than the computerized records (Trush, 1992). In addition, paper records are a poor tool for research as they are less legible, which makes extracting and reviewing data extremely difficult. Computer-generated anesthetic records, on the contrary, improve record completeness and legibility, reduce workload for anesthesiologists, facilitate record tracking and storage, and provide a large and a more reliable database of patients’ information for clinical research (Kadry, Feaster, Macario, & Ehrenfeld, 2012). Although the current electronic record device for veterinary use requires manually entering vital signs into the record keeping system during anesthesia, we can certainly advance animal safety by conducting retrospective studies of anesthetic records that are more accurate and retrievable (Riebold, 2018).

The lack of consistency in the definition of bradycardia and hypotension throughout the veterinary literature and the human literature makes it a challenge for researchers to investigate the incidence of intraoperative complications. A survey investigated whether there is a consensus on the values of hypotension and the threshold that is required for treatments in the diplomats of the American College of Veterinary Anesthesia and Analgesia (ACVAA) and the European of College of Veterinary Anesthesia and Analgesia (ECVAA). They considered hypotension as SAP < 87 mmHg or MAP < 62 mmHg for both surgery and diagnostic procedures from the respondents’ perspective (Ruffato, Novello, & Clark, 2015). The threshold that warranted treatments was close to the definition of hypotension. This result is also close to the definition (MAP < 60 mmHg or SAP < 80 mmHg) used by previous studies surveying morbidity related to anesthesia. (Gaynor et al.,1999; Redondo et al., 2007; Itami et al., 2017). Another way to define hypotension is by comparing the intraoperative blood pressure with the baseline value. This method is more commonly seen in the human literature although there is again a lack of consistency in the percentage decrease from the baseline blood pressure that is considered hypotension. Also, it is

arguable whether the relative threshold is superior to the absolute threshold (Ruffato et al., 2015). Recently, this issue has been investigated by Salmasi et al. (2017). They found that both absolute thresholds and relative thresholds possess a comparable ability to predict acute kidney injury and myocardial injury after noncardiac surgery.

Similarly, there is no universal agreement on the definition of bradycardia. It is generally believed that heart rate is negatively correlated with a subject's body weight (Noujaim et al., 2004). Nevertheless, this inverse association was not observed in 243 electrocardiogram recordings collected from healthy dogs with a wide range of body weights or from 60 dogs carrying a 24-h ambulatory electrocardiogram (Ferasin, Ferasin, & Little, 2010; Lamb, Meurs, & Hamlin, 2010). The original definition reference for bradycardia of 60 beat/min might have come from the ECG text book by Tilley & Burtnick. (1999), which was also used in other studies (Gaynor et al., 1999; Carter et al., 2017). We defined hypotension as MAP < 60 or SAP < 80 mmHg and bradycardia as HR < 60 beats/min since these thresholds seem to have been accepted for the purpose of investigating the complication rates during general anesthesia.

There are several limitations in the current study. First, the absence of a universal definition of intraoperative complications restricts the ability to directly compare the results across the literature. Second, there is no standard technique for measuring arterial blood pressure. Most of the blood pressure readings in our study were measured using the oscillometric method, which generally underestimates the MAP (Drynan & Raisis, 2013; McMillan, 2017) and therefore could have overestimated the incidence of hypotension and bradycardia with hypotension. Third, not all procedures that requires anesthesia had electronic records. Some of the procedures such as computed tomography imaging and urology-related procedures were commonly recorded in handwritten records, thus possibly creating a selection bias. Forth, as mentioned previously, due to the nature of a retrospective study, it is difficult to make a clear distinction between dysphoria and pain in the method of classification. Last, although we included patients with a variety of health statuses and undergoing different procedures, some variables, such as chronic preoperative medications and severe comorbidities that can be the important predictors of hypotension were not included.

CHAPTER 6. CONCLUSION

This study reported the frequency of bradycardia (45.6%), hypotension (45.2%), and bradycardia with hypotension (12.8%) in 250 anesthetized dogs. We identified the risk factors for bradycardia: the use of dexmedetomidine-based tranquilizers/sedatives, the longer duration of anesthesia, and the performance of orthopedic and neurosurgery. The risk factors for hypotension were the use of acepromazine-based tranquilizers/sedatives, the older or younger age of dogs, and the performance of neurosurgery. The risk factor for bradycardia with hypotension was the longer duration of anesthesia. A prospective study is needed to further confirm the association between intraoperative complications and the recovery quality.

Table 9 Summary of the studies reporting hypotension.

Article	Incidence/ proportion	Definition (mmHg)	Study design	Study population	Procedure	Anesthetic protocol
Gordon et al. (2006)	22% (13/59)	SAP < 90	Retrospective study	Relatively healthy patients (ASA I or II)	Elective surgery (ovariohysterectomy, onychectomy, castration, and dental procedure)	Premedication: atropine, morphine, acepromazine, and none Induction: ketamine with diazepam, and face mask Maintenance: isoflurane and sevoflurane
Redondo et al. (2007)	37.9% (362/955)	MAP < 60/ SAP < 80	Retrospective study	Dogs with various health status (ASA I-V)	Minor surgery (i.e., mastectomy and dental procedure, etc.), trauma surgery (i.e., fracture and luxation repair, etc.), abdominal surgery (i.e., enterectomy and caesarean section, etc.), diagnostic techniques (i.e., computerized axial tomography and radiography, etc.), thoracic surgery (patent ductus arteriosus and lung lobectomy, etc.), experimental anesthesia	Premedication: alpha 2 receptor agonists, acepromazine, and atropine Induction: propofol, thiopentone, ketamine, and halogenated anesthetics Maintenance: isoflurane, sevoflurane, desflurane, propofol, and ketamine

Table 9. Continued

Costa et al., (2013)	46% (87/188)	MAP < 60 for more than 10 min	Retrospective study	Healthy dogs (ASA I)	Elective neutering	Premedication: acepromacine, morphine, methadone Induction: propofol, alfaxalone, ketamine with diazepam Maintenance: isoflurane
Itami et al., (2017)	25% (1089/4310)	MAP < 60	Prospective study	Dogs with various health status (ASA I-V)	Surgical and diagnostic procedures	NA

MAP, mean arterial blood pressure; SAP, systolic arterial blood pressure; NA, not available.

REFERENCES

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Text Revision. American Psychiatric Association, Washington, DC.

Aldecoa, C. D., Bettelli, G. J., Bilotta, F., Sanders, R., Audisio, R., Borozdina, A., . . . Spies, C. (2017). European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. European Journal of Anaesthesiology, 34(4), 192-214.

Ansaloni, L., Catena, F., Chattat, R., Fortuna, D., Franceschi, C., Mascitti, P., & Melotti, R. (2010). Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. British Journal of Surgery, 97(2), 273-280.

Alibhai, H., Clarke, K., Lee, Y., & Thompson, J. (1996). Cardiopulmonary effects of combinations of medetomidine hydrochloride and atropine sulphate in dogs. Veterinary Record, 138(1), 11-3.

Armstrong, S. R., Roberts, B. K. and Aronsohn, M. (2005), Perioperative hypothermia. Journal of Veterinary Emergency and Critical Care, 15: 32-37.

Alvaides, R., Teixeira Neto, F., Aguiar, A., Campagnol, D., & Steagall, P. (2008). Sedative and cardiorespiratory effects of acepromazine or atropine given before dexmedetomidine in dogs. Veterinary Record, 162(26), 852-856.

Agrawal, A., Timothy, J., Cincu, R., Agarwal, T., & Waghmare, L. B. (2008). Bradycardia in neurosurgery. Clinical Neurology and Neurosurgery, 110(4), 321-327.

Block, F. (1991). Normal fluctuation of physiologic cardiovascular variables during anesthesia and the phenomenon of “smoothing”. Journal of Clinical Monitoring, 7(2), 141-145.

Brodal, P. (2010). The autonomic nervous system. In The central nervous system structure and function: The fourth Edition. Oxford

Bellows, J., Colitz, C., Daristotle, L., Ingram, D., Lepine, A., Marks, S., . . . Zhang, J. (2015). Common physical and functional changes associated with aging in dogs. Journal of the American Veterinary Medical Association, 246(1), 67-75.

Borghi, B., Casati, A., Iuorio, S., Celleno, D., Michael, M., Serafini, P., . . . Fanelli, G. (2002). Frequency of hypotension and bradycardia during general anesthesia, epidural anesthesia, or integrated epidural-general anesthesia for total hip replacement. Journal of Clinical Anesthesia, 14(2), 102-106.

Bloor, B. C., Frankland, M., Alper, G., Raybould, D., Weitz, J., & Shurtliff, M. (1992). Hemodynamic and sedative effects of dexmedetomidine in dog. The Journal of Pharmacology and Experimental Therapeutics, 263(2), 690-7.

Benson, M., Junger, A., Fuchs, C., Quinzio, L., Böttger, S., & Hempelmann, G. (2000). Use of an anesthesia information management system (AIMS) to evaluate the physiologic effects of hypnotic agents used to induce anesthesia. Journal of Clinical Monitoring and Computing, 16(3), 183-190.

Becker, W., Mama, K., Rao, S., Palmer, R., & Egger, E. (2008). Retrospective evaluation of anesthetic and patient factors on the development of dysphoria after stifle surgery in dogs. 9th Annual CSU-CVMBS Research Day Scientific Proceedings, Fort Collins, CO, 25.

Becker, W., Mama, K., Rao, S., Palmer, R., & Egger, E. (2013). Prevalence of dysphoria after fentanyl in dogs undergoing stifle surgery. Veterinary Surgery, 42(3), 302-307.

Brodbelt, D., Pfeiffer, D., Young, L., & Wood, J. (2008). Results of the confidential enquiry into perioperative small animal fatalities regarding risk factors for anesthetic-related death in dogs. Journal of the American Veterinary Medical Association, 233(7), 1096-104.

Bruce, A., Ritchie, C., Blizard, R., Lai, R., & Raven, P. (2007). The incidence of delirium associated with orthopedic surgery: A meta-analytic review. International Psychogeriatrics, 19(2), 197-214.

Beck, J., Staatz, A., Pelsue, D., Kudnig, S., Macphail, C., Seim, H., & Monnet, E. (2006). Risk factors associated with short-term outcome and development of perioperative complications in dogs undergoing surgery because of gastric dilatation-volvulus: 166 cases (1992-2003). Journal of the American Veterinary Medical Association, 229(12), 1934-9.

Bijker, J. B., Van Klei, W. A., Kappen, T. H., Van Wolfswinkel, L. G., Moons, K. J., & Kalkman, C. (2007). Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology, 107(2), 213-220.

Bijker, J. B., Van Klei, W. A., Vergouwe, Y. J., Eleveld, D. G., Van Wolfswinkel, L., Moons, K., & Kalkman, C. (2009). Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology, 111(6), 1217-1226.

Cooper, E. (2014). Hypotension. In Small Animal Critical Care and Medicine, second edition (pp. 46-50). Elsevier.

Clark-Price, S. (2015). Inadvertent perianesthetic hypothermia in small animal patients. Veterinary Clinics of North America: Small Animal Practice, 45(5), 983-994.

Copland, V.S., Haskins, S.C., & Patz, J.D. (1992). Cardiovascular and pulmonary effects of atropine reversal of oxymorphone-induced bradycardia in dogs. Veterinary Surgery, (5), 414-417.

Cheung, C. C., Martyn, Campbell, A., Frost, S., Gilbert, K., Michota, F., . . . Khan, N. A. (2015). Predictors of intraoperative hypotension and bradycardia. The American Journal of Medicine, 128(5), 532-538.

Chowdhury, T., Mendelowith, D., Golanov, E., Spiriev, T., Arasho, B., Sandu, N., . . . Schaller, B. (2015). Trigeminocardiac reflex: The current clinical and physiological knowledge. Journal of Neurosurgical Anesthesiology, 27(2), 136-147.

Carter, J., Motsinger-Reif, A., Krug, W., & Keene, B. (2017). The effect of heart disease on anesthetic complications during routine dental procedures in dogs. Journal of the American Animal Hospital Association, 53(4), 206-213.

Cook, R. I., McDonald, J. S., & Nunziata, E. (1989). Differences between handwritten and automatic blood pressure records. Anesthesiology, 71(3), 385-390.

Congdon, J., Marquez, M., Niyom, S., & Boscan, P. (2011). Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs. Journal of the American Veterinary Medical Association, 239(1), 81-9.

Colson, P., Ryckwaert, F., & Coriat, P. (1999). Renin angiotensin system antagonists and anesthesia. Anesthesia & Analgesia, 89(5), 1143-1155.

Costa, R., Raisis, A., Musk, G., & Hosgood. (2013). Frequency of hypotension in a historical cohort of anaesthetised dogs undergoing elective desexing. Australian Veterinary Practitioner, 43(2), 414-419.

Costa, R., Raisis, A., Hosgood, G., & Musk, G. (2015). Preoperative factors associated with hypotension in young anaesthetised dogs undergoing elective desexing. Australian Veterinary Journal, 93(4), 99-104.

Cooke, K.L., & Snyder, P.S. (1998). Calcium channel blockers in veterinary medicine. Journal of Veterinary Internal Medicine, (3), 123-131.

Chowdhury, T., & Schaller, B. (2017). The negative chronotropic effect during lumbar spine surgery: A systemic review and aggregation of an emerging model of spinal cardiac reflex. Medicine, 96(1), E5436.

Clark-Price, S. C., & Grauer, G. F. (2015). Physiology, pathophysiology, and anesthetic management of patients with renal disease. In K. A. Grimm, L. A. Lamont, W. J. Tranquilli, S. A. Greene, S. A. Robertson (Eds.), *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (pp. 679-697). Ames, IA: Wiley-Blackwell.

Dooney, N. (2010). Prone CPR for transient asystole during lumbosacral spinal surgery. Anaesthesia and Intensive Care, 38(1), 212-3.

Desborough, J. (2000). The stress response to trauma and surgery. BJA: International Journal of Anaesthesia, 85(1), 109-117.

Doxey, S., & Boswood, A. (2004). Differences between breeds of dog in a measure of heart rate variability. Veterinary Record, 154(23), 713-717.

Doyle, D., & Mark, J. (1990). Reflex bradycardia during surgery. Canadian Journal of Anaesthesia,37(2), 219-222.

Dunning, D., Monnet, E., Orton, C., & Salman, M. (1998). Analysis of prognostic indicators for dogs with pericardial effusion: 46 cases (1985-1996). Journal of The American Veterinary Medical Association, 212(8), 1276.

Drynan, E., & Raisis, A. (2013). Comparison of invasive versus noninvasive blood pressure measurements before and after hemorrhage in anesthetized greyhounds using the Surgivet V9203. Journal of Veterinary Emergency and Critical Care, 23(5), 523-531.

Devitt, J., Rapanos, H., Kurrek, T., Cohen, M., & Shaw, M. (1999). The anesthetic record: Accuracy and completeness. Canadian Journal of Anesthesia, 46(2), 122-128.

De Kock, I., Van Daele, C., & Poelaert, J. (2010). Sepsis and septic shock: Pathophysiological and cardiovascular background as basis for therapy. Acta Clinica Belgica, 65(5), 323-329.

Erhardt, W., Bohn, F., & Ehmann, H. (1990). Studies on the anticholinergic medication in the dogs before and during anesthesia. Berliner Und Munchener Tierarztliche Wochenschrift, 103(2), 42-49.

Edlund, A., Lundström, M., Bucht, G., Gustafson, Y., & Brännström, B. (2001). Delirium before and after operation for femoral neck fracture. Journal of the American Geriatrics Society, 49(10), 1335-1340.

Feher, J. (2017). Hypothalamus and pituitary gland. In *Quantitative Human Physiology* (2nd ed.). (pp. 870-882). St. Louis, MO: Elsevier.

Fernandes, D., & Assreuy, J. (2008). Nitric oxide and vascular reactivity in sepsis. SHOCK,30(7 Suppl 1), 10-13.

Ferasin, L., Ferasin, H., & Little, C. J. L. (2010). Lack of correlation between canine heart rate and body size in veterinary clinical practice. Journal of Small Animal Practice, 51(8), 412-418.

Fenn, J., Laber, E., Williams, K., Rousse, C., Early, P., Mariani, C., . . . Olby, N. (2017). Associations between anesthetic variables and functional outcome in dogs with thoracolumbar intervertebral disk extrusion undergoing decompressive hemilaminectomy. Journal of Veterinary Internal Medicine, 31(3), 814-824.

Finnerty, C., Mabvuure, N., Ali, A., Kozar, R., & Herndon, D. (2013). The surgically induced stress response. Journal of Parenteral and Enteral Nutrition, 37(5 Suppl), 21S-29S.

Frishman, W., & Saunders, E. (2011). β-Adrenergic blockers. Journal of Clinical Hypertension,13(9), 649-653.

Gelman, S. (2008). Venous function and central venous pressure: A physiologic story. Anesthesiology, 108(4), 735-748.

Geist, M. (2011). Case study: Acute kidney failure from hypotension in a dog. Retrieved from http://veterinarymedicine.dvm360.com/case-study-acute-kidney-failure-hypotension-dog

Griebling, T. (2011). Re: Preoperative risk factors for postoperative delirium (POD) after urological surgery in the elderly. The Journal of Urology, 186(6), 2302-2303.

Gustafson, Y., Berggren, D., Brännström, B., Bucht, G., Norberg, A., Hansson, L-I., & Winblad. (1988). Acute confusional states in elderly patients treated for femoral neck fracture. Journal of the American Geriatrics Society, 36(6), 525-530.

Groen, G., Baljet, J., & Drukker, B. (1988). The innervation of the spinal dura mater: Anatomy and clinical implications. Acta Neurochirurgica, 92(1), 39-46.

Greer, K. A., Canterberry, S.C., & Murphy, K.E. (2007). Statistical analysis regarding the effects of height and weight on life span of the domestic dog. Research in Veterinary Science, 82, 208-214.

Gryglewski, R., Dembínska-Kieć, A., & Korbut, R. (1978). A possible role of thromboxane A2 (TXA2) and prostacyclin (PGI2) in circulation. Acta Biologica Et Medica Germanica, 37(5-6), 715-23.

Gaynor, J.S., Dunlop, C.I., Wagner, A.E., Wertz, E.M., Golden, A.E., & Demme, W.C. (1999). Complications and mortality associated with anesthesia in dogs and cats. Journal of the American Animal Hospital Association, 35(1), 13-17.

Grubb, T. L., Perez Jimenez, T. E., & Pettifer, G. R. (2015). Senior and geriatric patients. In K. A. Grimm, L. A. Lamont, W. J. Tranquilli, S. A. Greene, S. A. Robertson (Eds.), *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (pp. 988-992). Ames, IA: Wiley-Blackwell.

Grasso, Stefania C., Ko, Jeff C, Weil, Ann B., Paranjape, Vaidehi, & Constable, Peter. (2015). Hemodynamic influence of acepromazine or dexmedetomidine premedication in isoflurane-anesthetized dogs. JAVMA: Journal of the American Veterinary Medical Association, 246(7), 754-764.

Gordon, A. M., & Wagner, A. E. (2006). Anesthesia-related hypotension in a small-animal practice. Veterinary Medicine, 101(1), 22-26.

Hainsworth, R. (1986). Vascular capacitance: Its control and importance. Reviews of Physiology, Biochemistry and Pharmacology, 105, 101-73.

Hughes, J. (2008). Anaesthesia for the geriatric dog and cat. Irish Veterinary Journal,61(6), 380-387.

Harrison, R., Clark, L., & Corletto, F. (2012). Comparison of mean heart rate in anaesthetized dachshunds and other breeds of dog undergoing spinal Magnetic Resonance Imaging. Veterinary Anaesthesia and Analgesia, 39(3), 230-235.

Hirsch, J., DePalma, G., Tsai, T., Sands, L., Leung, J., & Absalom, A. (2015). Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. British Journal of Anaesthesia, 115(3), 418-426.

Hagen, Ellen Merete, H. (2015). Acute complications of spinal cord injuries. 6(1), 17-23.

Hoell, T., Nagel, M., Beier, A., Kern, B., Meisel, J., & Mast, H. (2002). Temporary cardiac asystolia induced by intraoperative irritation of the eighth right sided anterior cervical nerve root. Acta Neurochirurgica, 144(12), 1311-1313.

Hosgood, G., & Scholl, D. T. (1998). Evalution of age as a risk factor for perianesthetic morbidity and mortality in the dog. Journal of Veterinary Emergency and Critical Care, 8(3), 222-236.

Itami, T., Aida, H., Asakawa, M., Fujii, Y., Iizuka, T., Imai, A., . . . Yanagawa, M. (2017). Association between preoperative characteristics and risk of anaesthesia-related death in dogs in small-animal referral hospitals in Japan. Veterinary Anaesthesia and Analgesia, 44(3), 461-472.

Idowu, O., & Heading, K. (2018). Hypoglycemia in dogs: Causes, management, and diagnosis. Canadian Veterinary Journal, 59(6), 642-649.

Joubert, K. (2007). Pre-anaesthetic screening of geriatric dogs. Journal of the South African Veterinary Association, 78(1), 31-5.

Jor, Maca, Koutna, Gemrotova, Vymazal, Litschmannova, . . . Cerny. (2018). Hypotension after induction of general anesthesia: Occurrence, risk factors, and therapy. A prospective multicentre observational study. Journal of Anesthesia, 32(5), 673-680.

Ju Tae Sohn, Sang Jeong Lee, Kyeong II Hwang, . . . Young Kyun Chung. (1998). Ketamine sodium thiopental venous capacitance. Korean Journal of Anesthesiology, 34(5), 896.

Kavanagh, K. (2002). Sick sinus syndrome in a bull terrier. Canadian Veterinary Journal, 43(1), 46-48.

Koch, D. A., Arnold, S. M., Hubler, M., & Montavon, P. (2003). Brachycephalic syndrome in dogs. Compendium on Continuing Education for the Practicing Veterinarian, 25(1), 48-55.

Khan, Z., Ferguson, C., & Jones, R. (1999). Alpha-2 and imidazoline receptor agonists their pharmacology and therapeutic role. Anaesthesia, 54(2), 146-165.

Kadry, B., Feaster, W., Macario, A., & Ehrenfeld, J. (2012). Anesthesia information management systems: past, present, and future of anesthesia records. Mount Sinai Journal of Medicine: A Journal of Translational and Personalized Medicine, 79(1), 154-165.

Kuusela, E., Raekallio, M., Väisänen, M., Mykkänen, K., Ropponen, H., & Vainio, O. (2001). Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. American Journal of Veterinary Research, 62(7), 1073-80.

Kinsella, S. M., & Tuckey, J. P. (2001). Perioperative bradycardia and asystole: Relationship to vasovagal syncope and the Bezold–Jarisch reflex. British Journal of Anaesthesia, 86(6), 859-868.

Kuusela, E., Vainio, O., Short, C., Leppäluoto, J., Huttunen, P., Ström, S., . . . Raekallio, M. (2003). A comparison of propofol infusion and propofol/isoflurane anaesthesia in dexmedetomidine premedicated dogs. Journal of Veterinary Pharmacology and Therapeutics,26(3), 199-204.

KuKanich, B., & Wiese, A. J. (2015). Opioids. In K. A. Grimm, L. A. Lamont, W. J. Tranquilli, S. A. Greene, S. A. Robertson (Eds.), *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (pp. 207-226). Ames, IA: Wiley-Blackwell.

Lipowski, Z. (1987). Delirium (Acute Confusional States). JAMA, 258(13), 1789-1792.

Lipowski, Z. (1990). Delirium: Acute confusional states. Rev. edn. Oxford University Press, New York.

Laflamme, D. (1997). Development and validation of a body condition score system for dogs. Canine Practice, (4), 10-15.

Lemke, K. A. (2004). Perioperative use of selective alpha-2 agonists and antagonists in small animals. Canadian Veterinary Journal, 45(6), 475-480.

Little, C. (2005). Hypoglycaemic bradycardia and circulatory collapse in a dog and a cat. Journal of Small Animal Practice, 46(9), 445-448.

Lipowsky, H. (2005). Microvascular rheology and hemodynamics. Microcirculation, 12(1), 5-15.

Lemke, K., Tranquilli, W., Thurmon, J., Benson, G., & Olson, W. (1993). Hemodynamic effects of atropine and glycopyrrolate in isoflurane-xylazine-anesthetlzed Dogs. Veterinary Surgery, 22(2), 163-169.

Lamb, A. P., Meurs, K. M., & Hamlin, R. L. (2010). Correlation of heart rate to body weight in apparently normal dogs. Journal of Veterinary Cardiology, 12(2), 107-110.

Lighthall, G., Singh, S., & Kertai, M. (2014). Perioperative maintenance of tissue perfusion and cardiac output in cardiac surgery patients. Seminars in Cardiothoracic and Vascular Anesthesia, 18(2), 117-136.

Muir, W. (1978). Effects of atropine on cardiac rate and rhythm in dogs. Journal of the American Veterinary Medical Association, 172(8), 917-21.

Muravchick, S. (1998). The aging process: Anesthetic implications. Acta Anaesthesiologica Belgica, 49(2), 85-90.

Marshall, J. (1998). Chemoreceptors and cardiovascular control in acute and chronic systemic hypoxia. Brazilian Journal of Medical and Biological Research, 31(7), 863-888.

McCorry, L. (2007). Physiology of the autonomic nervous system. American Journal of Pharmaceutical Education, 71(4), 78.

Mooney, C. (2011). Canine hypothyroidism: A review of aetiology and diagnosis. New Zealand Veterinary Journal,59(3), 105-114.

Murrell, J. (2015). Adrenergic agents. In K. A. Grimm, L. A. Lamont, W. J. Tranquilli, S. A. Greene, S. A. Robertson (Eds.), *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (pp. 183-193). Ames, IA: Wiley-Blackwell.

McMillan, M. (2017). Pitfalls and common errors of anaesthetic monitoring devices. Part 2: Non-invasive blood pressure monitoring. Veterinary Nursing Journal, 32(1), 9-13.

Monk, T. G., Bronsert, M. R., Henderson, W. G., Mangione, M. P., Sum-Ping, S. T., Bentt, D. R., . . . Hammermeister, K. E. (2015). Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiology, 123(2), 307-319.

McMillan, M., & Darcy, H. (2016). Adverse event surveillance in small animal anaesthesia: An intervention-based, voluntary reporting audit. Veterinary Anaesthesia and Analgesia, 43(2), 128-135.

Martirosyan, N., Feuerstein, J., Theodore, N., Cavalcanti, D., Spetzler, R., & Preul, M. (2011). Blood supply and vascular reactivity of the spinal cord under normal and pathological conditions A review. Journal of Neurosurgery-Spine, 15(3), 238-251.

Mirenda, J., & Grissom, T. (1991). Anesthetic implications of the renin-angiotensin system and angiotensin-converting enzyme inhibitors. Anesthesia and Analgesia, 72(5), 667-683.

Murrell, J., & Hellebrekers, L. (2005). Medetomidine and dexmedetomidine: A review of cardiovascular effects and antinociceptive properties in the dog. Veterinary Anaesthesia and Analgesia, 32(3), 117-127.

Möller Petrun, A., Kamenik, M., & Struys, M. (2013). Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: A double-blind, randomized, clinical trial. British Journal of Anaesthesia, 110(3), 388-396.

Mugford, A., Li, R., & Humm, K. (2013). Acute kidney injury in dogs and cats 1. Pathogenesis and diagnosis. In Practice, 35(5), 253-264.

Morais, H., & Muir Iii, W. (1995). The effects of medetomidine on cardiac contractility in autonomically blocked dogs. Veterinary Surgery, 24(4), 356-364.

Malek, M., & Nematbakhsh, M. (2015). Renal ischemia/reperfusion injury; from pathophysiology to treatment. Journal of Renal Injury Prevention, 4(2), 20-7.

Messina, E. J., Sun, D. S., Koller, A., Wolin, M., & Kaley, G. (1992). Role of endothelium-derived prostaglandins in hypoxia-elicited arteriolar dilation in rat skeletal muscle. Circulation Research,71(4), 790-796.

Monk, T. G., Saini, V. C., Weldon, B. C., & Sigl, J. (2005). Anesthetic management and one-year mortality after noncardiac surgery. Anesthesia & Analgesia, 100(1), 4-10.

Meyer, G., & Winter, D. (1970). Spinal cord participation in the Cushing reflex in the dog. Journal of Neurosurgery, 33(6), 662-75.

Monk, T. G., Weldon, B. C., Garvan, C. W., Dede, D. E., Van der Aa, M. T., Heilman, K. M., & Gravenstein, J. S. (2008). Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology, 108(1), 18-30.

Neal, J., Bernards, C., Butterworth, J., Di Gregorio, G., Drasner, K., Hejtmanek, M., . . . Weinberg, G. (2010). ASRA Practice advisory on local anesthetic systemic toxicity. Regional Anesthesia and Pain Medicine, 35(2), 152-161.

Noujaim, S.F., Lucca, E., Munoz, V., Persaud, D., Berenfeld, O., Meijler, F.L., & Jalife, J. (2004). From mouse to whale: A universal scaling relation for the PR Interval of the electrocardiogram of mammals. Circulation, 110, 2802-7322.

Noel-Morgan, J., & Muir, W. (2018). Anesthesia-associated relative hypovolemia: Mechanisms, monitoring, and treatment considerations. Frontiers in Veterinary Science, 5, 53.

Olsson, R. (1981). Local factors regulating cardiac and skeletal muscle blood flow. Annual Review of Physiology, 43(1), 385-395.

Olby, N. (1999). Current concepts in the management of acute spinal cord Injury. Journal of Veterinary Internal Medicine, 13(5), 399-407.

Olby, N. (2010). The pathogenesis and treatment of acute spinal cord injuries in dogs. The Veterinary Clinics of North America. Small Animal Practice, 40(5), 791-807.

Oliver, J., Clark, L., Corletto, F., & Gould, D. (2010). A comparison of anesthetic complications between diabetic and nondiabetic dogs undergoing phacoemulsification cataract surgery: A retrospective study. Veterinary Ophthalmology, 13(4), 244-250.

O'Grady, M. R., Holmberg, D. L., Miller, C. W., & Cockshutt, J. R. (1989). Canine congenital aortic stenosis: A review of the literature and commentary. The Canadian Veterinary Journal, 30(10), 811.

Pottie, R., Dart, C., Perkins, N., & Hodgson, D. (2007). Effect of hypothermia on recovery from general anaesthesia in the dog. Australian Veterinary Journal, 85(4), 158-162.

Packer, R., Hendricks, A., & Burn, C. (2012). Do dog owners perceive the clinical signs related toconformational inherited disorders as 'normal' for the breed? A potential constraint to improving canine welfare. Animal Welfare, 21(1), 81-93.

Partida, E., Mironets, E., Hou, S., & Tom, V. (2016). Cardiovascular dysfunction following spinal cord injury. Neural Regeneration Research, 11(2), 189-194.

Perkowski, S. Z. & Oyama, M.A. (2015). Pathophysiology and anesthetic management of patients with cardiovascular disease. In K. A. Grimm, L. A. Lamont, W. J. Tranquilli, S. A. Greene, S. A. Robertson (Eds.), *Veterinary Anesthesia and Analgesia: The Fifth Edition of Lumb and Jones* (pp. 496-508). Ames, IA: Wiley-Blackwell.

Patti, Saitta, Cusumano, Termine, & Di Vita. (2011). Risk factors for postoperative delirium after colorectal surgery for carcinoma. European Journal of Oncology Nursing, 15(5), 519-523.

Park, E., White, G., & Tieber, L. (2012). Mechanisms of injury and emergency care of acute spinal cord injury in dogs and cats. Journal of Veterinary Emergency and Critical Care, 22(2), 160-178.

Riebold, T. (2018). Anesthetic records. In K. G. Cooley & R. A. Johnson (Eds.), *Veterinary Anesthetic and Monitoring Equipment*, (pp. 323-333). Hoboken, NJ: Wiley-Blackwell.

Reiter, A. M., & Castejon-Gonzalez, A. (2018). Perioperative considerations in dentistry and oral surgery. In A. M. Reiter & M. Gracis (Eds.), *BSAVA Manual of Canine and Feline Dentistry and Oral Surgery* (4th ed.). (pp. 338-370). Quedgeley, Gloucester: BSAVA.

Rossmeisl, J., White, C., Pancotto, T., Bays, A., & Henao-Guerrero, P. (2013). Acute adverse events associated with ventral slot decompression in 546 dogs with cervical intervertebral disc disease. Veterinary Surgery, 42(7), 795-806.

Reich, D. L., Hossain, S. A., Krol, M., Baez, B., Patel, P., Bernstein, A., & Bodian, C. (2005). Predictors of hypotension after induction of general anesthesia. Anesthesia & Analgesia, 101(3), 622-628.

Ruffato, M., Novello, L., & Clark, L. (2015). What is the definition of intraoperative hypotension in dogs? Results from a survey of diplomates of the ACVAA and ECVAA. Veterinary Anaesthesia and Analgesia, 42(1), 55-64.

Rowena M. A. Packer, Anke Hendricks, Michael S. Tivers, & Charlotte C. Burn. (2015). Impact of facial conformation on canine health: Crachycephalic obstructive airway syndrome. PLoS ONE, 10(10), E0137496.

Redondo, J. I., Rubio, M., Soler, G., Serra, I., Soler, C., & Gómez-Villamandos, R. J. (2007). Normal values and incidence of cardiorespiratory complications in dogs during general anaesthesia. A Review of 1281 Cases. Journal of Veterinary Medicine Series A, 54(9), 470-477.

Redondo, J. I., Suesta, P., Serra, I., Soler, C., Soler, G., Gil, L., & Gómez-Villamandos, R. J. (2012). Retrospective study of the prevalence of postanaesthetic hypothermia in dogs. Veterinary Record, 171(15), 374.

Reich, D. L., Wood, R. K., Mattar, R., Krol, M., Adams, D. C., Hossain, S., & Bodian, C. A. (2000). Arterial blood pressure and heart rate discrepancies between handwritten and computerized anesthesia records. Anesthesia & Analgesia, 91(3), 612-616.

Sivertsson, R. (1979). Effect of blood pressure reduction on tissue perfusion. Acta Medica Scandinavica, 205(S628), 13-16.

Sharp, C. R. (2014). Hypotension. In D. C. Silverstein & K. Hopper (Eds.), *Small Animal Critical Care and Medicine* (2nd ed.). (pp. 649-52). St. Louis, MO: Elsevier.

Südfeld, S., Brechnitz, S., Wagner, J. Y., Reese, P.C., Pinnschmidt, H. O., Reuter, D.A., & Saugel, B. (2017). Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia. BJA: British Journal of Anaesthesia, 119(1), 57-64.

Smolders, L. A., Bergknut, N., Grinwis, Guy C. M., Hagman, R., Lagerstedt, A., Hazewinkel, Herman A. W., . . . Meij, B. P., (2013). Intervertebral disc degeneration in the dog. Part 2: Chondrodystrophic and non-chondrodystrophic breeds. The Veterinary Journal, 195(3), 292-299.

Saponaro, V., Crovace, A., De Marzo, L., Centonze, P., & Staffieri, F. (2013). Echocardiographic evaluation of the cardiovascular effects of medetomidine, acepromazine and their combination in healthy dogs. Research in Veterinary Science, 95(2), 687-692.

Steinmetz, J., Christensen, K., Lund, T., Lohse, N., & Rasmussen, L. (2009). Long-term consequences of postoperative cognitive dysfunction. Anesthesiology, 110(3), 548-55.

Schaller, B. F., Cornelius, J., Prabhakar, H., Koerbel, A., Gnanalingham, K., Sandu, N., . . . Buchfelder, M. (2009). The trigemino-cardiac reflex: An update of the current knowledge. Journal of Neurosurgical Anesthesiology, 21(3), 187-195.

Sinclair, M., & Dyson, D. (2012). The impact of acepromazine on the efficacy of crystalloid, dextran or ephedrine treatment in hypotensive dogs under isoflurane anesthesia. Veterinary Anaesthesia and Analgesia, 39(6), 563-573.

Steinbacher, R., & Dörfelt, R. (2013). Anaesthesia in dogs and cats with cardiac disease–An impossible endeavour or a challenge with manageable risk. Eur J Companion Anim Pract, 23, 4-22.

Sharif, H., & Hou, S. (2017). Autonomic dysreflexia: A cardiovascular disorder following spinal cord injury. Neural Regeneration Research, 12(9), 1390-1400.

Schweitzer, P., & Mark, H. (1980). The effect of atropine on cardiac arrhythmias and conduction. Part 1. American Heart Journal, 100(1), 119-127.

Saller, T., MacLullich, A. M. J., Schäfer, S. T., Crispin, A., Neitzert, R., Schüle, C., ... & Hofmann-Kiefer, K. F. (2019). Screening for delirium after surgery: Validation of the 4 A's test (4AT) in the post-anaesthesia care unit. Anaesthesia.

Salmasi, V. J., Maheshwari, K. I., Yang, D., Mascha, E., Singh, A., Sessler, D., & Kurz, A. (2017). Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology, 126(1), 47-65.

Sinclair, M., O'Grady, M., Kerr, C., & McDonell, W. (2003). The echocardiographic effects of romifidine in dogs with and without prior or concurrent administration of glycopyrrolate. Veterinary Anaesthesia and Analgesia, 30(4), 211-219.

Shaw, S., & Rush, J. (2007). Canine pericardial effusion: Pathophysiology and cause. Compendium (Yardley, PA), 29(7), 400-3.

Steagall, P., Simon, B., Teixeira Neto, F., & Luna, S. (2017). An update on drugs used for lumbosacral epidural anesthesia and analgesia in dogs. Frontiers in Veterinary Science, 4(MAY), 68.

Sharma, P., Sieber, F., Zakriya, K., Pauldine, R., Gerold, K., Hang, J., & Smith, T. (2005). Recovery room delirium predicts postoperative delirium after hip-fracture repair. Anesthesia and Analgesia, 101(4), 1215-20, table of contents.

Shepherd J. T & Vanhoutte P. M. (1979). Neurohumoral regulation. *The Human Cardiovascular System: Facts and Concepts* (pp.107–155). New York, NY: Raven Press.

Simmons, J. P., & Wohl, J. S. (2009). Hypotension. In D. Silverstein & K. Hopper (eds.), *Small Animal Critical Care Medicine* (pp.27-30). St. Louis, MO: Elsevier.

Son, Won-Gyun, Kim, Junyoung, Seo, Jong-Pil, Yoon, Junghee, Choi, Mincheol, Lee, Lyon Y, & Lee, Inhyung. (2011). Cranial epidural spread of contrast medium and new methylene blue dye in sternally recumbent anaesthetized dogs. Veterinary Anaesthesia and Analgesia, 38(5), 510-515.

Sun, L. Y., Wijeysundera, D. N., Tait, G. A., & Beattie, W. S. (2015). Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology, 123(3), 515-523.

Thrush, D. (1992). Are automated anesthesia records better? Journal of Clinical Anesthesia, 4(5), 386-9.

Taghavi, S., & Askari, R. (2018). Hypovolemic shock. Treasure Island, FL: StatPearls.

Tag, T., & Day, T. (2008). Electrocardiographic assessment of hyperkalemia in dogs and cats. Journal of Veterinary Emergency and Critical Care, 18(1), 61-67.

Tiret, L., Desmonts, J., Hatton, F., & Vourc'h, G. (1986). Complications associated with anaesthesia—A prospective survey in france. Survey of Anesthesiology, 30(6), 334.

Thooft, A., Favory, R., Salgado, D., Taccone, F., Donadello, K., De Backer, D., . . . Vincent, J. (2011). Effects of changes in arterial pressure on organ perfusion during septic shock. Critical Care, 15(5), R222.

Troncy, E., Junot, S., Keroack, S., Sammut, V., Pibarot, P., Genevois, J., & Cuvelliez, S. (2002). Results of preemptive epidural administration of morphine with or without bupivacaine in dogs and cats undergoing surgery: 265 cases (1997-1999). Journal of the American Veterinary Medical Association, 221(5), 666-72.

Tilley, L., & Burtnick, N. (eds.). (1999). In *ECG for the small animal practitioner*. Jackson, Wyo. : Teton NewMedia.

Uilenreef, J., Murrell, J., McKusick, B., & Hellebrekers, L. (2008). Dexmedetomidine continuous rate infusion during isoflurane anaesthesia in canine surgical patients. Veterinary Anaesthesia and Analgesia, 35(1), 1-12.

Valverde, A. (2008). Epidural analgesia and anesthesia in dogs and cats. Veterinary Clinics of North America-Small Animal Practice, 38(6), 1205.

Watts, S. (2010). Endothelin receptors: What's new and what do we need to know? American Journal of Physiology-Regulatory Integrative and Comparative Physi, 298(2), R254-R260.

Ware, W. A. (2014a). Cardiovascular system disorders. In R. W. Nelson & C. G. Couto (eds.), *Small animal internal medicine* (5th ed.). (pp. 130-143). St. Louis, MO: Elsevier.

Ware, W. A. (2014b). Cardiac arrhythmias and antiarrhythmic therapy. In R. W. Nelson & C. G. Couto (eds.), *Small animal internal medicine* (5th ed.). (pp. 74-94). St. Louis, MO: Elsevier.

Warltier, D. C., Campagna, J. A., & Carter, C. (2003). Clinical relevance of the Bezold–Jarisch reflex. Anesthesiology, 98(5), 1250-1260.

Walsh, M. J., Devereaux, P. X., Garg, A. N., Kurz, A. I., Turan, A., Rodseth, R., . . . Sessler, D. (2013). Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology, 119(3), 507-515.

Walters, B., Hadley, M., Hurlbert, R., Aarabi, B., Dhall, S., Gelb, D.Theodore, N. (2013). Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 Update. Neurosurgery, 60, 82-91.

Wesselink, Kappen, Torn, Slooter, & Van Klei. (2018). Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. British Journal of Anaesthesia, 121(4), 706-721.

Watterson, L. M., Morris, R. W., Westhorpe, R. N., & Williamson, J. A. (2005). Crisis management during anaesthesia: bradycardia. Quality & safety in health care, 14(3), e9.

Vuille C & Weyman AE. (1994). Left ventricle I: general considerations, assessment of chamber size and function. In C. Vuille & A. E. Weyman (Eds.), *Principles and Practice of Echocardiography* (2nd ed) (pp.575-611). Philadelphia, PA: Lippincott Williams & Wilkins.

Zacny, J., Lance Lichtor, P., Zaragoza, J., & Wit, J. (1992). Subjective and behavioral responses to intravenous fentanyl in healthy volunteers. Psychopharmacology, 107(2), 319-326.